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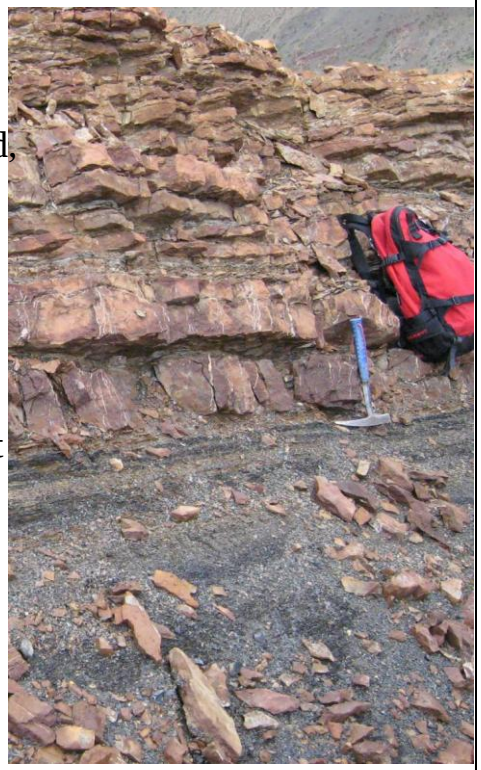
The cold exterminated all of them

Through age determinations that are using the radioactive decay of uranium, scientists have discovered that one of the greatest mass extinctions was due to an ice age and not to a warming of Earth temperature

The Earth has known several mass extinctions over the course of its history. One of the most important happened at the Permian-Triassic boundary 250 million years ago. Over 95% of marine species disappeared and, up until now, scientists have linked this extinction to a significant rise in Earth temperatures. But researchers from the University of Geneva (UNIGE), Switzerland, working alongside the University of Zurich, discovered that this extinction took place during a short ice age which preceded the global climate warming. It's the first time that the various stages of a mass extinction have been accurately understood and that scientists have been able to assess the major role played by volcanic explosions in these climate processes.



Permian-Triassic boundary in shallow marine sediments, characterised by a significant sedimentation gap between the black shales of Permian and dolomites of Triassic age. This gap documents a globally recognized regression phase, probably linked to a period of a cold climate and glaciation.
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This research, which can be read in Scientific Reports, completely calls into question the scientific theories regarding these phenomena, founded on the increase of CO_2 in the atmosphere, and paves the way for a new vision of the Earth's climate history.

Teams of researchers led by Professor Urs Schaltegger from the Department of Earth and Environmental Sciences at the Faculty of Science of the UNIGE and by Hugo Bucher, from the University of Zürich, have been working on absolute dating for many years. They work on determining the age of minerals in volcanic ash, which establishes a precise and detailed chronology of the earth's climate evolution. They became interested in the Permian-Triassic boundary, 250 million years ago, during which one of the greatest mass extinctions ever took place, responsible for the loss of 95% of marine species. How did this happen? For how long marine biodiversity stayed at very low levels ?

A technique founded on the radioactive decay of uranium

Researchers worked on sediment layers in the Nanpanjiang basin in southern China. They have the particularity of being extremely well preserved, which allowed for an accurate study of the biodiversity and the climate history of the Permian and the Triassic. "We made several cross-sections of hundreds of metres of basin sediments and we determined the exact positions of ash beds contained in these marine sediments," explained Björn Baresel, first author of the study. They then applied a precise dating technique based on natural radioactive decay of uranium, as Urs Schaltegger added: "In the sedimentary cross-sections, we found layers of volcanic ash containing the mineral zircon which incorporates uranium. It has the specificity of decaying into lead over time at a well-known speed. This is why, by measuring the concentrations of uranium and lead, it was possible for us to date a sediment layer to an accuracy of 35,000 years, which is already fairly precise for periods over 250 million years."

Ice is responsible for mass extinction

By dating the various sediment layers, researchers realised that the mass extinction of the Permian-Triassic boundary is represented by a gap in sedimentation, which corresponds to a period when the sea-water level decreased. The only explanation to this phenomenon is that there was ice, which stored water, and that this ice age which

lasted 80,000 years was sufficient to eliminate much of marine life. Scientists from the UNIGE explain the global temperature drop by a stratospheric injection of large amounts of sulphur dioxide reducing the intensity of solar radiation reaching the surface of the earth. "We therefore have proof that the species disappeared during an ice age caused by the activity of the first volcanism in the Siberian Traps," added Urs Schaltegger. This ice age was followed by the formation of limestone deposits through bacteria, marking the return of life on Earth at more moderate temperatures. The period of intense climate warming, related to the emplacement of large amounts of basalt of the Siberian Traps and which we previously thought was responsible for the extinction of marine species, in fact happened 500,000 years after the Permian-Triassic boundary.

This study therefore shows that climate warming is not the only explanation of global ecological disasters in the past on Earth: it is important to continue analysing ancient marine sediments to gain a deeper understanding of the earth's climate system.

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Cerebrospinal fluid shows promise as autism biomarker

Altered distribution of cerebrospinal fluid in high-risk infants can predict whether they will develop autism spectrum disorder

Researchers from the UC Davis MIND Institute, University of North Carolina (UNC) and other institutions have found that altered distribution of cerebrospinal fluid (CSF) in high-risk infants can predict whether they will develop autism spectrum disorder (ASD). The study appears March 6 in the journal Biological Psychiatry.

"Normally, autism is diagnosed when the child is two or three years old and beginning to show behavioral symptoms; there are currently no early biological markers" said David Amaral, director of research at the MIND Institute and a co-senior author on the paper. "That there's an alteration in the distribution of cerebrospinal fluid that we can see on MRIs as early as six months, is a major finding."

Produced by the brain, CSF was once cast as a neural shock absorber, keeping the brain from bumping up against the skull. More recent findings have shown that CSF can influence neuronal migration and other mechanisms associated with brain development, as well as removing dangerous molecules.

"CSF is like the filtration system in the brain," said Mark Shen, a former graduate student in the Amaral lab and now a postdoctoral fellow in Joseph Piven's lab at UNC. Piven is co-senior author on the paper, and Shen is first author. "As CSF circulates through the brain, it washes away waste particles that would otherwise build up. We believe that extra-axial CSF is an early sign that CSF is not filtering and draining when it should. The result is that there could be a buildup of neuro-inflammation that isn't being washed way."

This study confirms earlier research carried out at the MIND Institute that showed infants with increased CSF in the subarachnoid space (near the brain's perimeter) have increased risk of developing autism. The current study sought to validate the previous results in a larger sample of infants in the Infant Brain Imaging Study (IBIS), a national research network of institutions led by Piven at UNC, Washington University, Children's Hospital of Philadelphia and University of Washington.

To test whether CSF might indicate increased risk of developing ASD, the researchers examined MRIs from 343 infants at six, 12 and 24 months. In this group, 221 babies had older siblings with ASD and were therefore at higher risk for autism. The other 122 subjects had no family history.

Infants who later developed ASD had significantly more subarachnoid CSF at six months than those who did not develop the condition. Among high-risk infants, those who were ultimately diagnosed with ASD had 18 percent more. These measurements predicted ASD in the high-risk group with roughly 70 percent accuracy.

"The more extra-axial CSF present at six months, the more severe the autism symptoms when the kids were diagnosed at 24 months of age," noted Shen.

Finding biomarkers for autism, or any disorder, can be tricky. Quite often, early successes are never replicated. That this larger, more robust, follow-up study confirms the earlier finding is a significant step forward, the researchers said.

Still, this is early work and there are many unanswered questions. The researchers do not know whether the CSF accumulation contributes to autism or is simply an effect from another, more subtle, cause.

In addition, the biomarker is not sensitive enough to say with certainty that a child will develop ASD. However, the apparent link between increased CSF and autism could have significant clinical impact.

"Prior to our 2013 study, radiologists would often call this 'benign extra-axial fluid,' meaning it had no clinical significance," Amaral said. "This finding may alert radiologists and neurologists to the possible negative consequences of increased subarachnoid CSF."

Ultimately, with more study, CSF could help gauge a child's risk of developing ASD and possibly other neurological disorders.

"Neuroimaging CSF could be another tool to help pediatricians diagnose autism as early as possible," said Shen. "It could help signal risk using regular MRIs that you find in any hospital because it is easily seen with the naked eye on a standard MRI."

Other researchers included Sun Hyung Kim, Hongbin Gu, Heather C. Hazlett, Robert W. Emerson, Meghan R. Swanson and Martin A. Styner at the University of North Carolina; Christine W. Nordahl at UC Davis; Robert C. McKinstry and Kelly N. Botteron at Washington University; Dennis Shaw, Stephen R. Dager and Annette M. Estes at the University of Washington; Jed T. Elison at the University of Minnesota; Vladimir S. Fonov and Alan C. Evans at McGill University; Guido Gerig at NYU; Sarah Paterson at Temple University; Robert T. Schultz at the University of Pennsylvania; and Lonnie Zwaigenbaum at the University of Alberta.

This study was funded by the National Institutes of Health (R01-HD055741, R01- HD05571-S1, R01-HD059854, T32-HD040127 and U54HD086984), Autism Speaks and the Simons Foundation.

http://bit.ly/2n9sdFl

One-two punch may floor worst infections

McMaster researchers find combo therapy stops antibiotic drug resistance

Hamilton, ON - McMaster University researchers have found a new way to treat the world's worst infectious diseases, the superbugs that are resistant to all known antibiotics.

The discovery of an effective combination therapy has the potential to change medical practice for the treatment of the drug resistant infections which the World Health Organization (WHO) last week identified as of "critical priority" for their threat to human health.

The research was published in the journal Nature Microbiology today.

"We looked for compounds that would mess with these bacteria, and I think we're nailing it," said Eric Brown, senior author of the paper, a professor of biochemistry and biomedical science at McMaster's Michael G. DeGroote School of Medicine and a scientist of the Michael G. DeGroote Institute for infectious Disease Research.

His team focused on Gram-negative bacteria which are resistant to all antibiotics including last resort drugs, such as colistin, and lead to pneumonia, wound or surgical site and bloodstream infections, as well as meningitis in healthcare settings.

Gram-negative bacteria have an intrinsically impenetrable outer shell that is a barrier to many otherwise effective antibiotics, and this makes these infections deadly, particularly in hospital settings. His team tested a collection of 1,440 off-patent drugs in search of one that might compromise that barrier in the superbugs.

"These pathogens are really hard nuts to crack, but we found a molecule that shreds that shell and allows antibiotics to enter and be effective," said Brown.

The scientists discovered the antiprotozoal drug pentamidine disrupts the cell surface of Gram-negative bacteria, even the most resistant. The anti-fungal medication was particularly potent when used with antibiotics against multidrug resistant bacteria.

Pentamidine, when used with other antibiotics, was found to be particularly effective against two of the three pathogens which the WHO has identified as having the most critical priority for development of new antibiotics. Those were Acinetobacter baumannii and the enterobacteriaceae. The combo therapy also had some impact on the third most critical bacteria, Pseudomonas aeruginosa.

The discovery was found to be effective in the lab and in mice, but more work is needed to offset potential side effects and ensure human safety. Brown added that his lab is continuing to test more compounds as well. "One of the things we want to pursue further is why this is working so well."

The study was supported by grants from the Canadian Institutes of Health Research, the National Sciences and Engineering Research Council and Cystic Fibrosis Canada, among others.

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Early deaths from childhood cancer up to 4 times more common than previously reported

Death within a month of diagnosis is more likely in very young children

Treatments for childhood cancers have improved to the point that 5-year survival rates are over 80 percent. However, one group has failed to benefit from these improvements, namely children who die so soon after diagnosis that they are not able to receive treatment, or who receive treatment so late in the course of their disease that it is destined to fail. A study published today in the Journal of Clinical Oncology explores this challenging population, finding that death within a month of diagnosis is more likely in very young children and those from minority racial and ethnic groups even independent of low socioeconomic status. The study uses a large national database to find that the rate of deaths within one month of diagnosis has been previously under-reported in clinical trial data, with early deaths from some pediatric cancer subtypes up to four times as common as had been implied by clinical trial reports.

