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New precision medicine procedure fights cancer, advances treatment for pets and humans

MU veterinary oncologists develop a vaccine treatment for osteosarcoma, a common type of bone cancer in dogs, avoiding chemotherapy and opening the door for human clinical trials

In a first-of-its-kind study, scientists at the University of Missouri have helped advance a patient-specific, precision medicine treatment for bone cancer in dogs. By creating a vaccine from a dog's own tumor, scientists worked with ELIAS Animal Health to target specific cancer cells and avoid the toxic side effects of chemotherapy, while also opening the door for future human clinical trials.

Osteosarcoma, or bone cancer, is not common in humans, representing only about 800-900 new cases each year in the U.S. About half of those cases are reported in children and teens. However, for dogs this disease is much more common, with more than 10,000 cases a year occurring in the U.S.

"A vaccine is made out of the dog's own tumor for the dog's immune system to recognize," said Jeffrey Bryan, a professor of oncology at the MU College of Veterinary Medicine and director of Comparative Oncology Radiobiology and Epigenetics Laboratory. "The dogs received no chemotherapy and received only immunotherapy after their surgery. It's the first time that dogs with osteosarcoma have experienced prolonged survival without receiving chemotherapy, which is really exciting."

In the study, researchers partnered with ELIAS Animal Health to test a vaccine to treat osteosarcoma by using a dog's own lymphocytes. Overall, the dogs receiving this therapy had more than 400 days of remission compared to about 270 days for dogs receiving chemotherapy in a separate study by the National Cancer Institute.

"Lymphocytes are immune cells that recognize where pathogens are hiding in the body and then kill the cells harboring those pathogens," Bryan said. "After we remove the tumor, we create a vaccine using the dog's tumor cells to stimulate anti-tumor lymphocytes. These lymphocytes are then collected by apheresis and expanded outside the body by Elias Animal Health to create a transfusion of the patient's immune cells. These cells are activated and essentially really angry at whatever they are supposed to attack. When put back into the body, they should identify and destroy tumor cells. Ideally, this immune response would destroy every last tumor cell."

Mizzou researchers hope to continue immunotherapy discovery with dogs in order to optimize the new therapy for future human clinical trials with the hopes of treating osteosarcoma and other cancers, especially metastatic osteosarcoma in children. They are currently continuing this work through another immunotherapy trial in progress with a grant by the Morris Animal Foundation through the National Cancer Institute Comparative Oncology Trials Consortium.

Brian Flesner, an assistant professor of oncology at the MU College of Veterinary Medicine, presented this research at the 2018 Veterinary Cancer Society Annual Conference in Louisville, Kentucky. The same data was shared at the 2018 Paws 4 a Cure Conference in Boston by Jeffrey Bryan.

https://wb.md/2GkwaTV

Could This Be Behind the Early Puberty Trend in Girls?

Although environmental causes have been suspected, the reasons for earlier puberty have been somewhat of a mystery.

George W. Citroner

The 'Early Puberty' Trend

During the past couple of decades, the age of puberty onset in US girls has been declining.[1] Although environmental causes have been suspected, the reasons for earlier puberty have been somewhat of a mystery.

It is a concern because early puberty can come with significant health risks.[2] Molly Regelmann, MD, a pediatric endocrinologist at Children's Hospital at Montefiore, Bronx, New York, said "Early

menarche, the first menstrual period, is associated with higher rates of obesity, cardiovascular disease, polycystic ovarian syndrome, and certain cancers, such as breast cancer, later in life." Regelmann, who was not associated with this study, added "The normal range for the start of puberty in girls is between 8 and 13 years."

Kim Harley, PhD, from the University of California, Berkeley, said, "The onset of puberty has been getting younger for girls over the last 15 to 20 years, and we're concerned." She continued, "Obesity has something to do with it. We're in the middle of a childhood obesity epidemic, and we know that overweight girls enter puberty at earlier ages."[3]

Other research suggests high levels of psychosocial stress might influence the onset of puberty.[4,5]

However, Harley said that exposure to certain endocrine-disrupting chemicals in our environment may be a significant factor. Her research at the University of California has shown that the daughters of mothers with high levels of diethyl phthalate, triclosan, phenols, and parabens in their bodies during pregnancy entered puberty earlier than their peers.[6] These chemicals are commonly found in a broad range of cosmetics, toothpaste, soaps, and other personal care products.

Harley explained, "Chemicals in household products and in the environment seem to mimic estrogen and other hormones,[7] and we wanted to find out if these hormone-disrupting chemicals were also contributing to this shift in earlier puberty we've observed."

Endocrine-Disrupting Chemical Exposure in Pregnancy

Harley's study looked at 179 girls and 159 boys in California who were born to mothers who were pregnant between 1999 and 2000. It is the first study to look at how prenatal exposure to endocrine-disrupting chemicals may influence age at puberty.

Harley said, "Other studies have looked at the chemicals in these personal care products. A few studies have looked at childhood exposure to these chemicals and whether that was associated with earlier puberty."

Many commonly used perfumes, deodorants, shampoos, cosmetics, and other scented products contain phthalates. Parabens may be added to these products as a preservative, and toothpaste, soap, lipstick, and skin lotions often contain phenols.

"In our study, we looked at the prenatal period. We were looking at exposure in the womb, and that's important because we know that hormone-disrupting chemicals have these windows of susceptibility, and the prenatal period is a particular window of susceptibility," explained Harley.

The study participants were mothers and children who were enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS),[8] a longitudinal birth cohort that examined the effects of in utero and early-life environmental exposures on children's health and development.

Mothers were interviewed twice during pregnancy (at an average of 14.0 and 26.9 weeks), and again when their children were 9 years old. Pubertal assessments of the children were conducted every 9 months between ages 9 and 13 years, and included clinical Tanner staging. The investigators measured the levels of various chemicals in urine samples of mothers during pregnancy, and in the children at age 9 years.

The study population was predominantly Latino, and 73% of the mothers had lived in the United States fewer than 11 years at the time of their pregnancies. By 9 years of age, 55% of the children were overweight or obese, and 69% were living below the federal poverty threshold.

Differential Effects on Puberty

Associations between higher prenatal chemical exposure and early onset of puberty were seen in girls. High prenatal monoethyl phthalate concentrations were associated with earlier development of

pubic hair, whereas high levels of prenatal triclosan, propyl paraben, and 2,4-dichlorophenol were linked to earlier onset of menarche in the children. Methyl paraben and 2,5-dichlorophenol in urine were associated with earlier breast and pubic hair development. The daughters of women with the highest levels of these substances in their urine started their periods an average of 4 months earlier. However, there was no evidence that boys were similarly affected by prenatal chemical exposure.

Timothy N. Hickman, MD, a board-certified reproductive endocrinologist at Houston Methodist Hospital in Texas, who was not associated with the study, said "There is biologic plausibility that [prenatal] exposure to exogenous estrogen and other toxins in the environment is affecting sexual development in girls."

The endocrine-disrupting chemicals detected in this study have estrogenic activity, which is known to affect sexual development.[9] "We can show a link that makes sense. We already have evidence from laboratory research that these chemicals mimic estrogen. We have evidence from animal studies[10] that they may significantly impact reproductive development and timing of puberty," Harley said.

Harley also acknowledged that "this is an observational study; it's epidemiologic, so we can't prove causality. This is the first study of its kind, and more research will be needed."

A growing number of studies, however, suggest that the cause for concern is not misplaced. Regelmann confirms that population and cohort studies, as well as case reports, "make a strong case for the association of endocrine-disrupting chemicals and early onset of puberty."[11-13]

Minimizing Exposure

The levels of chemicals found in the bodies of women and children in this study are not unusual. In the United States, well over 90% of women have been shown to have detectable concentrations of phthalate, phenol, and parabens metabolites in their urine.[14-16]

Regelmann offered suggestions for reducing exposure to endocrine-disrupting chemicals during pregnancy. "Wash fruits and vegetables to remove potential chemicals used in farming practices, and try to limit the use of plastics and synthetic materials for food preparation and storage."

She also recommends "limiting exposures to tea tree oil and lavender, because there are reports of exposure being associated with early breast development."[17]

Harley advised, "If someone is concerned, they can easily find personal care products that don't contain phthalates or parabens. They can just go to the natural or 'green' section of the store and find products that specifically say 'no parabens, no phthalates.' If people change the products that they're using, they can rapidly reduce the levels of these chemicals in their bodies."

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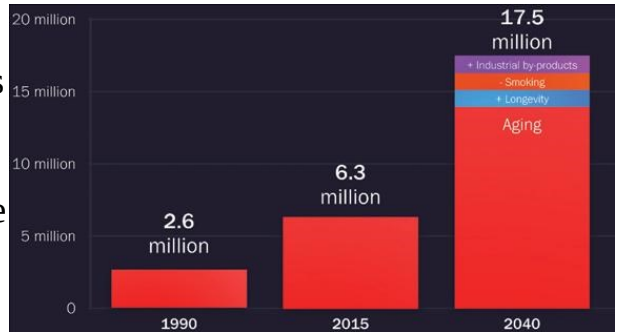
Emerging evidence of an impending Parkinson's disease pandemic identified

Experts discuss reasons for the increasing number of patients with Parkinson's disease and the challenges that need to be overcome to prevent and slow down a pandemic

Amsterdam, NL - For most of human history Parkinson's disease (PD) has been a rare disorder. However, demography and the by-products of industrialization are now contributing to an impending Parkinson's pandemic, according to experts writing in a supplement to the *Journal of Parkinson's Disease*. They say that this pandemic can be addressed by the Parkinson's community forming a "PACT" to prevent the disease, advocate for policies and resources aimed at slowing its spread, care for all those affected, and treat with effective and novel therapies.

Neurological disorders are now the leading cause of disability globally, and the fastest growing neurological disorder in the world is PD, a slowly progressive disorder that affects movement, muscle control, and balance. In 1855, forty years after Dr. James Parkinson first described the condition, approximately 22 people of 15 million in England and Wales died of PD. In 2014, roughly 5,000 to 10,000 individuals of 65 million in the UK died of PD. From 1990 to 2015, the number of people with PD doubled worldwide to over six million.



Projected global burden of Parkinson's disease accounting for changes in aging, longevity, smoking rates, and industrialization, 1990-2040.

Department of Neurology and Center for Health and Technology, University of Rochester Medical Center, Rochester, NY, USA

Driven principally by aging, this number is projected to double again to over 12 million by 2040, and additional factors, including increasing longevity, declining smoking rates, and increasing industrialization, could raise the burden to over 17 million.

"By 2040, we can truly talk about a pandemic that will result in increased human suffering, as well as rocketing societal and medical costs. How can the community be made aware of this scenario and implement changes in research priorities and care programs to lessen the burden of the upcoming pandemic?" cautioned Patrik Brundin, MD, PhD, Van Andel Research Institute, Grand Rapids, MI, USA, Editor-in-Chief of the *Journal of Parkinson's Disease*.

According to lead author Ray Dorsey, MD, from the Department of Neurology and Center for Health and Technology, University of

Rochester Medical Center, Rochester, NY, USA, "The tide of PD is rising and spreading. PD exacts an enormous human toll on those with the disease and those around them. The strain of caregiving has adverse health consequences of its own. The economic costs of PD are also substantial, poised to grow, and at least in the US, overwhelmingly directed at institutional care, which few desire."

The incidence of PD increases with age and the world's population is aging, as the number and proportion of individuals over 65 is rapidly growing. The combined result of these two factors is an unprecedented rise in the number of people with PD.

Independent of PD, global life expectancy has increased by six years in the last two decades. This will likely increase the number of individuals with advanced PD who are more difficult to treat and can have limited access to care. Numerous studies have found that the risk of PD decreases among smokers by approximately 40%. If the association is causal, which remains to be determined, decreasing smoking rates could lead to higher rates of PD.