"During my pediatric residency a teenager came in with leukemia, but had so much cancer when he presented that he had multi-organ failure and died within about 24 hours of coming to our attention, before we could even start treatment. I wanted to find out who these kids are in hopes that as a system we could learn to spot them earlier, when treatment still has a chance of success," says Adam Green, MD, investigator at the University of Colorado Cancer Center and pediatric oncologist at Children's Hospital Colorado. Green originated this study during his clinical fellowship at Dana Farber Cancer Institute, working with Carlos Rodriguez Galindo, MD.

Green and colleagues used data from the Surveillance, Epidemiology and End Results (SEER) database, finding 36,337 cases of pediatric cancer between the years 1992 and 2011. Of these young patients, 555 or 1.5 percent died within one month of cancer diagnosis. Overall, the strongest predictor of patients who would die soon after diagnosis was age below one year.

"In general, babies are just challenging, clinically, because they can't tell you what they're feeling. Parents and physicians have to pick the ones with cancer from the ones with a cold, without the patient being able to tell you about symptoms that could be diagnostic. Babies tend to get aggressive cancers, it's hard to tell when they're getting sick, and some are even born with cancers that have already progressed. These factors combine to make very young age the strongest predictor of early death in our study," Green says.

Additionally, black race and Hispanic ethnicity predicted early death, even beyond the influence of socioeconomic status. Green hopes that future studies will be able to discover whether biologic or cultural factors may be responsible for these disparities, or if higher rates of early death in minority populations could be due to factors built into insurance and health care systems.

He also points out that the rate of early deaths due to pediatric cancers is higher than previously reported.

"Most of what we know about outcomes for cancer patients come from clinical trials, which have much more thorough reporting rules than cancer treated outside trials. However, these kids in our study aren't surviving long enough to join clinical trials," Green says.

For example, the paper shows that a clinical trial against childhood Acute Myeloid Leukemia (AML) reported early death in 16 of 1,022 young patients, or 1.6 percent of these cases. In contrast, the SEER database, which collects about 15 percent of all cancer outcomes across the United States (representing a geographic and socioeconomic cross-section), shows 106 early deaths in 1,698 diagnoses, or 6.2 percent of all cases, almost four times as high as previously reported. When comparing the rates of early deaths seen in the SEER database to rates of early deaths reported in clinical trial data, early death was higher for all cancer subtypes (0.7 versus 1.3 percent in non-infant ALL; 2.0 versus 5.4 percent in infant ALL; 1.4 versus 3.8 percent in hepatoblastoma; 0.04 versus 0.5 percent in Wilms tumor).

"I had a hunch this was a bigger problem than we thought. Now we see that is indeed the case," says Green.

Now that Green has shown the fact of early death in this population, he hopes to work with CU Cancer Center colleagues to design a national prospective study that could more closely examine the factors associated with this outcome. "So that whenever a family has a child who dies of cancer within a month of diagnosis, we could contact the family to gather information about timing of symptoms and their experience accessing care. We can already act on our findings in this current study to improve early identification of these patients. But with prospective, patient-level data, we can move from understanding the scope and risk factors for early death to identifying problems in the diagnostic process we can fix," Green explains.

The overall goal of this ongoing line of research is to change potential early deaths to long-term survivors.

"This is a population that deserves our attention," Green says.

http://bit.ly/2mJHi35

New method rescues donor organs to save lives

Columbia engineers and surgeons revive historic technique, pioneer new technology to recover damaged donor lungs

New York, NY - A multidisciplinary team led by Gordana Vunjak-Novakovic, Mikati Foundation Professor of Biomedical Engineering and Medical Sciences at Columbia Engineering, and Matt Bacchetta, associate professor of surgery at Columbia University Medical Center and NewYork-Presbyterian has--for the first time--maintained a fully functional lung outside the body for several days. In a study published today on Nature Biomedical Engineering's website, the researchers describe the cross-circulation platform that maintained the viability and function of the donor lung and the stability of the recipient over 36 to 56 hours. They used the advanced support system to fully recover the functionality of lungs injured by ischemia (restricted blood supply), and made them suitable for transplant.

The team was inspired by the critical need to expand the pool of donor lungs. Transplantation remains the only definitive treatment for patients with end-stage lung disease, but the number of donor lungs is much smaller than the number of patients in need, and many patients die while on the wait list. In addition, lungs quickly lose their function outside the body and during transport: four out of five lungs evaluated at transplant centers are rejected. If these lungs could be kept viable outside the body long enough, it would be possible to improve their function and use them for transplantation.

Over the past five years, Vunjak-Novakovic has been collaborating with Bacchetta and Hans Snoeck, professor of medicine, to investigate how to improve low-quality donor lungs and possibly bioengineer lungs for transplantation. Rather than attempting to build new lungs, they developed strategies to rescue damaged donor lungs. One approach was to use a stem cell therapy of the lung to replace defective cells with new therapeutic cells derived from the transplant recipient. While this technique was applicable to low-quality lungs

that are rejected for transplantation, there was a problem: the support of the lung outside the body was too short for the therapeutic cells to start improving lung function.

As often happens, unmet clinical needs inspire new ideas and drive the development of new technologies. The Columbia team realized that "cross circulation"--an abandoned surgical procedure used in the 1960s to exchange blood flow between two patients--could enable long-term support of living organs outside the body by providing critical systemic and metabolic factors that are missing from all current technologies. The team embraced this idea and devised an entirely new approach to support lungs outside the body long enough to enable therapeutic interventions needed to recover their health and normal function.

"This is the most complex study we have ever done, and the one with the highest potential for clinical translation," Vunjak-Novakovic says. "The lung is a masterpiece of 'engineering by nature,' with its more than 40 cell types, and a gas exchange surface area of 100 square meters - half a tennis court. It is amazing that such an intricate organ can be maintained outside the body and even recovered following injury."

"Our team worked hard to innovate a suite of imaging and targeted delivery technologies and ultimately completed this challenging, paradigm-shifting study in less than a year. This was only possible because of our uniquely talented team of bioengineers and surgeons, and the highly collaborative environment at Columbia that fosters innovation," Vunjak-Novakovic says.

The team's breakthrough was realizing that cross-circulation could be re-configured to help recover damaged donor organs. The study's lead authors, PhD candidate John O'Neill and postdoctoral research fellow Brandon Guenthart, looked at clinical studies from the 1960s that used cross-circulation of blood between a healthy individual and a patient suffering from a critical but potentially reversible illness. Working in Vunjak-Novakovic's Laboratory for Stem Cells and Tissue Engineering, they developed a radically new technology to support fully functional lung outside the body for several days.

"Our cross-circulation platform will likely allow us to extend the duration of support to a week or longer if needed, potentially enabling the recovery of severely damaged organs," observes O'Neill. "Beyond prolonging support time, we also demonstrated several therapeutic interventions that vastly improve and accelerate recovery."

As the team was developing their cross-circulation platform, they overcame many challenges to keep the lungs viable outside the body much longer than any platform had before. To prevent the outer surface of the lung from drying out and to provide normal body temperature, they designed a humidification system with ambient temperature control and a re-circulating warm water organ basin to provide normal body temperature to mimic the chest cavity.

Then they needed to tackle the perfusion circuit. To allow for adequate blood flow into and out of the lungs during cross-circulation, they developed new components and techniques and used a donor vessel as a "bio-bridge." They engineered a dynamic system capable of height and hydrostatic pressure adjustments and feedback-regulated pressure-controlled flow. They also developed image-guided techniques for the controlled delivery of drugs and cells in precisely targeted regions of the lung without the need for repeated lung biopsies.

"As our work progressed, we continued to innovate out of necessity and refine and streamline our cross-circulation setup and procedure," says Guenthart.

The researchers say their new platform could be readily extended to recover other organs that are in high demand for transplant or in need of repair, including livers and kidneys, and they have already begun studies in these directions.

"Cross-circulation has proven to be a valuable tool for investigation and has fostered interdisciplinary collaborations," Bacchetta says. "Our study is giving researchers new opportunities to investigate

donor-recipient immunologic interactions, therapeutic cell delivery, stem cell differentiation, acute lung injury, and the development of new pulmonary theranostics."

Vunjak-Novakovic adds, "Our goal was to develop a platform that harnesses the full potential of tissue engineering and regenerative medicine toward organ rescue. We hope that our unique technology will benefit the many patients in need and help them live fuller and happier lives."

The study was supported by grants from the National Institutes of Health (R01 HL120046 and U01 HL134760), Irving Institute for Clinical and Translational Research at Columbia University (CaMPR grants), the Richard Bartlett Foundation and the Azmi Mikati Foundation.

The authors declare no competing financial interests.

The study is titled "Cross-circulation for extracorporeal support and recovery of the lung." The authors include: John D. O'Neill1†, Brandon A. Guenthart1,2†, Jinho Kim1, Scott Chicotka2, Dawn Queen1, Kenmond Fung3, Charles Marboe4, Alexander Romanov5, Sarah X. L. Huang6,7, Ya-Wen Chen6,7, Hans-Willem Snoeck6,7,8,9, Matthew Bacchetta2 and Gordana Vunjak-Novakovic1,7**

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http://bit.ly/2mJRCbv

Dawn identifies age of Ceres' brightest area

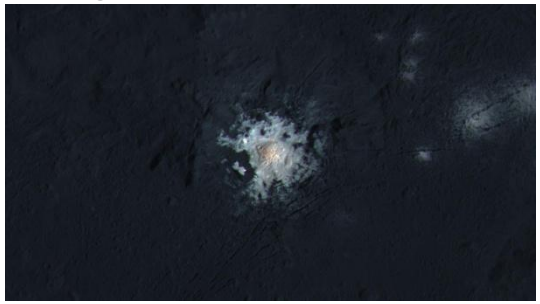
Intriguing bright feature on the dwarf planet is only about 4 million years old

The bright central area of Ceres' Occator Crater, known as Cerealia Facula, is approximately 30 million years younger than the crater in which it lies, according to a new study in the Astronomical Journal. Scientists used data from NASA's Dawn spacecraft to analyze Occator's central dome in detail, concluding that this intriguing bright feature on the dwarf planet is only about 4 million years old—quite recent in terms of geological history.

Researchers led by Andreas Nathues at the Max Planck Institute for Solar System Research (MPS) in Gottingen, Germany, analyzed data from two instruments on board NASA's Dawn spacecraft: the framing camera, and the visible and infrared mapping spectrometer.

The new study supports earlier interpretations from the Dawn team that this reflective material - comprising the brightest area on all of Ceres - is made of carbonate salts, although it did not confirm a particular type of carbonate previously identified.

The secondary, smaller bright areas of Occator, called Vinalia Faculae, are comprised of a mixture of carbonates and dark material, the study authors wrote.



The bright spots in the center of Occator Crater on Ceres are shown in enhanced color in this view from NASA's Dawn spacecraft. **Credit:NASA/JPL-Caltech/UCLA/MPS/DLR/IDA/PSI/LPI**

New evidence also suggests that Occator's bright dome likely rose in a process that took place over a long period of time, rather than forming in a single event. They believe the initial trigger was the impact that dug out the crater itself, causing briny liquid to rise closer to the surface. Water and dissolved gases, such as carbon dioxide and methane, came up and created a vent system. These rising gases also could have forced carbonate-rich materials to ascend toward the surface. During this period, the bright material would have erupted through fractures, eventually forming the dome that we see today.

http://bit.ly/2n2OTdD

Study suggests complex life was present on Earth 2.33 billion years ago

An exhaustive genetic analysis of modern-day organisms has revealed new insights into Earth's earliest forms of complex life.

March 7, 2017 by Jennifer Chu

The findings, reported by MIT earth scientists today in Nature, suggest that eukaryotes—the domain of life comprising animals, plants, and protists—were present on Earth as early as 2.33 billion

years ago, right around the time when oxygen became a permanent fixture in the atmosphere.

This new time-stamp for ancient life significantly predates the earliest sign of eukaryotes found in the fossil record —1.56 billion-year-old macroscopic fossils that scientists widely agree are the remains of multicellular algae-like organisms.

The MIT researchers arrived at their estimate not by examining rocks for fossil evidence but by using a technique called "molecular clock analysis." This approach involves first sifting through DNA databases to trace the evolution of particular gene sequences across hundreds of modern species. Then, using ages derived from the fossil animal and plant relatives, these sequences can be tied backward in time to the earliest point at which those sequences must have been expressed in ancestral eukaryotes.