Finally, the by-products of industrialization may be contributing to the rising rates of PD. Specific pesticides, solvents, and heavy metals, have been linked to PD - exposure to these agents is preventable.

"In the past century, society has successfully confronted pandemics of polio, breast cancer, and HIV to varying degrees. Central to the success of these efforts was unbridled activism," stated Dr. Dorsey. Following these examples, the authors propose that the Parkinson's community form a "PACT" to prevent, advocate for, care, and treat the disease through understanding the root causes (environmental, genetic, and biological), expanding new care models that seek to bring expert care to all, and developing new highly effective therapies. The most effective therapy (levodopa) is now fifty years old.

"We hope that this article will raise awareness of the challenge and form the basis for a community-led response to address one of the great health challenges of our time," added co-author and Associate Editor of the *Journal of Parkinson's Disease* Bastiaan R. Bloem, MD, PhD, from the Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Neurology, Nijmegen, The Netherlands.

"The PD pandemic is preventable, not inevitable," conclude the authors.

NOTES FOR EDITORS

"The Emerging Evidence of the Parkinson Pandemic," by E. Ray Dorsey, MD; Todd Sherer, PhD; Michael S. Okun, MD; and Bastiaan R. Bloem, MD, PhD (DOI: 10.3233/JPD-181474) published in the Journal of Parkinson's Disease, *Volume 8, Supplement 1 by IOS Press. It is openly available at https://content.iospress.com/articles/journal-of-parkinsons-disease/jpd181474.*

http://bit.ly/2t0TSN2

Newborn babies have inbuilt ability to pick out words, study finds

Newborn babies are born with the innate skills needed to pick out words from language

Newborn babies are born with the innate skills needed to pick out words from language, a new study published in *Developmental Science* reveals.

Before infants can learn words, they must identify those words in continuous speech. Yet, the speech signal lacks obvious boundary markers, which poses a potential problem for language acquisition.

Studies have found that by the middle of the first year, infants seem to have solved this problem, but it is unknown if segmentation abilities are present from birth, or if they only emerge after sufficient language exposure and/or brain maturation.

Near-Infrared Spectroscopy

An international team of researchers from the University of Liverpool, SISSA in Italy, the Neurospin Centre in France and The University of Manchester conducted experiments to find the cues crucial for the segmentation of human speech.

The researchers played the infants a three-and-a-half minute audio clip in which four meaningless words, were buried in a stream of syllables.

Using a painless technique called Near-Infrared Spectroscopy, which shines red light into the brain, they were able to measure how much was absorbed, telling them which parts of the brain were active.

'Key Insight'

The researchers discovered two mechanisms in three-day-old infants, which give them the skills to pick out words in a stream of sounds.

The first mechanism is known as prosody, the melody of language, allow us to recognise when a word starts and stops.

The second is called the statistics of language, which describes how we compute the frequency of when sounds in a word come together.

The discovery provides a key insight into a first step to learning language.

Important tools

Dr Alissa Ferry, University of Manchester, said: "We think this study highlights how sentient newborn babies really are and how much information they are absorbing. That's quite important for new parents and gives them some insight into how their baby is listening to them."

Dr Perrine Brusini, University of Liverpool, said: "We then had the infants listen to individual words and found that their brains responded differently to the words that they heard than to slightly different words. "This showed that even from birth infants can pick out individual words from language."

Dr Ana Flò, Neurospin, said: "Language in incredibly complicated and this study is about understanding how infants try to make sense of it when they first hear it. We often think of language as being made up of words, but words often blur together when we talk. So one of the first steps to learn language is to pick out the words.

"Our study shows that at just three days old, without understanding what it means, they are able pick out individual words from speech. And we have identified two important tools that we are almost certainly born with, that gives them the ability to do this."

The study was funded by the European Research Council. The full study, entitled 'Newborns are sensitive to multiple cues for word segmentation in continuous speech', can be found here https://onlinelibrary.wiley.com/doi/abs/10.1111/desc.12802

http://bit.ly/2GcUozf

Ancient crystals offer evidence of the start of Earth's core solidifying

Evidence of the starting period for the solidification of Earth's core

by Bob Yirka

A quartet of researchers from the University of Rochester and the University of California has found evidence of the starting period for the solidification of Earth's core.

In their paper published in the journal *Nature Geoscience*, Richard Bono, John Tarduno, Francis Nimmo and Rory Cottrell describe their analysis of ancient crystals found in eastern Canada, what they found, and why they believe their results offer clues about the formation of Earth's inner core.

Peter Driscoll, with the Carnegie Institution for Science, has written a News and Views piece on the study in the same journal issue.

Planetary scientists have found strong evidence that suggests the Earth has an inner and an outer core. The inner core is believed to be solid, while the outer core is made up of molten material.

Prior evidence has also indicated that the entire core was once liquid, but as the interior cooled, the innermost part began to crystallize.

It is at this point that scientists disagree—some suggest the start of solidification began as far back as 2.5 billion years ago. Others believe it was much more recent—perhaps as recent as just 500

million years ago. In this new effort, the researchers have found evidence that supports the latter theory.

The work by the researchers involved carefully analyzing plagioclase and clinopyroxene crystals, which have been dated to approximately 565 million years ago. The crystals are important because they contain bits of metal called inclusions. The inclusions are very small and needle-shaped and aligned themselves with the Earth's magnetic field as they became embedded in the crystal. Since the Earth's magnetic field is generated by activity in the inner core, the inclusions are a means of determining the state of the core during the time when the crystals formed.

The researchers report that their analysis showed that the magnetic field was significantly weaker than it is today, suggesting that solidification of the core must have occurred soon thereafter or the magnetic field would have collapsed altogether. The reason it did not, theory suggests, is because as the inner core solidified, he magnetic field became stronger.

More information: *Richard K. Bono et al. Young inner core inferred from Ediacaran ultra-low geomagnetic field intensity, Nature Geoscience (2019). DOI: 10.1038/s41561-018-0288-0*

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Vaccination with Streptococcus mitis could protect against virulent sibling, Streptococcus pneumonia

Suggests that vaccination of humans with live S. mitis *might offer protection from some of the many serotypes of* S. pneumoniae

Vaccinating laboratory mice with *Streptococcus mitis* bacteria prevents their virulent sibling, *Streptococcus pneumoniae* from infecting the mice.