"We've again demonstrated the feasibility of using modern DNA to provide insights about early life," says Roger Summons, professor of geobiology in MIT's Department of Earth, Atmospheric and Planetary Sciences (EAPS). "We have no concrete records of early life. We have a few fossil microbes, which are often disputed, and some geochemical signals, but it's not enough to reconstruct an informed history of life. What we're saying is, you can look at what's on the planet today, and you can tell something important about what the organisms' ancient ancestors were doing."

The analysis was carried out by Summons and lead author David Gold, a former MIT postdoc who is currently at Caltech, along with Abigail Caron, a senior research support associate at MIT, and Gregory Fournier, the Cecil and Ida Green Career Development Assistant Professor in EAPS.

The oldest enzymes

The team focused its genetic search on DNA sequences that code for the biosynthesis of sterol, a class of molecules found in all eukaryotes that influences the characteristics and behavior of their cell membranes.

"[Sterol] determines how a membrane changes shape and mediates behavior—for example, the ability to engulf a piece of food," Summons says. "A single-celled eukaryote can engulf and digest its food, whereas most bacteria have to excrete enzymes to break something down before taking it in."

The group looked to trace the genetic evolution of the first two enzymes involved in sterol production: SQMO, or squalene monooxygenase, which inserts an atom of oxygen into squalene; and OSC, or oxidosqualene cyclase, which folds the oxidosqualene molecule up to form the classic four-ring configuration of a sterol, the best known example of which is cholesterol.

The two enzymes represent the beginning steps in the biosynthesis of sterol, which over time has evolved to include many more enzymes that improve sterol function and effectivness. The researchers reasoned that if they could trace back the evolution of the enzymes in the first steps of sterol biosynthesis , they could then infer when some of the earliest eukaryotes were present on Earth.

Tracing a tree

The team looked for SQMO and OSC in the National Center for Biotechnology Information protein database, a vast compendium of genetic sequences for thousands of modern species, contributed by scientists all over the world. The researchers wrote algorithms to efficiently cull through the genetic data, looking for those species that expressed the DNA sequences coding for SQMO and OSC.

Then, for each enzyme they drew up a phylogentic tree—a branching diagram showing the evolutionary relationship among those species expressing either SQMO or OSC.

"When you plot the trees for both enzymes, you find they're eerily similar," Summons says. "To me, this was an astonishing fact: These histories of these two enzymes across the eukaryote tree, and also including some bacteria, look pretty close to identical. The genes always move together. It's very rare to find one without the other right next to it."

In particular, the researchers noted two early points along both evolutionary trees, where it appeared that each enzyme was genetically transferred between eukaryotes and bacteria. These genetic jumps, known as horizontal gene transfers, mark the times when organisms shared these genes.

To identify these points, the researchers performed a "molecular clock analysis," a technique which measures time according to random changes in DNA, as these mutations occur at relatively constant rates. Summons and his colleagues used other algorithms based on the "topology," or rate of genetic mutation, in each evolutionary tree.

They calibrated the algorithm with data from known fossil records, including confirmed ages of certain species within each tree, including ancient corals, starfish, and algae. They then ran the algorithm—their molecular clock—backward in time to determine when the genes for sterol were transferred between bacteria and eukaryotes. Running the clock in subtly different ways, along with error propagations, gave dates that converged around one point, 2.3 billion years ago.

"The age of eukaryotes has been argued for decades, and there are widely differing opinions," Summons says. "We're putting out this piece of evidence that we think is significant, that says we believe that sterol was being made at least 2.3 billion years ago, and that the earliest eukaryotes were here at least that long."

Evolution, unraveled

In 2016, Summons' group determined that another life-shifting event took place around 2.3 billion years ago: Oxygen became a permanent fixture in the Earth's atmosphere, in what is now regarded as the Great Oxidation Event. Summons says the possibility that eukaryotes may have existed around the same time makes sense, as they would have required ample amounts of oxygen to synthesize sterols in order to maintain their cell membranes.

Going forward, the team plans to trace the evolutionary history of enzymes further down in the sterol pathway—particularly those involved in synthesizing cholesterol—again by using modern genetic sequences to, as Summons puts it, "unravel its evolutionary story."

"People have known for many years that they can work out ancestries from DNA, including the ancestry of humanity," Summons says. "We know a lot about the connections between Neanderthals, Denisovans, and other early groups of humans from pieces of DNA in bone. But that's projecting back a couple million years. We're projecting back 2.3 billion years. So we're showing modern DNA can be used to understand key events in the history of life, billions of years ago."

More information: David A. Gold et al. Paleoproterozoic sterol biosynthesis and the rise of oxygen, Nature (2017). DOI: 10.1038/nature21412

http://bit.ly/2m5L17K

Caffeine boosts enzyme that could protect against dementia, finds IU study

New analysis reveals 24 compounds that can help reduce impact of harmful proteins in the brain

BLOOMINGTON, Ind. - A study by Indiana University researchers has identified 24 compounds -- including caffeine -- with the potential to boost an enzyme in the brain shown to protect against dementia.

The protective effect of the enzyme, called NMNAT2, was discovered last year through research conducted at IU Bloomington. The new study appears today in the journal Scientific Reports.

"This work could help advance efforts to develop drugs that increase levels of this enzyme in the brain, creating a chemical 'blockade' against the debilitating effects of neurodegenerative disorders," said Hui-Chen Lu, who led the study. Lu is a Gill Professor in the Linda and Jack Gill Center for Biomolecular Science and the Department of Psychological and Brain Sciences, a part of the IU Bloomington College of Arts and Sciences.

Previously, Lu and colleagues found that NMNAT2 plays two roles in the brain: a protective function to guard neurons from stress and a "chaperone function" to combat misfolded proteins called tau, which

accumulate in the brain as "plaques" due to aging. The study was the first to reveal the "chaperone function" in the enzyme.

Misfolded proteins have been linked to neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases, as well as amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease. Alzheimer's disease, the most common form of these disorders, affects over 5.4 million Americans, with numbers expected to rise as the population ages.

To identify substances with the potential to affect the production of the NMNAT2 enzyme in the brain, Lu's team screened over 1,280 compounds, including existing drugs, using a method developed in her lab. A total of 24 compounds were identified as having potential to increase the production of NMNAT2 in the brain.

One of the substances shown to increase production of the enzyme was caffeine, which also has been shown to improve memory function in mice genetically modified to produce high levels of misfolded tau proteins. Lu's earlier research found that mice altered to produce misfolded tau also produced lower levels of NMNAT2.

To confirm the effect of caffeine, IU researchers administered caffeine to mice modified to produce lower levels of NMNAT2. As a result, the mice began to produce the same levels of the enzyme as normal mice.

Another compound found to strongly boost NMNAT2 production in the brain was rolipram, an "orphaned drug" whose development as an antidepressant was discontinued in the mid-1990s. The compound remains of interest to brain researchers due to several other studies also showing evidence it could reduce the impact of tangled proteins in the brain.

Other compounds shown by the study to increase the production of NMNAT2 in the brain -- although not as strongly as caffeine or rolipram -- were ziprasidone, cantharidin, wortmannin and retinoic acid. The effect of retinoic acid could be significant since the compound derives from vitamin A, Lu said.

An additional 13 compounds were identified as having potential to lower the production of NMNAT2. Lu said these compounds are also important because understanding their role in the body could lead to new insights into how they may contribute to dementia.

"Increasing our knowledge about the pathways in the brain that appear to naturally cause the decline of this necessary protein is equally as important as identifying compounds that could play a role in future treatment of these debilitating mental disorders," she said.

Other researchers on the study were assistant research scientist Yousuf O. Ali and graduate student Gillian Bradley, both of the Linda and Jack Gill Center for Biomolecular Science at IU Bloomington. Ali and Lu are co-corresponding authors on the paper.

This study was funded by the National Institutes of Health's National Institute of Neurological Disorders and Stroke and the Belfer Family Foundation.

http://bit.ly/2m329Kv

Snake bit? UCI chemists figure out how to easily and cheaply halt venom's spread

Molecular gel could save millions globally from death or disfigurement

Irvine, Calif. - Chemists at the University of California, Irvine have developed a way to neutralize deadly snake venom more cheaply and effectively than with traditional anti-venom -- an innovation that could spare millions of people the loss of life or limbs each year.

In the U.S., human snakebite deaths are rare -- about five a year -- but the treatment could prove useful for dog owners, mountain bikers and other outdoor enthusiasts brushing up against nature at ankle level. Worldwide, an estimated 4.5 million people are bitten annually, 2.7 million suffer crippling injuries and more than 100,000 die, most of them farmworkers and children in poor, rural parts of India and sub-Saharan Africa with little healthcare.

The existing treatment requires slow intravenous infusion at a hospital and costs up to $100,000. And the antidote only halts the damage inflicted by a small number of species.

"Current anti-venom is very specific to certain snake types. Ours seems to show broad-spectrum ability to stop cell destruction across

species on many continents, and that is quite a big deal," said doctoral student Jeffrey O'Brien, lead author of a recent study published in the Journal of the American Chemical Society.

Zeroing in on protein families common to many serpents, the UCI researchers demonstrated that they could halt the worst effects of cobras and kraits in Asia and Africa, as well as pit vipers in North America. The team synthesized a polymer nanogel material that binds to several key protein toxins, keeping them from bursting cell membranes and causing widespread destruction. O'Brien knew he was onto something when the human serum in his test tubes stayed clear, rather than turning scarlet from venom's typical deadly rupture of red blood cells.

Chemistry professor Ken Shea, senior author of the paper, explained that the venom -- a "complex toxic cocktail" evolved over millennia to stay ahead of prey's own adaptive strategies -- is absorbed onto the surface of nanoparticles in the new material and is permanently sequestered there, "diverted from doing harm."

Thanks to the use of readily available, nonpoisonous components, the "nanodote" has a long shelf life and costs far less. The existing antidote is made by injecting horses with venom, waiting weeks for the animals to develop antibodies, then extracting their blood and shipping it from Mexico or Australia to places that can afford it. The process is not allowed in the U.S. Major suppliers have discontinued shipments to many markets.

In contrast, "our treatment costs pennies on the dollar and, unlike the current one, requires no refrigeration," O'Brien said. "It feels pretty great to think this could save lives."

Since publishing their findings, the researchers have discovered that scorpion and spider bite infections may also be slowed or stopped via their invention. They have patents pending and are seeking public and private funding to move forward with clinical trials and product development. Additionally, Shea's group pioneered a synthetic antidote for bee melittin -- the ingredient in stings that can kill people who have an allergic reaction -- using similar methods.

"The goal is not to save mice from venom and bee stings," Shea said, "but to demonstrate a paradigm shift in thinking about solutions to these types of problems. We have more work to do, and this is why we're seeking a fairly significant infusion of resources."

The U.S. Department of Defense's research arm financed the first phase of the laboratory work. "The military has platoons in the tropics and sub-Saharan Africa, and there are a variety of toxic snakes where they're traipsing around," Shea said. "If soldiers are bitten, they don't have a hospital nearby; they've got a medic with a backpack. They need something they can use in the field to at least delay the spread of the venom."

In addition to the Defense Advanced Research Projects Agency, the National Science Foundation and the National Institutes of Health provided funding.

http://bit.ly/2lHCICN

Don't relax drug approval process, experts warn

Nature report on plans to deregulate FDA drug testing and approvals system

The warming follows a speech to Congress last week by President Trump in which he said the US Food and Drug Administration's drug approval process was "too slow and burdensome," and where he promised to "slash the restraints, not just at FDA but across our government."

Trump's claims reinforce comments he made in January to pharmaceutical industry executives, where he said: "We're going to be cutting regulations at a level that nobody's ever seen before," - adding that up to 80 per cent of regulations could be slashed.

In a report today in the medical journal Nature, three experts say moves to deregulate the drug testing and approvals system will harm health everywhere, not just in the US, and that such moves will also stifle innovation and waste patients' and taxpayers' money.

One of the letter's authors, Professor John Rasko from the University of Sydney and Royal Prince Alfred Hospital, says Trump's argument is consistent with a history of neoliberal economic thinking that claims regulatory agencies are systematically biased towards excessive caution, and that the burden of testing a drug's efficacy before it comes to market outweighs the benefits.

"They argue that potentially harmful drugs can be identified quickly after they go on sale," says Professor Rasko, "and that the FDA runs an overly stringent system that withholds or delays safe and effective drugs from patients. These arguments are wrong, he says.