The research suggests that vaccination of humans with live *S. mitis* might offer protection from some of the many serotypes of *S. pneumoniae* that vaccines currently do not exist for. This pathogen is one of the most common causes of severe pneumonia, and can also cause meningitis, bloodstream and sinus infections, endocarditis, and middle ear infections in young children. The research is published in Applied and Environmental Microbiology.

S. pneumoniae afflicts about 14 million children, annually, killing 2-3 million, including around a million under age five. Resistance to antibiotics is an increasing problem, underscoring the need for vaccines, according to the report. And current vaccines target only 13 of more than 90 serotypes of *S. pneumoniae*.

S. mitis, which lacks many of the virulence genes present in *S. pneumoniae*, but is otherwise quite similar, commonly inhabits the oral cavity and the upper respiratory tract, living in peaceful coexistence with the host.

The investigators intranasally vaccinated mice with two different versions of *S. mitis*, to compare their efficacy: wild type *S. mitis*, and *S. mitis* which they had genetically engineered to express a sugar coat that is found on the exterior of the cell wall of *S. pneumoniae*. Serotype 4, they posited, might strengthen the antibody response to S. pneumoniae.

Vaccination with the *S. mitis* vaccine boosted production of IgG and IgA antibodies, as well as Th17 cells (the investigators did not examine production of such antibodies and cells following vaccination with the engineered vaccine), said principal investigator Fernanda C. Petersen, DDS, PhD, Professor of molecular microbiology, University of Oslo, Norway.

IgG is an important antibody in the blood and other bodily fluids, and IgA is critical in secretions, especially those of the mucus epithelium of the intestinal and respiratory tracts. Th17 cells are pro-inflammatory cells that play an important role in fighting invading pathogens.

The engineered vaccine worked as expected, boosting protection against *S. pneumoniae* serotype 4, but not against *S. pneumoniae* serotype 2, as compared to the wild type vaccine.

Co-corresponding author Sudhanshu Shekhar, PhD, a postdoctoral researcher in Dr. Petersen's group, noted that one must be cautious in extrapolating results from mouse models to humans, and emphasized that protection of humans would remain hypothetical until human studies have been performed.

The report also noted that commensal live vaccines circumvent the main limitation of vaccinations with attenuated live pathogens: reversion to virulence.

"Bacterial live vaccines can be highly efficient because they mimic the natural infection," said Dr. Petersen. "They have been known for decades to prevent respiratory and enteric infections in humans. The main challenge, however, is to engineer attenuated versions that are safe as vaccines, but still offering protection. Our study reveals that *S. mitis* a natural human colonizer that resembles *S. pneumoniae* but seldom causes diseases, can be the answer offered by nature for a safe vaccine against *S. pneumoniae*."

http://bit.ly/2UyPpwv

Takeda dengue vaccine meets main goal of trial; detailed results to come

Experimental dengue vaccine appears to be safe and effective at preventing all four types of the mosquito-borne disease

CHICAGO - Takeda Pharmaceutical Co. said Tuesday that its experimental dengue vaccine appears to be safe and effective at preventing all four types of the mosquito-borne disease, meeting the main goal of the drugmaker's late-stage clinical trial.

The company said no significant safety concerns have emerged to date with the vaccine called TAK-003.

Takeda did not disclose how the vaccine performed in people who had never been previously exposed to dengue, a group that experienced an increased risk of severe disease with Sanofi SA's Dengvaxia, the world's first dengue vaccine.

Sanofi had not collected blood samples on all subjects prior to beginning its trials. By the time the company confirmed the safety risk in 2017, the vaccine had already been used in more than 800,000 schoolchildren in the Philippines.

Takeda collected blood samples from all 20,000 children aged 4 to 16 from Asia and Latin America who participated in the Phase III TIDES trial. The study looked at the vaccine's safety and efficacy both in children who had been exposed to dengue and those who had not.

Takeda said it will release full details of how the vaccine fared at 15 months after the first dose in a peer-reviewed journal as quickly as possible.

The vaccine is administered in two doses three months apart. The first efficacy results include 11 months of follow-up.

Part two of the trial, which includes another six months of patient data, will review how the vaccine performed in each of the four different types of dengue, as well as its performance according to prior dengue exposure and the number of participants who contracted severe dengue.

Those two parts will form the basis of Takeda's filings seeking regulatory approvals. A third part of the study will evaluate long-term safety by following participants for another three years.

Dr. Rajeev Venkayya, president of Takeda's vaccines business, said in a phone interview that the upcoming publication will include preliminary data on the vaccine's performance against each dengue strain and data on prior dengue exposure of trial subjects.

The first safety problems with Sanofi's vaccine only became apparent in the third year after vaccination. After the Sanofi experience, some experts believe governments will require several years of follow-up data before incorporating Takeda's vaccine into mass vaccination campaigns.

Venkayya would not speculate on how much follow-up regulators or health authorities will require, but said, “I do think it’s going to be more than one year.”

While Sanofi’s vaccine was based on a Yellow fever virus with dengue genes added in, TAK-003 is based on a weakened dengue 2 virus plus genes from the three other dengue types. Some infectious disease experts think the all-dengue design may trigger a broader immune response.

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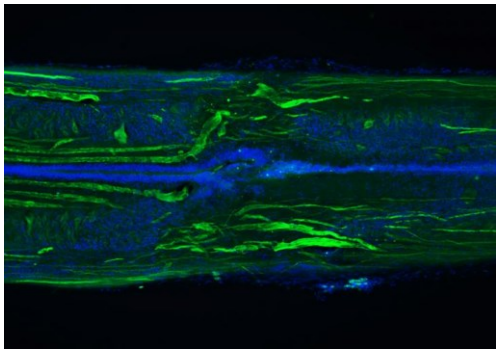
The lamprey regenerates its spinal cord not just once -- but twice

Marine Biological Laboratory scientists discover persistent regenerative capacity in lamprey

WOODS HOLE, Mass.-- Spontaneous recovery from spinal cord injury is almost unheard of in humans and other mammals, but many vertebrates fare better. The eel-like lamprey, for instance, can fully regenerate its spinal cord even after it's been severed: Within 3 months the lamprey is swimming, burrowing, and flipping around again, as if nothing had happened.