"The most extreme proponents of deregulation say the market should be the sole arbiter of utility: if a medicine sells well, then it must, therefore, be safe and effective.

"A more moderate version of this argument says reliable information on safety and efficacy can be collected after a drug is on sale, through observational studies or using biomarkers.

But Rasko and his co-authors, biologist, Douglas Sipp and health economist, Christopher McCabe, say relaxing the FDA's regulatory system will subject patients to drugs that may be toxic.

They point to the iconic example of thalidomide - a 1950s drug prescribed for nausea during pregnancy - that caused more than 10,000 birth defects worldwide.

"Even in the past dozen years, initially promising drugs, such as torcetrapib (for reducing cholesterol and heart-disease risk) and semagacestat (for improving cognition in people with Alzheimer's disease), were found to cause harm only after they had been tested in large, mandatory trials -- effects that were not seen in the smaller trials," say the authors.

Another problem with deregulatory arguments is the issue of safe but 'useless' drugs. "Untested drugs can be reasonably safe but provide no benefit," says Rasko, "and unregulated markets are hopeless at sifting out these 'futile drugs'. We only have to consider the multibillion-dollar industries in homeopathy and other pseudo-medicines to see this.

"These ineffective pills and potions are a massive waste of money and provide false hope to millions of people worldwide. What's more, for progressive diseases such as cancer or multiple sclerosis, if a doctor were to prescribe a drug that didn't work, she'd be giving a disease a free pass."

Meanwhile, the current regulatory system is working well, say Rasko and his colleagues. In January 2017, the FDA released a report identifying 22 products that were initially promising but disappointed in later-stage clinical trials: 14 for lack of efficacy, one for lack of safety, and seven for both reasons.

Rasko says it's important to consider how far we have come thanks to regulatory agencies like the FDA, and what's at stake right now as President Trump considers appointing a possibly radical new FDA commissioner.

"The 1938 US Food, Drug, and Cosmetic Act required only that drugs demonstrate safety," he says. "In 1962, new legislation demanded that marketed drugs also go through well-controlled studies to test for therapeutic benefit.

"More than 1,000 medical products were subsequently withdrawn after reviews found little or no evidence of efficacy. The free market that existed before 1962 revealed no connection between a drug's ability to turn a profit and its clinical usefulness." The same is likely to be true of any future deregulated market, the experts warn in Nature.

"Patients and doctors must have access to reliable information to make educated and ethical choices. "But reliable information costs money and no one will invest in producing good quality evidence if they can make the same profit on a drug or technology without it.

"Rigorous clinical studies are still the best way to learn whether a drug works, and regulation is essential to ensure that these studies are conducted."

http://bit.ly/2n3Hj2l

Neanderthals may have medicated with penicillin and painkillers

What a difference 1000 kilometres make. Neanderthals living in prehistoric Belgium enjoyed their meat – but the Neanderthals who lived in what is now northern Spain seem to have survived on an almost exclusively vegetarian diet.

By Colin Barras

This is according to new DNA analysis that also suggests sick Neanderthals could self-medicate with naturally occurring painkillers and antibiotics, and that they shared mouth microbiomes with humans – perhaps exchanged by kissing.

Neanderthals didn't clean their teeth particularly well – which is lucky for scientific investigators. Over time, plaque built up into a hard substance called dental calculus, which still clings to the ancient teeth even after tens of thousands of years.

Researchers have already identified tiny food fragments in ancient dental calculus to get an insight into the diets of prehistoric hominins. Now Laura Weyrich at the University of Adelaide, Australia, and her colleagues have shown that dental calculus also carries ancient DNA that can reveal both what Neanderthals ate and which bacteria lived in their mouths.

The team focused on three Neanderthals – two 48,000-year-old specimens from a site called El Sidrón in Spain and a 39,000-year-old specimen from a site called Spy in Belgium. The results suggested that the Spy Neanderthal often dined on woolly rhinoceros, sheep and mushrooms – but no plants. The El Sidrón Neanderthals ate more meagre fare: moss, bark and mushrooms – and, apparently, no meat.

Vegetarian cannibals?

"That was really a surprise to us," says Weyrich. "I think the assumption has always been that Neanderthals had diets based around heavy meat consumption. For us not to find any meat in the El Sidrón individuals was quite strange."

There is a certain irony to that finding, says Paola Villa at the University of Colorado Museum, Boulder, given that cut marks on Neanderthal bones from El Sidrón are often interpreted as evidence of cannibalism. "They may have had a diet of mostly plants but paradoxically they provided meat to the Neanderthals that killed them," she says.

Other researchers say it makes sense that Neanderthals would have adapted to eat a plant-rich diet if there was less opportunity to hunt animals in their local environment. "To imagine otherwise would be a bit simplistic," says Amanda Henry at Leiden University in the Netherlands.

But Henry cautions against taking the new DNA findings too literally. "The overwhelming component of the DNA is from the oral bacteria," she says – only about 0.3 per cent of it comes from the animals, plants and fungi that the Neanderthals ate. "To suggest they are recovering the entirety of the diet here is a bit premature."

Henry's earlier work has, in fact, suggested that the Spy Neanderthals ate roots and tubers as well as meat. The new DNA work didn't recover evidence of those plants, hinting that it provides an incomplete picture.

It's likely that the Spy diet did contain substantial quantities of plants or mushrooms, says Luca Fiorenza at Monash University in Clayton, Australia, because humans – and probably Neanderthals – can't cope with a diet exclusively based on animal protein (with little or no animal fat). "You begin to show signs of what is called rabbit starvation," he says. "It leads to diarrhoea, fever, and even death."

The study also adds to emerging evidence that mushrooms and other fungi were an important component of ancient human diets – they were eaten both at Spy and El Sidrón.

"Mushrooms have often been forgotten by archaeologists," says Hannah O'Regan at the University of Nottingham, UK – they are unlikely to be preserved intact at ancient sites.

Neanderthal "doctors"

One of the two El Sidrón individuals – a teenage boy – is known to have had a large dental abscess. The new DNA analysis shows he had a diarrhoea-causing gut parasite in his system, too. "It's likely he wasn't a very happy individual," says Weyrich.

Previous studies have suggested the teenager was eating plants with anti-inflammatory properties. The new study also finds DNA sequences of poplar plants, which are known to contain the natural pain killer salicylic acid (closely related to the active ingredient in aspirin). That may not have been the only medication or self-medication he did: there was DNA from *Penicillium* fungus – the source of penicillin – in his dental calculus.

However, it is difficult to say for sure whether Neanderthals actively consumed the fungus for its medicinal properties. *Penicillium* grows naturally on plant material as it moulds, so they could have eaten it by coincidence. "It's difficult to tell these specific moulds apart unless you have a hand lens," says O'Regan.

But Weyrich points out that the *Penicillium* was only in the dental calculus of the sick teenager – none was found in the calculus of the second El Sidrón individual, who is thought to have led a healthy life. "They might have had some knowledge that mouldy grains could help them when they were sick – we just don't really know," she says.

Evidence of foreplay?

There was one more surprise in the dental calculus of the sick teenager. Weyrich and her colleagues extracted enough DNA to reconstruct the genome of a species of oral bacteria called *Methanobrevibacter oralis*. At 48,000-years-old it is the oldest microbial genome ever sequenced, according to Weyrich and her colleagues.

Comparing the ancient genome with the *M. oralis* genome found in the mouths of living people, the researchers discovered that the Neanderthal and modern human versions both descended from a common ancestor that lived about 110,000 to 140,000 years ago.

This date roughly coincides with when we think humans and Neanderthals first interbred.

"It's really well understood that bacteria are swapped between people when they kiss," says Weyrich. It's possible that humans and Neanderthals kissed during sex 110,000 years ago, which could explain why the descendants of those interbreeding events – including both the El Sidrón Neanderthals and modern humans – ended up with similar forms of *M. oralis* bacteria in their mouths.

It's an interesting idea, says Adam Siepel at the Cold Spring Harbor Laboratory in New York, although he thinks there may be more mundane ways for oral bacteria to be shared. "Once humans and Neanderthals began to occupy the same geographical ranges, it is likely that they drank from the same streams, perhaps salvaged food from one another," he says. This may be how oral bacteria were swapped.

Weyrich agrees that there are several ways oral bacteria can be exchanged, but the possibility of kissing is still a thought-provoking one, particularly since it is unclear whether the ancient interbreeding events were forced or consensual. "It's a very different interaction from brash interbreeding," she says. "It's very intimate."

Journal reference: Nature, DOI: 10.1038/nature21674

http://bit.ly/2mF5ao4

Novel compound that engages 'second arm' of immune system reduces breast tumors and metastases

Findings suggest a way to bring the full repertoire of the immune system to bear on cancer in humans

BOSTON - For all the success of a new generation of immunotherapies for cancer, they often leave an entire branch of the immune system's disease-fighting forces untapped. Such therapies act on the adaptive immune system, the ranks of specialized cells that mount precision attacks on foreign and diseased cells. The other arm of the immune system, known as innate immunity, may not be merely idle during this battle, but may actually abet tumor growth.

In a new study in the journal Nature, Dana-Farber Cancer Institute scientists report that a compound able to reverse the allegiance of

innate immune system cells - turning them from tumor enablers into tumor opponents - caused breast tumors in mice to shrink and withdraw from distant metastases. When combined with chemotherapy or another immunotherapy, the new compound significantly extended the period of tumor remission.

The findings suggest a way to bring the full repertoire of the immune system to bear on cancer in humans, the authors said.

"Most current forms of cancer immunotherapy influence the behavior of T cells - white blood cells that are part of the adaptive immune system - by 'teaching' them to attack tumor cells or removing impediments to such an attack," said the study's lead author Jennifer Guerriero, PhD, of Dana-Farber. "This strategy has been effective against several types of cancer, but generally only a subset of patients benefit. We wanted to see if harnessing both arms of the immune system could produce superior results."

The targets of the new study were innate immune system cells known as tumor-associated macrophages (TAMs). They're often found deeply embedded within tumors, but although they're part of the immune system - the body's defense against disease - they frequently promote tumor growth. In doing so, they're responding to cues issued by the tumor itself.

The roles that macrophages play - whether protective or destructive - depend on signals from their environment. In wound healing, for example, macrophages marshal the elements of the immune system that clear away damaged tissue and restore the affected area. Tumor macrophages manage to hijack some of these supportive functions for their own purposes. Not without reason is cancer sometimes referred to as a wound that doesn't heal.

In previous research, the Dana-Farber scientists and their colleagues showed that a compound known as TMP195 could convert TAMs from aiding tumor growth to organizing an attack on it. A selective, first-in-class, class IIa HDAC inhibitor, TMP195 switches the macrophage response by altering gene activity within TAMs.

In this current study, TMP195 sharply reduced the rate of tumor growth in mice with breast tumors, researchers found. They next combined TMP195 with various chemotherapy regimens and with a form of immunotherapy known as T-cell checkpoint blockade. In both cases, the combinations produced longer-lasting remissions of breast cancer than TMP195 alone did.

"Once they've undergone conversion, macrophages act as the orchestrators of the immune system attack on the tumor," said Anthony Letai, MD, PhD, of Dana-Farber, co-senior author of the study with Michael A. Nolan, PhD, of GlaxoSmithKline. "Our findings demonstrate that class IIa HDAC inhibitors can be an effective way of harnessing the anti-tumor potential of macrophages in cancer therapy.

"The future of cancer treatment is likely to involve combinations of therapies that act on both the innate and adaptive arms of the immune system, as well as therapies, such as chemotherapy, radiation therapy, or targeted therapy, that act on cancer cells themselves," he continued. "The ability to engage the innate immune system is an exciting new front in cancer therapy."

Co-authors of the study are Alaba Sotayo, Holly E. Ponichtera, PhD, Jessica A. Castrillon, MS, Alexandra L. Pourzia, Sara Schad, Shawn F. Johnson, and Suzan Lazo of Dana-Farber; Ruben D. Carrasco, MD, PhD, of Brigham and Women's Hospital; Roderick T. Bronson, DVM, of Harvard Medical School; and Scott P. Davis, MS, and Mercedes Lobera, PhD, of GlaxoSmithKline.