Longitudinal section of a lamprey spinal cord at 11 weeks post-injury, showing many regenerated axons (green) and a repaired central canal (blue tubelike structure). The original lesion site is in the center of the image. **S. Allen and J. Morgan**

In a new study, Marine Biological Laboratory (MBL) scientists report that lampreys recover and regenerate just as impressively after a second complete spinal cord injury at the same location. The study opens up a new path for identifying pro-regenerative molecules and potential therapeutic targets for human spinal cord injury.

"We've determined that central nervous system (CNS) regeneration in lampreys is resilient and robust after multiple injuries. The regeneration is nearly identical to the first time, both anatomically and functionally," said senior author Jennifer Morgan, Director of the MBL's Eugene Bell Center for Regenerative Biology and Tissue Engineering.

Morgan's lab has been focusing on the descending neurons, which originate in the brain and send motor signals down to the spinal cord. Some of these descending neurons regenerate after CNS injury in lamprey, while others die.

"We are beginning to isolate individual descending neurons and look at their transcriptional profiles (gene activity) to see if we can determine what makes some of them better at regenerating than others," Morgan said.

"The 'good' regenerators, for example, may express molecules that are known to promote growth during development. That's one hypothesis," she said.

Observing how the descending neurons respond to a second CNS injury can help the team tease out the factors required for repeated, resilient regeneration, which could have implications for designing better strategies for treatments aimed at promoting CNS re-growth after injury or disease.

This study was conducted by first author Kendra L. Hanslik and other former research assistants in Morgan's lab.

"These are all young scientists, many who have since gone on to graduate school," Morgan said. "This paper was their labor of love. To go through two rounds of regeneration in the lamprey -- that's nearly 6 months of waiting before they could collect the [spinal cord] tissue and begin the analysis. I'm really proud of their heroic efforts in pulling off this work."

Video: https://vimeo.com/314092587

http://bit.ly/2CY2zwc

Researchers find antidepressants significantly raise risk of GI, intracranial bleeding

Severe bleeding up to 40 percent more likely for patients on SSRIs, according to review in the Journal of the American Osteopathic Association

CHICAGO - Patients taking anti-depressant medications classified as selective serotonin reuptake inhibitors (SSRIs) are 40 percent more likely to develop severe gastrointestinal bleeding, particularly when they also use common over-the-counter pain relievers, according to a research review in the Journal of the American Osteopathic Association.

Nearly 13 percent of Americans 12 years and older take an antidepressant, and SSRIs are among the most frequently prescribed because they are relatively low-cost, effective and safe. However, they also carry risks for gastrointestinal and intracranial bleeding that compound when taken with other medications.

The most common and concerning interactions occur with nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen (Advil, Motrin) and naproxen (Aleve), anticoagulants like warfarin (Coumadin) or antiplatelet medications such as aspirin and clopidogrel (Plavix).

"The real risk comes from the assumption that each of these drugs is relatively safe and benign. But they all carry a risk for bleeding, and that risk increases when these medications are taken concurrently," says lead author Wei Cheng Yuet, PharmD, assistant professor of pharmacotherapy at University of North Texas Health Science Center. While gastrointestinal bleeding is most common, in rare instances patients can develop intracranial bleeding, which is a life-threatening event.

SSRIs are used to treat major depression, anxiety disorders, obsessive-compulsive disorders and post-traumatic stress disorder. A significant portion of SSRI prescriptions are written by primary care physicians.

Yuet says that the risk for bleeding is well established but not well known among patients. She encourages physicians to take a full inventory of the medications their patients take, including over-the-counter NSAIDs.

"Whenever physicians discover their patients are taking any combination of these medications, they should begin assessing the risks and benefits and determine whether there are alternative treatment plans," says Yuet. "For example, physicians should periodically assess antidepressant use even when patients are stable on therapy."

Otherwise, Yuet says it is important for physicians educate their patients on how to recognize symptoms of gastrointestinal bleeding, such as bright red blood in their stool or dark, tarry stool. She also recommends physicians monitor their patients closely for symptoms of gastrointestinal bleeding during the first 30 days of SSRI therapy, especially if patients are taking concurrent medications that may increase bleeding risk.

http://bit.ly/2RxKNoR

HIV hidden in patients' cells can now be accurately measured

Researchers can now quickly and accurately count a hidden, inactive form of the human immunodeficiency virus (HIV) that lurks in patients' cells.

This version of HIV embeds into cells' genomes and can persist despite otherwise successful therapies - thwarting attempts to cure the infection.

Using a new genetic technique developed by Howard Hughes Medical Institute Investigator Robert Siliciano and colleagues, researchers will finally be able to measure just how much of this viral

form is hiding in the body - a crucial part of evaluating the effectiveness of new treatments, Siliciano says.

Previous tools overestimated the number of this HIV form by 10-to-100-fold, potentially obscuring meaningful declines produced by experimental therapies, according to his team's report in the journal Nature on January 30, 2019. "We may still be a long way from a cure," he says, "but now at least we can measure our progress."

Current HIV therapy involves combinations of antiretroviral drugs, each of which inhibits a specific stage of the HIV lifecycle. When drugs that block two or more stages are given to a patient simultaneously, the virus cannot replicate, and its presence in the bloodstream drops below detection limits. This relieves patients' symptoms and keeps them healthy for decades. But the virus sticks around in the body, in a latent form that's challenging to detect, much less count; HIV's genetic instructions, or template, remain integrated within the genome of certain cells.

HIV exclusively infects immune cells called CD4 cells. A subset of these routinely become dormant and store a record of known infectious agents. Like vivid memories, these cells persist indefinitely. But their persistence comes with a downside: they can unwittingly safeguard the instructions for making HIV. Once the cells are "awakened," these viral templates snap back into action making viruses. So patients infected with HIV must remain on antiretroviral therapy forever - unless scientists can figure out how to destroy this so-called "latent reservoir" of HIV.

The first step is figuring out how big each patient's latent reservoir is, so researchers can track their progress depleting it. But that's been a serious challenge, says Siliciano, an HIV researcher at the Johns Hopkins University. When he and his lab members first demonstrated the existence of the latent reservoir in 1995, they did so using a technique they developed called quantitative viral outgrowth assays (QVOAs). The method involves growing HIV-infected cells in the lab, which is difficult and takes weeks to complete.

To skirt those issues, most scientists use a simpler technique that relies on a genetic reaction called PCR to measure how much viral DNA is present in CD4 cells. The problem, says Siliciano, is that 98 percent of the HIV instruction books are so defective they're harmless, so the method overestimates the number that matters to patient health.

Siliciano's team instead designed a PCR reaction that can distinguish between defective and intact viral templates, using fluorescent probes in two different colors. The probes target areas prone to mutations that can cause defects, and a color read-out indicates whether the HIV instructions are defective or not.

That means that scientists can use the new technique to assess whether a given intervention - an experimental drug, or cocktail of drugs, for example - is affecting the pool of hidden HIV instructions that actually threaten patients' lives.

"For decades, the field has been clamoring for an accurate measure for these hidden viral templates," Siliciano says. "Now, we have a good way to know if we are making a dent in their numbers."

Citation:

Katherine M. Bruner, et al., *"A Novel Quantitaive Approach for Measuring the Reservoir of Latent HIV-1 Proviruses,"* Nature. *Published online January 30, 2019. doi: 10.1038/s41586-019-0898-8*

http://bit.ly/2G46hrO

BIDMC researchers ID, treat faulty brain circuitry underlying symptoms of schizophrenia

Study: Non-invasive brain stimulation alleviates the chronic, treatment-resistant symptoms of schizophrenia

BOSTON - Schizophrenia is a chronic and disabling mental illness that affects more than three million Americans. Anti-psychotic medication can control schizophrenia's psychotic symptoms, including the hallucinations and delusions that are well-known

hallmarks of the disease. However, there are no effective treatments for the disease's 'negative symptoms' - so-called because they involve a loss of normal function. The negative symptoms of schizophrenia include an inability to feel pleasure, a lack of motivation and difficulty with non-verbal communication. These symptoms can seriously impact patients' employment prospects, housing, relationships and overall quality of life.

In a first-of-its-kind study, researchers at Beth Israel Deaconess Medical Center (BIDMC) used imaging data to determine the underlying anatomical cause of schizophrenia's negative symptoms and then applied non-invasive brain stimulation to ameliorate them. The scientists found, as they reported today in the American Journal of Psychiatry, that these symptoms arise from a breakdown in a network between the brain's prefrontal cortex and the cerebellum. Moreover, the team demonstrated that a novel type of non-invasive brain stimulation restored this crucial network's function, which in turn improved schizophrenia's most debilitating and treatment resistant symptoms in patients with the disease.

"There's an enormous body of research asking how people with schizophrenia are different from people without it, but there is scant literature using imaging in people with schizophrenia to pin down the biological differences between those who are very symptomatic and those who are less so," said lead author Roscoe Brady Jr., MD, PhD, assistant professor of psychiatry at BIDMC. "If we can pin down what's different, maybe we can intervene."

In stage one of this two-pronged study, Brady and colleagues examined functional magnetic resonance imaging (fMRI) scans of 44 patients with schizophrenia. Their analysis revealed that a breakdown in the neural connectivity between the prefrontal cortex and cerebellum was linked to more severe negative symptoms. (The network in question was not associated with hallucinations or delusions.)

"We wanted to find out if we could restore that brain circuit through non-invasive brain stimulation, and if we could, would people get better?" said corresponding author Mark Halko, PhD, assistant professor of neurology at BIDMC's Berenson-Allen Center for Non-Invasive Brain Stimulation. "The answer is they absolutely do get better. It's a very provocative finding."

Halko, an expert in non-invasive brain stimulation, focuses on using the technology - which modifies brain activity using powerful magnetic fields - to relieve symptoms of anxiety, depression and other mental illnesses. In 2012, Halko was principal investigator on a clinical trial testing whether non-invasive brain stimulation could improve symptoms in patients with schizophrenia. But without a known circuit to explain treatment response, the study raised more questions than it answered. Then a mutual colleague introduced Brady and Halko. "When we started looking at our data sets together, we came to the conclusion that if Dr. Brady's work could identify the networks that are responsible for these symptoms of the illness, then the brain modulation we've been doing could change that exact network," Halko said. To test that idea, the researchers recruited patients diagnosed with schizophrenia, quantified and scored their negative symptom severity and conducted baseline brain imaging. Next, Halko and colleagues administered either active non-invasive brain stimulation or a sham (placebo) treatment as a control. Participants received two brain stimulation sessions per day, four hours apart, for five consecutive days.

Follow-up brain scans and clinical evaluation revealed that patients with schizophrenia who experience increased connectivity between the brain's prefrontal cortex and cerebellum after brain stimulation also experienced a reduction in symptom severity.

"For some people with schizophrenia, the non-invasive brain stimulation had a powerful impact; for others, it wasn't as powerful," said Brady. "In all cases, re-connecting the network explained how much improvement the patient experienced. For the first time, we know what brain circuit to go after."