This work was supported by the National Institutes of Health (grants F32CA180733 and R01CA205967); the Friends of Dana-Farber; Dancing for a Cure; and a sponsored research agreement from GlaxoSmithKline.

http://bit.ly/2meLSSy

Diabetes drug shows promise for safely treating, detecting Alzheimer's disease

First time tested in humans

Boston - As the number of patients with Alzheimer's disease (AD) rapidly increases, new treatments as well as blood tests that are simple and can be easily performed in a doctor's office to diagnose are urgently needed.

A new study has found treatment with the diabetes drug amylin (or pramlintide) safely improves learning and memory function in AD patients and reduces the AD pathology in their brains. The findings, which appear in the Journal Translational Research and Clinical Interventions, also may lead to the development of a blood test for AD. Currently, lumbar punctures to detect biomarkers in cerebrospinal fluid and positron emission tomography imaging scans are used to diagnose AD. Unfortunately many patients are fearful of these procedures and the high cost is prohibitive.

"A single injection of pramlintide into our patients was well tolerated and reduced the amyloid burden as well as lowered the concentrations of amyloid-β peptides, a major component of AD in the brain," explained corresponding author Wendy Qiu, MD, PhD, associate professor of psychiatry and pharmacology and experimental therapeutics at Boston University School of Medicine.

"Our study suggests a potential role for the creation of a blood test that relies on pramlintide, which could cross the blood-brain barrier and help to translocate the biomarkers related to AD pathology including amyloid-β peptides and neuroinflammation, from the brain into the bloodstream where they can be detected," added Qiu.

Funding for this study was provided by grants from the Alzheimer's Disease Association (IIRG-13-284238), NIA (R21 AG045757A1), and Ignition Award (to W.Q.Q), and from Boston University Alzheimer's Disease Center pilot grant (to H.Z.).

http://bit.ly/2mWcuw9

Oral delivery system could make vaccination needle-free

Patients could one day self-administer vaccines using a needleless, pill-sized technology that jet-releases a stream of vaccine inside the mouth, according to a proof-of-concept study conducted at UC Berkeley.

The study did not test vaccine delivery in people, but demonstrated that the technology, called MucoJet, is capable of delivering vaccine-sized molecules to immune cells in the mouths of animals. The technology is a step toward improved oral vaccine delivery, which holds the promise of building immunity in the mouth's buccal region of cells, where many infections enter the body. When patients hold the MucoJet against the inside of their cheek, the device releases a jet stream that directly targets the buccal region. This region is rich in immune cells but underutilized in immunology because of the challenge of efficiently penetrating the thick mucosal layer in this part of the oral cavity with existing technologies, such as the oral spray often used for influenza vaccination.

In laboratory and animal experiments, the research team showed that the MucoJet can deliver a high-pressure stream of liquid and immune system-triggering molecules that penetrate the mucosal layer to stimulate an immune response in the buccal region. The jet is pressurized, but not uncomfortably so, and would remove the sting of needles.

"The jet is similar in pressure to a water pick that dentists use," said Kiana Aran, who developed the technology while a postdoctoral scholar at Berkeley in the labs of Dorian Liepmann, a professor of mechanical and bioengineering, and Niren Murthy, a professor of bioengineering. Aran is now an assistant professor at the Keck Graduate Institute of Claremont University.

The portable technology, designed to be self-administered, stores vaccines in powder form and could one day enable vaccine delivery to remote locations, but years of further study are needed before the device would be commercially available.

The study will be published March 8 in the journal Science Translational Medicine and is available for download on EurekAlert!.

MucoJet is a 15-by-7-milimeter cylindrical, two-compartment plastic device. The solid components were 3D-printed from an inexpensive biocompatible and water-resistant plastic resin. The exterior compartment holds 250 mililiters of water. The interior compartment is composed of two reservoirs separated by a porous plastic membrane and a movable piston. One interior compartment is a vaccine reservoir, containing a 100-ml chamber of vaccine solution with a piston at one end and a sealed 200-micrometer (m) diameter delivery nozzle at the

other end. The other interior compartment is the propellant reservoir, which contains a dry chemical propellant (citric acid and sodium bicarbonate) and is separated from the vaccine reservoir at one end by the built-in porous membrane and movable piston and is sealed at the other end from the exterior compartment with a dissolvable membrane

To administer the MucoJet, a patient clicks together the interior and exterior compartments. The membrane dissolves, water contacts the chemical propellant and the ensuing chemical reaction generates carbon dioxide gas. The gas increases the pressure in the propellant chamber, causing the piston to move. The free-moving piston ensures uniform movement of the ejected drug and blocks the exit of fizz from the carbon dioxide through the nozzle. When the pressure in the propellant chamber is high enough, the force on the piston breaks the nozzle seal of the vaccine reservoir. The vaccine solution is then ejected from the MucoJet nozzle, penetrates the mucosal layer of the buccal tissue, and delivers the vaccine to underlying vaccine targets, called antigen-presenting cells.

To test the MucoJet's delivery system, researchers designed a laboratory experiment in plastic dishes using mucosal layers and buccal tissues from pigs. They tested the MucoJet's ability to deliver ovalbumin, an immune stimulating protein, across the mucosal layer. The experiments showed an eightfold increase in the delivery of ovalbumin over the course of three hours compared to a control experiment of administering ovalbumin with a dropper (similar to how oral vaccines, such as for the flu, are administered today).

The researchers then tested different pressures of the vaccine jet and found that increasing the MucoJet output pressure increased the ovalbumin delivery to the tissue, indicating that the delivery efficiency improves with increased pressure.

"The pressure is very focused, the diameter of the jet is very small, so that's how it penetrates the mucosal layer," Aran said.

The researchers then tested the MucoJet's ability to deliver ovalbumin to buccal tissue in rabbits. The MucoJet delivery resulted in a sevenfold increase in the delivery of ovalbumin compared to control experiments with droppers. Animals treated with ovalbumin by MucoJet had key antibodies in their blood that were three orders of magnitude higher than in the blood from rabbits treated with ovalbumin by a dropper.

The study did not compare the MucoJet to vaccine delivery with a needle, but data suggests that the MucoJet can trigger an immune response that is as good or better than delivery with a needle, especially for mucosal pathogens.

The next step in MucoJet's development is to test the delivery of a real vaccine in larger animals. The researchers hope the MucoJet can be available in five to 10 years. They also hope to engineer a version of the MucoJet that can be swallowed and then release vaccines internally.

The researchers are considering other shapes, sizes and designs to simplify vaccine administration procedures and increase patient compliance, especially for children. For example, the MucoJet could be fabricated into a lollipop.

"Imagine if we could put the MucoJet in a lollipop and have kids hold it in their cheek," Aran said. "They wouldn't have to go to a clinic to get a vaccine."

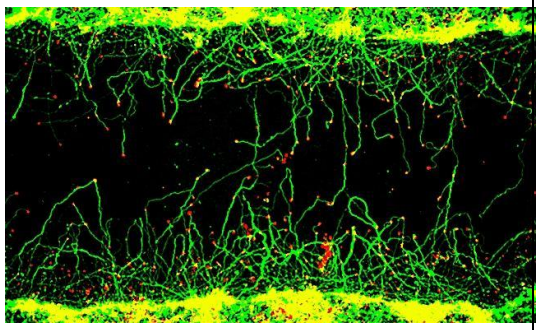
http://bit.ly/2lPVMyF

Molecule shown to repair damaged axons

Discovery could be key to treating brain and spinal cord injury

A foray into plant biology led one researcher to discover that a natural molecule can repair axons, the thread-like projections that carry electrical signals between cells. Axonal damage is the major culprit underlying disability in conditions such as spinal cord injury and stroke.

Andrew Kaplan, a PhD candidate at the Montreal Neurological Institute and Hospital of McGill University, was looking for a pharmacological approach to axon regeneration, with a focus on 14-3-3, a family of proteins with neuroprotective functions that have been under investigation in the laboratory of Dr. Alyson Fournier, professor of neurology and neurosurgery and senior author on the study.



Treatment with fusicoccin-A induces the regeneration of damaged axons towards the center of the injury. The axons are stained in green and the tips of the growing axons, called growth cones, are stained in red. **The Neuro**

During his search, he found research describing how plants respond to a specific type of fungal infection. When plants are exposed to fusicoccin-A, a small molecule produced by a certain strain of fungus, the leaves of the plant wilt but the roots grow longer. Fusicoccin-A affects 14-3-3 activity by stabilizing its interactions with other proteins.

"While 14-3-3 is the common denominator in this phenomenon, the identity of the other proteins involved and the resulting biological activities differ between plants and animals," says Kaplan.

Kaplan theorized that fusicoccin-A could be an effective way of harnessing 14-3-3 to repair axons. To test this theory, he and his fellow researchers treated mechanically damaged neurons in culture with the molecule and observed the results.

"When I looked under the microscope the following day the axons were growing like weeds, an exciting result that led us to determine that fusicoccin-A can stimulate axon repair in the injured nervous system," says Kaplan.

Besides brain and spinal cord injury, axonal damage is a factor in many other disorders and diseases, including multiple sclerosis and neurodegenerative conditions. The team's discovery means that fusicoccin-A and similar molecules could be the starting point to develop drugs that treat axonal damage. Kaplan says future work should focus on better understanding the mechanisms by which fusicoccin-A improves axon repair.

In particular, a protein called GCN1 holds promise. The team found that the physical bonding of 14-3-3 and GCN1 is an important factor in fusicoccin-A-induced axon growth. Now scientists can examine the function of GCN1 in the nervous system and test whether the bonding with 14-3-3 could serve as a drug target for more tailored therapies.

"We have identified a novel strategy to promote axon regeneration with a family of small molecules that may be excellent candidates for future drug development," says Fournier. "This is an exciting advance because the field has struggled to find treatments and identify targets for drugs that stimulate axon repair."

Their paper, published in the journal Neuron on March 8, 2017, was funded by the Canadian Institutes for Health Research.

http://nyti.ms/2myr4aw

Our Universe's Very Dusty Early, Early Beginnings

To the list of cosmic superlatives must now be added a new item: the oldest dust.

By DENNIS OVERBYE MARCH 8, 2017

It's not behind your refrigerator or underneath the bed. It's in a galaxy with only a number for a name in a constellation called Sculptor, and so far away that its distance barely has any meaning. The light from A2744_YD4, as it is known, has been on its way to us for 13.2 billion years, since the universe was only 600 million years old.

Where the galaxy is "now" is only a mathematical extrapolation — about 30 billion light-years from here, according to the standard cosmological math. An international team led by Nicolas Laporte of University College London, using the Atacama Large Millimeter/submillimeter Array, or ALMA, a radio telescope in Chile, was able to see this galaxy only because its light had been amplified by the gravity of a massive cluster of galaxies lying right in front of it.

Interspersed with radio emissions from stars, the astronomers were surprised to find the characteristic heat emanations from some six million solar masses of dust. The dust consisted of tiny grains of carbon, silicon and aluminum — an austere and unevolved version of the same stuff under your fingernails, and in the dust bunnies under your bed. The big news is that it existed in such quantities only 600 million years after the Big Bang.

The primordial universe, as it emerged from the Big Bang, consisted almost entirely of hydrogen and helium, the simplest and lightest elements, according to astronomers, with only a slight trace of lithium. The heavier elements, needed for planets and us among other things, were manufactured in stars, which then blew up. As the story goes, the exploding stars scattered their ashes across space where they could be incorporated into new stars and repeat the cycle, gradually enriching the chemistry of the cosmos.

The new observations show that this relentless progression from dust to better-and-better dust had already been jump-started by the time the universe was just 600 million years old. The first stars had already been born and died in less than 200 million years in a wave of supernova explosions, according to Richard Ellis, of the European Southern Observatory and the University College London, and one of the leaders of a paper published in Astrophysical Journal Letters.

At the time, in the baby boom years of the universe, the young galaxy was feeling its oats, pumping out 20 new stars a year. By comparison the Milky Way, our own galaxy, today births only one star a year.

The new results augur a bright future for the ALMA telescope, a $1.5 billion array of antennas tuned to record the heat emanations of stars and dust, and NASA's coming James Webb Space Telescope, designed to investigate the early days of the universe. "More observations should pinpoint the period when galaxies began to be first polluted by heavy elements," Dr. Ellis said in an email from London.

"Until now, studies of early galaxies have largely been based on measures of colors and masses," he said. "Now, finally, we are using chemistry."

http://wb.md/2lPZtEI

Hypercorrect Is a Variant of Wrong

Who remembers having a patient who was "euboxic"? That relic of medical terminology traces to the early days of computerized applications of medicine, so extraordinarily expanded today.