In addition to Brady and Halko, co-investigators included Ivy Lee, Larry J. Seidman, PhD, Matcheri S. Keshavan, MD, and Alvaro Pascual-Leone, MD, PhD, of Beth Israel Deaconess Medical Center; Dost Öngür, MD, PhD, of McLean Hospital; Irene Gonsalvez, MD, of St. Elizabeth's Medical Center; Jeremy D. Schmahmann, MD, of Massachusetts General Hospital; Shaun M. Eack, PhD, of University of Pittsburgh. This work was supported in part by awards from the National Institutes of Health, including the National Institute of Mental Health, the National Center for Research Resources, and the National Center for the Advancement of Translational Science (NIMH K23 MH100623; R01 MH111868; R01 MH092440; K24 MH104449; UL1 RR025758). Additional partial support was provided by Sidney R. Baer Jr. Foundation; MINDlink Foundation; Harvard Catalyst; and The Harvard Clinical and Translational Science Center.

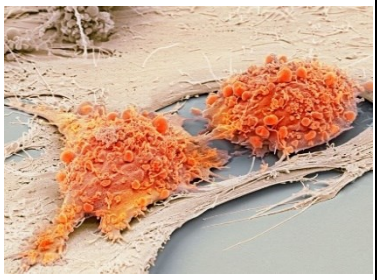
The team discloses that Dost Öngür served on the scientific advisory board for Neurocrine, Inc, in 2016; Pascual-Leone serves on the scientific boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics and Neosync and is listed as an inventor of several issued and pending patents on the real-time integration of transcranial magnetic stimulation with EEC and MRI; Schmahmann serves on the scientific advisory board for Cadent, consults with Biogen, Biohaven and Pfizer, and holds the license with the General Hospital Corporation to the Brief Ataxia Rating Scale and the Cerebellar Cognitive Affective / Schmahmann Syndrome Scale.

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

Japan should put the brakes on stem-cell sales

Unproven therapies should not be marketed to patients.

Healing spinal-cord injuries has been one of the most difficult — and doggedly pursued — quests in medicine, and among the most symbolic goals for the field of stem cells and regenerative medicine.



Progress, however, has been frustratingly slow. Dozens of seemingly promising efforts, based on animal studies, have fallen flat.

Japan is taking another unwise step to commercialize unproven stem-cell therapies. **Steve Gschmeissner/SPL**

Last week, a Californian company called Asterias Biotherapeutics released promising results from a 12-month first phase clinical trial, in which embryonic stem cells are converted into oligodendrocytes — cells of the central nervous system that support neurons and can stimulate their growth — and then injected into the backs of people with a spinal-cord injury. The data show that injected cells do stick around at the injury site, and that most patients (21 out of 22) showed improved movement.

But these are still early-stage results. It is not clear yet whether the improvements are the result of the cells, or whether something else, such as the body's own regenerative capacity, was at work. To find out, the company wants permission to move forward with a randomized, controlled phase II clinical trial. That's the right way to do things: stepping carefully, slowly and rigorously forward.

Meanwhile, in Japan, a more worrisome approach is unfolding. Last month, researchers at Sapporo Medical University leapfrogged all other spinal-cord injury treatments that use stem cells — including the one being investigated by Asterias — and received market approval for injections of a type of cell called a mesenchymal stem cell. There are reasons to be sceptical, or at least to delay the sale of this procedure to patients.

The very nature of these cells — in particular, whether they function as stem cells and do turn into neurons as suggested by the Japanese group — is subject to fierce debate (D. Sipp *et al*. *Nature* **561**, 455–457; 2018). The clinical trials that demonstrated efficacy were based on only 13 participants. There was no control group and the trial data remain unpublished.

Through a fast-track process for regenerative medicine, launched in 2014 to speed treatments to patients and spur innovation, the Japanese government gave the mesenchymal stem-cell treatment, called Stemirac, 'conditional approval' to enter the market. It can be sold to patients, and the company was given seven years to show that it works. How that evidence will be collected once the treatment is on the market is an unanswered question.

A better way would have been to run a randomized controlled clinical trial, with both participants and physicians unaware of who received

the cells and who received a placebo. But under Japan's fast-track system, researchers at the university didn't have to do this. The researchers also should have published the clinical data already collected, but in Japan they are discouraged from doing so.

This seems surprising. Some companies might not want to publish clinical results to protect their trade secrets. But in this case, it is Japan's health ministry that seems to be telling researchers not to publish data. Although it is not a blanket ban — the propriety of publishing such data is evaluated on a case-by-case basis — a ministry representative told *Nature* that in this instance it would be discouraged. That's because published data could be used as "promotional materials" and unduly influence patients or officials, according to the health ministry official.

Japan has set up a bizarre situation. The university has made promises about the treatment in an advertisement unencumbered by data, but the inclusion of scientific evidence, in a form that the world's experts can evaluate, is considered too potentially misleading to publish. The Kafkaesque logic at play here seems to be that promoting a medicine without data is better than promoting it with.

The Japanese team has promised results so dramatically convincing that controlled trials would be unnecessary. Let's hope that is the case. But it is more likely that ambiguous results from the uncontrolled trial will allow the treatment to continue in use indefinitely. That is fair neither to the patients who are willing to try the treatment, nor to other companies that are putting therapies through truly rigorous trials.

Japan could and should introduce a better and more transparent system, one that requires the production of sound clinical efficacy data through controlled trials, when possible, and that encourages broad evaluation of those data — in scientific publications, when feasible — by the international medical research community. Japan could, in other words, learn a lot from the way it's being done in California. Until then, offering people such stem-cell treatments is premature and unfair.

Nature ***565***, *535-536 (2019) doi: 10.1038/d41586-019-00332-5*

http://bit.ly/2RyQ67v

Sonar Can Literally Scare Whales to Death, Study Finds

Sonar in certain frequencies terrifies some whales so much that the experience overrides a slower heartbeat

By Mindy Weisberger, Senior Writer

Naval sonar has been linked to mass strandings of otherwise-healthy whales for nearly two decades, but the precise mechanisms of how it affects whales has eluded scientists.

Now, researchers have explained key details of how this disruptive signal triggers behavior in some whales that ends in death.

A Cuvier's beaked whale, part of a mass stranding that took place in 1996 in Greece's Kyparissiakos Gulf. **Alexandros Frantzi s/Splashdowndirect /Shutterstock**

Previously, necropsies of beaked whales from multiple stranding incidents found nitrogen bubbles in their body tissues, a hallmark of decompression sickness, or "the bends." This dangerous condition also affects scuba divers when they rise too rapidly from deep water; it can cause pain, paralysis and even death.