Richard M. Plotzker, MD

Back then, patients would have serum drawn, the autoanalyzer would run 15 or so tests, and a printer would generate a report. Each test would have a vertical line with a black dot indicating the result. A segmental line would connect each dot.

The normal range for each value would be depicted by a gray rectangle. If all 15 values fell in the gray boxes, that patient would be deemed euboxic.

Richard M. Plotzker, MD

At 95% confidence intervals for each test, the likelihood of a normal person falling into that esteemed category of normality for all 15 tests would be 0.95 X 15 = 0.46, meaning less than half of all seemingly normal subjects had all 15 tests in the normal range.

As more tests were added to the panel—eventually reaching 27 before the Centers for Medicare & Medicaid Services wisely replaced them with the more rational basic metabolic panel and comprehensive metabolic panel—the prospects for being euboxic became vanishingly small. Yet, each lab abnormality needed some type of assessment if not treatment.

Hyperparathyroidism went from being a disease of bone and kidneys to a disorder of the autoanalyzer. Many other endocrine disorders—from minimal thyroid-stimulating hormone variants to incidental CT findings—similarly pose the dilemma of how much medical care to

offer for these minor abnormalities, separating the trivial from the significant.

Although we can't avoid the unexpected lab or anatomic abnormality, perhaps we are making too much of an effort to seek them out by ordering tests that will take us and our patients down the road of excessive unproductive care.

Pointing Fingers

While rounding with my resident on elective last month, we saw a fellow with new transaminase elevations that had not been retested for a few days. We ordered the hepatic function panel for comparison but noted that basic metabolic panel, phosphorus, and magnesium levels were appearing on his chart every day—to the neglect of what really needed to be measured instead.

I asked the resident why this was, and he told me that the attending hospitalists insisted on it. We rounded a little more and found a few more patients who had repetitively normal or at least not dangerous magnesium and phosphorus levels.

As I encountered each hospitalist randomly over the next few days, I asked why they insisted on repetitive testing of this type on so many patients. They each denied requiring residents to order these.

Finally, the plug got pulled one day when one of our consults got riders of intravenous potassium, phosphate, and magnesium for values that were only 0.1 mg/dL below the lab norms.

Widespread Problem?

Although excessive care and its potential misadventures can be a little like Justice Stewart's definition of pornography (ie, you don't quite know what it is, but you know it when you see it), two recent contributions to the medical literature tried to analyze the downside of doing testing that would have been better not being requested. These publications attempted to view the consequences of ordering testing when the treating physician's current information was already sufficient.

The first comes from the British Medical Journal.[1] It is an American study from the Mayo Clinic looking at about 31,000 patients with stable diabetes, defined as two consecutive glycated hemoglobin (A1c) values below 7% taken 6 months apart and no other confounding illness. The accepted standard of care would be two measurements 6 months apart.

Allowing for the vagaries of people seeing multiple doctors, the study authors identified 6% of patients getting five or more tests per year and 55% getting more than two consecutive tests in less than a 3-month interval. These were stable patients, so quite a lot of them were on no medication at the beginning and end of the observation period, yet 5% of the untreated people also received excessive testing.

Although some patients just drifted along perfectly fine on whichever medication they were on regardless of how many A1c measurements took place, as a composite, more testing resulted in more changes in treatment from one class of drugs to another. Because of the means of accessing the database, the investigators could not tell what the tolerance was to the agents that were changed.

Replacing one poorly tolerated drug with another and retesting seems reasonable. However, there was a clear correlation between the number of tests and the number of drug changes, even though all A1c values were stable.

Of course, the people who did the most testing were my fellow endocrinologists.

Old Habits Die Hard

The second poke at me and my colleagues—and probably most medical school graduates—comes from the US Preventive Services Task Force, who recently updated their recommendations[2] on screening for thyroid cancer, which were first issued in 1996. Both then and now, we are advised against routine screening unless a person has high-risk factors such as a radiated gland or family history of thyroid cancer. Both palpation and ultrasound are potential screening modalities. Palpation tends to be not very sensitive and

correlates with experience as an examiner. Ultrasound finds a lot of what you wish you hadn't found.

Almost 100% of patients who come to my exam room for any reason will have their thyroid area examined and a few comments made about it in the electronic health record, even though I am not looking for anything in particular.

From my first physical diagnosis course as a second-year medical student until my current status as senior physician, I have seen the more experienced docs belittling the less experienced docs for not being sufficiently thorough in examining patients. My professors would term me lazy if I did not examine the thyroid. My fellowship mentors would be a little uppity if their exam found something that my exam did not.

As residents come for elective, I have them examine thyroid glands and describe what they feel, shining a light on it from their cell phones to describe what they see. But it's all for naught, as the experts suggest that patients might be better off without our experienced fingers looking for 1- to 2-cm spheres of abnormality that might lead to surgical complications for a disorder that never would have harmed them had benign neglect prevailed.

It's just hard not to examine that inviting anterior neck when the patient is sitting on the exam table at just the right height.

So, we return to that final aphorism of the Fat Man, hero of Samuel Shem's novel, The House of God: "The delivery of good medical care is to do as much nothing as possible."

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http://bit.ly/2lQj73i

The intestine has a reservoir of stem cells that are resistant to chemotherapy

These comprise a small group of passive stem cells -quiescent- that are activated when needed and have the capacity to produce any kind of intestinal cell. Quiescent cells are relevant for tissue regeneration and for participation in tumor development

The intestine has a high rate of cellular regeneration due to the wear and tear originated by its function degrading and absorbing nutrients and eliminating waste. The entire cell wall is renewed once a week approximately. This explains why the intestine holds a large number of stem cells in constant division, thereby producing new cell populations of the various types present in this organ.

Researchers at the Institute for Research in Biomedicine (IRB Barcelona) headed by ICREA investigator Eduard Batlle, head of the Colorectal Cancer Laboratory, have discovered a new group of intestinal stem cells with very different characteristics to those of the abundant and active stem cells already known in this organ. Performed in collaboration with the Centro Nacional de Análisis Genómico (CNAG-CRG), the study has been published in Cell Stem Cell. These new group of stem cells are quiescent, that is to say, they do not proliferate and are apparently dormant.

The researchers describe them as a reservoir of stem cells--it is estimated that there is one quiescent cell for every 10 active intestinal stem cells. In healthy conditions, these cells have no apparent relevant function. However, they are important in situations of stress, , for example, after chemotherapy, in inflammatory processes, and in tissue infections--all conditions in which the population of "normal/active" stem cells is depleted. These quiescent cells would serve to regenerate the organ by giving rise to the various types of cells present in the intestine, renewing the population of "normal/active" stem cells, and restoring balance to the tissue.

Eduard Batlle explains that the discovery of quiescent stem cells in the intestine reveals that stem cell biology is more complex that previously appreciated and that it does not follow ahierarchical model of cell organisation. "In intestinal cell hierarchy, there are no cells above others, so the two populations are in a continual balance to ensure the proper function of the organ".

Most drugs against cancer have a secondary effect on the cells that are dividing in our tissues. "Because quiescent stem cells divide infrequently, they are resistant to many types of chemotherapy and they regenerate the tissue that this treatment has damaged," explains Eduard Batlle, head of one of the labs of international prestige in research into intestinal stem cells and their involvement in colorectal cancer.

Quiescent cells are present in many kinds of tissue. However, in spite of their relevance in tissue regeneration, increasing evidence points to their involvement in tumour development. "It is difficult to study these cells, mainly because they are scarce and there are technical limitations with respect to monitoring, straining and distinguishing them from the others," explains Francisco Barriga, first author of the study and current postdoctoral fellow at the Memorial Sloan Kettering Cancer Center in New York.

Using advanced techniques, such as genetic tracing of cell lineages and transcriptomic analysis of individual cells, performed by CNAG-CRG and the Bioinformatics and Biostatistics Unit at IRB Barcelona, the group has identified the distinct genetic programme used by quiescent stem cells with respect to normal intestinal ones. This work has been done over six years.

The researchers have labelled this cell population with a specific marker, the Mex3a protein, which has allowed them to track it over time. "We intend to continue studying quiescent stem cells in health and disease and to discover the function of the genes that distinguish them in the colon and in other organs," says Batlle.

Francisco M. Barriga, Elisa Montagni, Miyeko Mana, Maria Mendez-Lago, Xavier Hernando-Momblona , Marta Sevillano, Amy Guillaumet-Adkins,Gustavo Rodriguez-Esteban, Simon J. A. Buczacki, Marta Gut, Holger Heyn, Douglas J. Winton, Omer H. Yilmaz, Camille Stephan-Otto Attolini, Ivo Gut, and Eduard Batlle
Mex3a marks a slowly dividing subpopulation of Lgr5+ intestinal stem cells
Cell Stem Cell (2017). doi: 10.1016/j.stem.2017.02.007

http://bit.ly/2niqoGp

Could fast radio bursts be powering alien probes?

Mysterious phenomena called fast radio bursts could be evidence of advanced alien technology

The search for extraterrestrial intelligence has looked for many different signs of alien life, from radio broadcasts to laser flashes, without success. However, newly published research suggests that mysterious phenomena called fast radio bursts could be evidence of advanced alien technology. Specifically, these bursts might be leakage from planet-sized transmitters powering interstellar probes in distant galaxies.

"Fast radio bursts are exceedingly bright given their short duration and origin at great distances, and we haven't identified a possible natural source with any confidence," said theorist Avi Loeb of the Harvard-Smithsonian Center for Astrophysics. "An artificial origin is worth contemplating and checking."

As the name implies, fast radio bursts are millisecond-long flashes of radio emission. First discovered in 2007, fewer than two dozen have been detected by gigantic radio telescopes like the Parkes Observatory in Australia or the Arecibo Observatory in Puerto Rico. They are inferred to originate from distant galaxies, billions of light-years away. Loeb and his co-author Manasvi Lingam (Harvard University) examined the feasibility of creating a radio transmitter strong enough for it to be detectable across such immense distances. They found that, if the transmitter were solar powered, the sunlight falling on an area of a planet twice the size of the Earth would be enough to generate the needed energy. Such a vast construction project is well beyond our technology, but within the realm of possibility according to the laws of physics.

Lingam and Loeb also considered whether such a transmitter would be viable from an engineering perspective, or whether the tremendous energies involved would melt any underlying structure. Again, they found that a water-cooled device twice the size of Earth could withstand the heat.

They then asked, why build such an instrument in the first place? They argue that the most plausible use of such power is driving interstellar light sails. The amount of power involved would be sufficient to push a payload of a million tons, or about 20 times the largest cruise ships on Earth.

"That's big enough to carry living passengers across interstellar or even intergalactic distances," added Lingam.

To power a light sail, the transmitter would need to focus a beam on it continuously. Observers on Earth would see a brief flash because the sail and its host planet, star and galaxy are all moving relative to us. As a result, the beam sweeps across the sky and only points in our direction for a moment. Repeated appearances of the beam, which were observed but cannot be explained by cataclysmic astrophysical events, might provide important clues about its artificial origin.

Loeb admits that this work is speculative. When asked whether he really believes that any fast radio bursts are due to aliens, he replied, "Science isn't a matter of belief, it's a matter of evidence. Deciding what's likely ahead of time limits the possibilities. It's worth putting ideas out there and letting the data be the judge."

The paper reporting this work has been accepted for publication in the Astrophysical Journal Letters and is available online.

http://bit.ly/2mhfuj1

Final biomedical trial on captive chimpanzees is first oral Ebola vaccine for saving wild apes

The results from the final biomedical research trial on captive chimpanzees for the foreseeable future have been published today in the journal Scientific Reports.

The trial was of a vaccination for Ebola: the first orally administered vaccine for any disease developed specifically for the purpose of conserving wild apes.

In addition to poaching and forest loss, diseases such as Ebola and anthrax have devastated wild ape populations. Ebola alone is estimated to have killed one third of the world's wild gorillas over the last three decades.

Now, new findings have shown an effective oral vaccine for Ebola in chimpanzees, and that the captive animals involved in the trial exhibited very few signs of stress as a result. Researchers say the work demonstrates a model that could be harnessed for other diseases and ape species in the wild.

However, after decades using chimpanzees to test vaccines destined for humans, changes in the law have seen enforced retirement of captive populations and the closing of chimpanzee research facilities in the US -- the last developed country where biomedical testing on chimpanzees was legal.

In what researchers describe as a "horrible irony", they say these reforms -- a victory for long-standing campaigns by animal welfare groups -- will ultimately prove detrimental to chimpanzees and gorillas in the wild, as any vaccination for wild animals must be tested in captivity first to ensure its safety.

Consequently, the promising new vaccine model may never progress to the point where it can be used to inoculate endangered wild apes, say the research team from the universities of Cambridge, UK, and Thomas Jefferson and Louisiana, US.

"In 2014 the world was gripped by fears of an Ebola virus pandemic. Yet few people realise that Ebola has already inflicted pandemic scale mortality on our closest relatives," says lead researcher Dr Peter Walsh from the University of Cambridge.

"African apes are also threatened by naturally occurring pathogens like anthrax, and the increasing overspill of human pathogens such as

measles. A glimmer of hope lies in the fact that many of the disease threats are now vaccine preventable.

"We have developed a very promising tool for inoculating ape species against the myriad deadly diseases they face in the wild, but continued progress relies on access to a small number of captive animals.

"This may be the final vaccine trial on captive chimpanzees: a serious setback for efforts to protect our closest relatives from the pathogens that push them ever closer to extinction in the wild."

Previous attempts to vaccinate wild apes have resorted to administering individual animals with hypodermic darts - a laborious task feasible for only a small number of apes habituated to human approach. By contrast, oral vaccines encased in appealingly edible baits could be distributed across wild ape territories to inoculate large numbers over longer periods.

Such an approach has already proved successful in other species: almost eliminating fox rabies (and the consequent need to cull foxes) across continental Europe.

The latest study was carried out with ten chimpanzees in one of the last remaining chimpanzee research facilities in the US in New Iberia, Louisiana. Six received the oral vaccine, while four were injected as a control group.

All the animals displayed a robust immunity without side effects after 28 days - when the trial was terminated due to new Endangered Species Act regulations banning biomedical research on chimpanzees.

Throughout the trial, scientists closely monitored animal behaviour and physiology for signs of severe stress. Other than very minor weight loss (2% of body mass), they say that signs of trauma were "entirely absent".

"Some pressure groups argue that all research on captive chimpanzees is tantamount to torture, not just because of procedures but also due to confinement," says Walsh.

"Enclosures and animal care are now of a very high standard, with chimpanzees housed in large social spaces. The modest traces of stress we detected during our trial were akin to the values observed in college students anticipating exams."

Captive chimpanzee trials are technically still legal in the US in instances that benefit the species. However, Walsh says that the limited funds available for conservation research makes it unviable for biomedical facilities to retain populations, while zoos and sanctuaries are either "ideologically opposed" or unwilling to risk any public backlash from testing.

Further work to enhance the vaccine, such as ensuring effectiveness after exposure to high tropical forest temperatures, may now never get done due to the closure of captive chimpanzee facilities.

"In an ideal world, there would be no need for captive chimpanzees," says Walsh. "But this is not an ideal world. It is a world where diseases such as Ebola, along with rampant commercial poaching and habitat loss, are major contributors to rapidly declining wild ape populations.

"Oral vaccines offer a real opportunity to slow this decline. The major ethical debt we owe is not to a few captive animals, but to the survival of an entire species we are destroying in the wild: our closest relatives."

http://bit.ly/2mhlKXt

Hair loss and prostate drug linked to persistent erectile dysfunction in men

Longer exposure to finasteride or dutasteride associated with higher risk of persistent erectile dysfunction

CHICAGO --- Men with longer exposure to the drugs finasteride and dutasteride had a higher risk of getting persistent erectile dysfunction than men with less exposure, reports a new Northwestern Medicine study. The persistent erectile dysfunction continued despite stopping these drugs, in some cases for months or years.

Among young men, prolonged exposure to the drugs posed a greater risk of persistent erectile dysfunction (PED) than all other assessed risk factors. This means there is a stronger relationship between taking

these drugs and having PED than having diabetes, hypertension or smoking, which are other risk factors.

Erectile dysfunction is difficulty achieving and maintaining a sufficient erection to have sex. Persistent erectile dysfunction continued despite stopping the drug and continued despite taking sildenafil (Viagra) or similar drug.

Prior to the new study, there was no strong evidence that finasteride and dutasteride cause sexual problems that continue after men stop taking them. There also was no strong evidence that taking these drugs for a longer time increases the chance of experiencing sexual problems.

"Our study shows men who take finasteride or dutasteride can get persistent erectile dysfunction, in which they will not be able to have normal erections for months or years after stopping finasteride or dutasteride," said lead study author Dr. Steven Belknap, a research assistant professor of dermatology at Northwestern University Feinberg School of Medicine.

Finasteride and dutasteride are drugs that are male hormone blockers. These drugs block the conversion of testosterone to its more active form, 5 alpha dihydrotestosterone. Finasteride is prescribed to some men with prostate enlargement or baldness. Dutasteride is prescribed to some men with prostate enlargement. Propecia and Proscar are brand names for finasteride. Avodart is a brand name for dutasteride. Jalyn is a combination drug containing dutasteride and tamsulosin.

The new findings of an association between debilitating sexual dysfunction and exposure to finasteride or dutasteride should be of particular interest to prescribers and patients considering medical management of androgenic alopecia (hair loss) or symptomatic treatment of enlarged prostate, Belknap said.

The study will be published March 9 in the journal PeerJ. Among the men studied, 167 of 11,909 (1.4 percent) developed persistent erectile dysfunction that continued for a median of 1,348 days after stopping the drugs. Young men under 42 years old who had more than 205 days of finasteride or dutasteride exposure had 4.9-fold higher risk of persistent erectile dysfunction than men with shorter exposure.

The study evaluated data from 11,909 men for PED. Eligible subjects for evaluation for new PED were men 16 to 89 years old with at least one clinical encounter and one diagnosis from January 1992 to September 2013. The study was made possible by the Northwestern Medicine Electronic Data Warehouse, an electronic medical record data repository for patients of Northwestern Medicine.

The findings follow a 2015 JAMA Dermatology study by Belknap showing published reports of clinical trials provide insufficient information to adequately establish the safety of finasteride for treatment of hair loss in men. This was the first meta-analysis of the quality of safety reporting in clinical trials of finasteride for treatment of male hair loss.

The study was supported by grants 5R01CA102713-04 and 1R01 CA125077-01A1 from the National Cancer Institute and grants UL1TR001422, UL1TR000150 and UL1RR025741 from the National Center for Advancing Translational Sciences, all of the National Institutes of Health. The Post-Finasteride Syndrome Foundation also supported the study.

http://bit.ly/2lRLEFH

Medical Mystery: Why Are Some Obese People 'Metabolically Healthy'?

A lucky few are obese, and yet don't have any typical risk factors for heart disease or diabetes

By Rachael Rettner, Senior Writer | March 9, 2017 05:56pm ET

Obesity often brings with it a host of health problems, such as high blood pressure, diabetes and risky cholesterol levels. But a lucky few appear to buck the trend: They are obese, and yet don't have any of these typical risk factors for heart disease or diabetes, a new study finds.

Researchers analyzed information from about 1.3 million U.S. adults who were either overweight or obese. None had previously been diagnosed with diabetes. The researchers looked to see whether these participants had any of four common risk factors for heart disease and

diabetes: High blood pressure, high levels of fat in the blood, low levels of "good" cholesterol or elevated blood sugar levels.

Among those who were obese, 10 percent did not have any of these four risk factors. It's not clear why some people with obesity are able to avoid these problems. In the past, researchers have dubbed this group the "metabolically healthy obese."

However, people who fall into this group may still not be totally healthy, said study researcher Gregory Nichols, a senior investigator at Kaiser Permanente Center for Health Research in Portland. Obesity also increases the risk of other conditions, such as cancer, joint problems and kidney disease, he said.

"They might be metabolically healthy, but that does not necessarily mean they are healthy overall," Nichols told Live Science. What's more, although these participants were free of metabolic risk factors at the time of the study, they could soon develop them in the coming years, he said. Some previous studies have found that even "metabolically healthy" obese people are at higher risk of developing type 2 diabetes, compared with people of normal weight.

Thus, people who are obese should still aim to lose weight, even if they appear otherwise healthy, Nichols said. "Weight loss could improve other types of health [problems], and might reduce the likelihood of developing cardiometabolic risk factors," he said.

For the study, the researchers analyzed electronic health care records from members of four health care systems that together serve 12 million people in 11 U.S. states and Washington, D.C. They defined being overweight as having a body mass index (BMI) of 25.0 to 29.9. Obesity was defined as having a BMI of 30 or more, while morbid obesity was a BMI of 40 or more. They found that 18.6 percent of the people who were overweight did not have any of the four metabolic risk factors, and 9.6 percent of those who were obese did not have any of the four. Looking at only those who were morbidly obese, they found that 5.8 percent did not have any of the four risk factors.

Being "metabolically" healthy was more common among those who were younger — about 30 percent of all adults ages 20 to 34 in the study did not have any of the four metabolic risk factors, compared with just 6.3 percent of those ages 65 to 79. Several factors could explain why some overweight people and some obese people remain metabolically healthy. "Diet and exercise almost certainly play a role," Nichols said. However, the new study did not assess these factors.

In addition, the distribution of a person's fat can also affect their risk of cardiovascular disease, with fat stores in the belly area (visceral fat) posing a greater risk to health than fat found just beneath the skin (subcutaneous fat) in other parts of the body. Some previous studies have found that obese people who are metabolically healthy have less visceral fat than obese people who aren't metabolically healthy. However, a person's BMI measurement, used in this new study, cannot distinguish between visceral fat and subcutaneous fat.

Ultimately, future studies are needed to follow metabolically healthy obese people forward in time, to see if they remain metabolically healthy over a long period, or even a lifetime, Nichols said. Such studies could determine whether metabolically healthy obesity "is even a real thing, or merely a matter of timing," Nichols said.

In addition, studies should look at the order in which people develop metabolic risk factors, and whether this order affects their risk of developing subsequent heart disease and diabetes, he said.

The study was published March 9 in the journal Preventing Chronic Disease.

http://bit.ly/2ne9trI

Mayo discovers high-intensity aerobic training can reverse aging processes in adults

Everyone knows that exercise is good for you, but what type of training helps most, especially when you're older -- say over 65?

ROCHESTER, Minn. - A Mayo Clinic study says it's high-intensity aerobic exercise, which can reverse some cellular aspects of aging. The findings appear in Cell Metabolism.

Mayo researchers compared high-intensity interval training, resistance training and combined training. All training types improved lean body mass and insulin sensitivity, but only high-intensity and combined training improved aerobic capacity and mitochondrial function for skeletal muscle. Decline in mitochondrial content and function are common in older adults.

High-intensity intervals also improved muscle protein content that not only enhanced energetic functions, but also caused muscle enlargement, especially in older adults. The researchers emphasized an important finding: Exercise training significantly enhanced the cellular machinery responsible for making new proteins. That contributes to protein synthesis, thus reversing a major adverse effect of aging. However, adding resistance training is important to achieve significant muscle strength.

"We encourage everyone to exercise regularly, but the take-home message for aging adults that supervised high-intensity training is probably best, because, both metabolically and at the molecular level, it confers the most benefits," says K. Sreekumaran Nair, M.D., Ph.D., a Mayo Clinic endocrinologist and senior researcher on the study. He says the high-intensity training reversed some manifestations of aging in the body's protein function. He cautioned that increasing muscle strength requires resistance training a couple of days a week.

The study's goal was to find evidence that will help develop targeted therapies and exercise recommendations for individuals at various ages. Researchers tracked metabolic and molecular changes in a group of young and older adults over 12 weeks, gathering data 72 hours after individuals in randomized groups completed each type of exercise. General findings showed:

Cardio respiratory health, muscle mass and insulin sensitivity improved with all training.

Mitochondrial cellular function declined with age but improved with training.

Increase in muscle strength occurred only modestly with high-intensity interval training but occurred with resistance training alone or when added to the aerobic training.

Exercise improves skeletal muscle gene expression independent of age.

Exercise substantially enhanced the ribosomal proteins responsible for synthesizing new proteins, which is mainly responsible for enhanced mitochondrial function.

Training has little effect on skeletal muscle DNA energy transfer but promotes skeletal muscle protein expression with maximum effect in older adults.

Co-authors on the article are all from Mayo Clinic:

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http://bit.ly/2neusur

The hazards of English spelling

New findings make it less hazardous than previously thought

Linguistic Society of America

(Washington, DC) - A new study of English spelling practices demonstrates that the way we spell words is much more orderly and self-organizing than previously thought. The study "Self-organization in the spelling of English suffixes: The emergence of culture out of anarchy," by Kristian Berg (University of Oldenburg) and Mark Aronoff (Stony Brook University) was published in the March, 2017 issue of the scholarly journal *Language*.

A pre-print version of the article may be found at: http://www.linguisticsociety.org/sites/default/files/Berg_Aronoff.pdf .

Their research examines previously unnoticed systematic aspects of English spelling and explains how the system emerged. One suffix that the authors report on is -ous, found in words like nervous and hazardous, which turns nouns like nerve and hazard into adjectives. They discovered that the final letter sequence ous may serve as a flag,

informing readers that a word must be an adjective. The sound of this suffix is a short vowel (linguists call it schwa) followed by s: ?s. The authors found that any written English word that ends in the three letter ous is an adjective and conversely that a word that that ends in the sound ?s but is not an adjective is never spelled with ous: service, genius, menace. They also have found similar patterns for other adjective suffixes, including the -ic of allergic, the -al of final, and the -y of funny.

For each of these affixes, the authors analyzed a large sample of written English documents dating back close to a thousand years. For every word that follows each of the regular pattern nowadays (e.g., hazardous, allergic, final, and funny), the linguists looked at every instance in their sample, keeping track of how it was spelled. They found a number of spellings for each suffix over time (e.g., ose, ows, is, owse, ys, es, ouse, us, and ous for modern ous). For every suffix, though, one spelling eventually won out and each suffix followed the sort of pattern that is known from biological competition between species.

This is a striking example of self-organization: No one is or was in charge of English spelling. As opposed to countries like Italy and France and Israel, where national academies oversee the written language, no English-speaking country has a language academy. And yet, somehow, the written language slowly but gradually evolved a system of marking word categories in cases like nervous - despite the fact that this system was never purposely designed. What is apparently a nuisance - we can spell one word ending in more than one way - is actually the trade-off for the grammatical 'flag' that says (in case of -ous), 'This word is an adjective'.

As a follow-up to this research, the authors are now testing their findings experimentally on fluent readers of English. Do they use the regularities that we found when they read? Furthermore, can these be used to help children and adults to learn to read more quickly and more fluently?

The Linguistic Society of America (LSA) publishes the peer-reviewed journal, Language, four times per year. The LSA is the largest national professional society representing the field of linguistics. Its mission is to advance the scientific study of language.

http://bbc.in/2mAFuqA

The biggest killer you may not know

"I flat-lined seven times, it was very uncertain for a long time whether I would make it," says Patrick Kane.

By James Gallagher Health and science reporter, BBC News website

He nearly died from a condition that kills more people in the UK each year than bowel, breast and prostate cancer combined.

Patrick was just nine months old when one morning he became poorly, floppy and "generally unresponsive". The family GP said he just needed Calpol, but Patrick's mother was still concerned and took him to hospital. But on the journey things got rapidly worse. "It really was a sudden thing... upon arrival I had multiple organ failure," he says.

Patrick spent three and a half months in St Mary's hospital in London, lost his right leg below the knee, his left arm and fingers on his right hand. What he had was sepsis. "Either you know someone who's had sepsis, or you've never heard of it," Patrick tells the BBC.

The 19-year-old is now studying biochemistry at university in Edinburgh.

What is sepsis?

Sepsis is triggered by infections, but is actually a problem with our own immune system going into overdrive.

It starts with an infection that can come from anywhere - even a contaminated cut or insect bite.

Normally, your immune system kicks in to fight the infection and stop it spreading. But if the infection manages to spread quickly round the body, then the immune system will launch a massive immune response to fight it.

This can also be a problem as the immune response can have catastrophic effects on the body, leading to septic shock, organ failure and even death.

In the UK, there are 44,000 deaths from the condition each year.

What are the symptoms?

The UK Sepsis Trust lists six symptoms to be aware of:

- ***slurred speech***
- ***extreme shivering or muscle pain***
- ***passing no urine in a day***
- ***severe breathlessness***
- ***"I feel like I might die"***
- ***skin mottled or discoloured***

Symptoms in young children include:

- ***looks mottled, bluish or pale***
- ***very lethargic or difficult to wake***
- ***abnormally cold to touch***
- ***breathing very fast***
- ***a rash that does not fade when you press it***
- ***a seizure or convulsion***

Patrick says "there's no magic symptom" but people need to be asking "could this be sepsis?"

Is anything being done about sepsis?

The NHS is doing more than it used to, but still not enough. A report in 2015 said four in 10 patients being admitted to accident and emergency units were not being reviewed quickly enough and uncovered delays in giving antibiotics in nearly a third of cases. The National Institute for Health and Care Excellence - which advises doctors on best practice - is coming up with new rules.

Prof Gillian Leng, the organisation's deputy chief executive, says: "We know from recent case reviews that there are inconsistencies in how people's symptoms are assessed in different settings. "More can be done to provide rapid treatment."

The organisation says patients should be assessed rapidly and those with life-threatening sepsis should be treated within one hour.

Previous guidance said doctors and other healthcare staff must treat sepsis with the same urgency as a suspected heart attack.

Health Secretary Jeremy Hunt said there was a "relentless drive" to raise awareness.

http://bbc.in/2lS6813

Post-partum psychosis: Why I thought I'd killed my baby

Mother's Day is approaching but as any mother knows, stepping in to the role can be a turbulent time. For some it can be devastating. As many as one in 500 are thought to suffer from post-partum psychosis.

University lecturer Sally Wilson was one of them.

The photo shown above is of me, my husband Jamie and our two-year-old daughter, Ella, taken on a skiing break in France a few weeks ago. It looks no different to any other happy family holiday snap does it? But the events leading up to it, the beginning of our family life, is wildly different to that of other new parents.

It is a story of ruin, of living the most terrifying, inescapable nightmare day after day, of being in such utter pain and despair that I constantly thought of walking into the sea near our home in north Wales.

Before giving birth to Ella I was totally unaware of a condition called post-partum psychosis (PP). Two years on, I have virtually fully recovered. It's not been easy and involved some controversial treatment. But the day I thought would never come is here; when I enjoy the familiarity of the old me.

In 2013, Jamie and I got married and, as planned, started a family a year-or-so later. My pregnancy was good. I was a week overdue and had some signs of pre-eclampsia, a condition in late pregnancy which can be dangerous if not treated, so I was induced.

My labour was painful, no shock there. But as the hours went by, things began to deteriorate. I became terribly confused. I had difficulty grasping the notion of time. I barely slept and felt feverish.

The medics ramped up hormones for induction and I was given gas and air and pethidine. Ella's heart rate kept dropping and she was in distress. She was born early in the morning in March 2015 by Caesarean section. As I came round from the anaesthetic, something very sinister was unfolding. My confusion was by now off the scale. I

kept saying I didn't understand what was going on, asking why there were doctors in the room. A brain scan for a suspected stroke and blood tests came back negative.

At one point I remember my eyes rolling back in my head and I slumped onto the bed. At night I pleaded with the nurses to sit with me as I was so scared. I was also paranoid that the midwives were talking about me. By now I was very panicky, convinced I was doing something wrong and would get upset. A few days later things got a lot worse. I got up to go to the toilet and collapsed. I was sobbing and refused to get up.

In my mind there was a strange realisation that I'd died. I could see everyone around me, the midwives and Jamie behind me. I saw a midwife take Ella away, I believed they were taking her to be resuscitated because I'd harmed her.

I now know that I was having a psychotic episode. My reality had shifted, I believed I had died and was living in an afterlife. I began to hallucinate. The sound of babies crying was deafening, the whirr of air conditioning unit overwhelmed me and the canteen trolleys sounded like trains crashing through the ward; lights being switched were like explosions and I could see shadows on the wall.

I was convinced that because I'd hurt my baby I had died and was now living in the 'after life', a kind of hell. The most terrifying nightmare imaginable was now my reality. The nurses brought Ella to see me, to reassure me she was ok. I was convinced they'd swapped her. This wasn't my baby. My baby was dead. I had killed her.

"What's wrong with Jamie? Why's he crying?" He's not crying Sally, look he's fine. "Who are those people outside the door in white coats?" There's no one outside the door Sally. "Yes, there are. They've come to get me and take me to prison. Oh God… how could I have harmed my baby?"

It was horrific.

I was transferred to the psychiatric ward and Jamie was told I was suffering from PP. I was prescribed anti-psychotic and anti-anxiety medication.

All I can recall is being led into a terrifying maze where I'd see people pacing around as grotesquely exaggerated caricatures. I would refuse to have bloods taken, convinced there was a conspiracy against me.

Jamie and my parents would visit with Ella and I'd hold her but couldn't understand that she was mine. I felt no connection.

We went to the café and she needed her nappy changed. The toilets were near to the labour ward and I became really stressed out and upset as I didn't want to go anywhere near there. I thought I couldn't be trusted on the labour ward as I was convinced I'd hurt my own baby.

A week later I had a review with the consultant and I told him things were better than they were just to be allowed out of there.

A home treatment team was arranged to visit me every day but things didn't improve much. I'd manage to help meet Ella's basic needs, change and feed her. But I was going through the motions.

I still 100% believed that I'd killed my baby. I hit an extreme low, a bleak depression punctuated with psychotic symptoms.

I'd read a news article about a murder at a caravan park which had happened on the day I had the psychotic episode in hospital. In my mind I'd committed the murder.

The sound of birds was really loud, particularly crows. I then discovered the collective noun for crows is 'murder' - I interpreted meaning to that, of what I'd done in the hospital. I had an obsession with a certain number bus which always seemed to pass when I left the house. This was part of the conspiracy and had a hidden meaning.

Over-powering, intrusive images constantly flashed into my mind, of walking out into the sea near our home and ending it all.

Ten months after coming home, I told Jamie that I couldn't go on. My husband, who'd done so much to help me, was distraught.

Determined to help, Jamie did a literature review on PP treatments. Electro-convulsive therapy (ECT) came up a lot.

My psychiatrist contacted Ian Jones, Professor of psychiatry at Cardiff University, National Centre for Mental Health director and a world expert in PP. He agreed that ECT might help me. You immediately think it's a barbaric horrible treatment, involving being strapped to a chair and electrocuted. t's fairly dramatic - you're anaesthetised and electrical currents are passed through your brain to trigger a seizure.

Half way through the 10 sessions, there was a shift in my thinking. Something terrible was being lifted from me. It saved my life.

Gradually I've grown stronger and bonded with Ella.

It's sad to think about what I've missed out on but now I look at her and get excited that everything's ok, we're here, happy and healthy.

I can't say I'm the same person. But I'm back at work a few days a week and I'm pre-occupied with the everyday challenges of parenting. Life is good again.

Once you've suffered from PP there's a very high chance of it recurring with subsequent pregnancies. It's a very personal choice, but even if there was only a slight risk of going through that again, for us, it's just not worth it.

But it's very important to me to give hope to others going through the horrors of PP. You'll be convinced it will never, ever end. I was convinced too. But this is a day I thought would never come when life feels good once again.

The facts on PP

What exactly is it?

Of wide spectrum of post-natal mental health problems, PP is one of the most severe. Post-natal depression affects something like one in 10 women, and PP one in 500 to 1000. Includes psychotic symptoms, believing things that are not true and prominent mood symptoms - both high and low

How does it manifest?

PP can come on quickly, out of the blue. Within hours women can go from perfectly well to as ill as we see people needing psychiatric care. In others, it might not be so rapid or obvious

Who is vulnerable?

For around 50% PP is the first episode of mental illness they've had. The other 50% will have had previous psychiatric illnesses. Bi-polar disorder are at particularly high risk, a 20% (1 in 5) chance. Extremely high risk are those with previous PP episodes with a 50-60% chance of reoccurrence

What causes it?

There are many hypotheses - big hormonal changes, sleep disruption or immunological changes. An important role, and an aspect of our ongoing research, are genetic factors.

Prof Ian Jones, Cardiff University