Whales are adapted for deep-sea diving, and beaked whales are the record-holders for the longest and deepest dives. But the new research explains how sonar in certain frequencies disorients and terrifies some beaked whales so much that the experience overrides an important adaptation for deep diving: a slower heartbeat. Extreme

fear accelerates a whale's heart rate, which can lead to decompression sickness; the intense pain of this condition incapacitates the whales, so they strand on beaches and eventually die, scientists reported in a new study.

Mass strandings of Cuvier's beaked whales (*Ziphius cavirostris*) were almost unheard of prior to 1960, but that changed with the introduction of midfrequency active sonar (MFAS) in naval exercises in the open ocean. This type of sonar, developed in the 1950s for submarine detection, operates in a range of 4.5 to 5.5 kHz, according to the study.

After this sonar appeared, mass stranding events soon skyrocketed for beaked whales, with 121 such strandings taking place between 1960 and 2004, the researchers wrote.

Scientists first noted a connection between mass strandings of Cuvier's beaked whales and naval exercises using sonar in the late 1980s, lead study author Yara Bernaldo de Quirós, a researcher at the Institute for Animal Health and Food Safety at the University of Las Palmas de Gran Canaria in Spain, told Live Science in an email.

That link strengthened after similar stranding events in Greece in 1996 and in the Bahamas in 2000, de Quíros added. And in September 2002, when 14 beaked whales stranded in the Canary Islands during a NATO naval exercise, veterinary pathologists discovered lesions in the animals that were "consistent with a decompression sickness," de Quirós said.

Fight or flight

In 2017, biologists studying beaked whales gathered for a workshop to analyze findings about strandings from the past decades, looking at mass strandings that were linked to nearby naval exercises using sonar.

Between 2002 and 2014, six mass strandings took place in Greece, the Canary Islands and Almería in southeastern Spain, but the dead whales did not appear to be malnourished or sick.

However, they displayed "abundant gas bubbles" throughout their veins, blood clots in multiple organs and microscopic hemorrhages "of varying severity" in body tissues.

Beached whales may have experienced "a fight or flight response" that overrode a key diving adaptation: the lowering of heart rate, which reduces oxygen consumption and prevents nitrogen accumulation. The result was hemorrhages and "massive bubble formation in their tissues," de Quirós explained.

These symptoms of decompression sickness likely afflicted the whales after they were spooked by sonic blasts, according to the study.

"The temporal and spatial association with naval exercises with use of sonar is very clear," de Quíros said in the email. What's more, behavioral studies have shown that whales that have never encountered sonar (or that have been exposed to it only occasionally) typically exhibit a stronger response than animals living near military outposts, she added.

In 2004, Spain banned sonar in Canary Islands waters, a mass-strandings hotspot. No mass strandings have taken place since the ban was enacted, "proving the effectiveness of this mitigation," de Quíros said.

Based on their findings, the study authors recommended more-widespread bans on military exercises using sonar across the Mediterranean Sea, where atypical mass strandings of beaked whales still take place.

Further research will determine the long-term impact of mass strandings on beaked whale populations, the authors wrote in the study.

The findings were published online today (Jan. 30) in the journal Proceedings of the Royal Society B.

https://wb.md/2DQVLlL

Bone, Joint Infections Treatable With Oral Antibiotics

Oral antibiotic therapy associated with shorter length of hospital stay and fewer complications than intravenous therapy

Ricki Lewis, PhD

A course of oral antibiotics is noninferior to prolonged intravenous antibiotic therapy in managing complex orthopedic infections for some patients, according to results published online today in the *New England Journal of Medicine*.

"In this trial, with regard to treatment failure assessed at 1 year, oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks of treatment for bone and joint infection; our results thereby challenge a widely accepted standard of care," write Ho-Kwong Li, MRCP, of Oxford University Hospitals NHS Foundation Trust and colleagues. "Oral antibiotic therapy was associated with a shorter length of hospital stay and with fewer complications than intravenous therapy."

Because prolonged use of intravenous antibiotics is associated with inconvenience, substantial risks, and higher costs than oral antibiotics, the researchers conducted an open-label, randomized noninferiority trial comparing the two delivery routes. The trial was unblinded to avoid exposing participants to the risks of intravenous placebo.

The researchers recruited adults being treated for bone or joint infection at 26 centers in the United Kingdom. Diagnoses were native osteomyelitis of the extraaxial skeleton, native joint infection requiring excision arthroplasty, prosthetic joint infection, orthopedic fixation device infection, or vertebral osteomyelitis with or without associated diskitis or soft-tissue infection.

Participants were randomly assigned to receive either intravenous or oral antibiotics for the first 6 weeks of therapy, beginning within 7 days after surgery or within 7 days after the start of antibiotic treatment for nonsurgical management. Patients in both groups could continue oral antibiotics after the assessment period.

Rifampin was allowed in both groups. This is a common adjunctive treatment for certain biofilm-associated infections.

Of the 1054 recruited participants, 1015 remained for the modified intention-to-treat group and 909 for the per-protocol analysis. Median total duration of therapy was 78 days (interquartile range, 42-99) in the intravenous group and 71 days (interquartile range, 43-94) in the oral group (P = .63).

Definitive treatment failure within 1 year, which was the primary endpoint for the trial, occurred in 74 of the 506 participants (14.6%) in the intravenous antibiotics group and for 67 of the 509 participants (13.2%) in the oral antibiotics group. Treatment failure was defined as meeting at least one criterion that was clinical (eg, a draining sinus tract arising from bone or a prosthesis or nearby pus), microbiologic (eg, bacteria in biopsy or aspirate), or histologic (eg, inflammatory infiltrate or microorganisms).

The difference in the risk of definitive treatment failure (oral group vs intravenous group) in the intention-to-treat population was −1.4 percentage points (90% confidence interval [CI], −4.9 to 2.2; 95% CI, −5.6 to 2.9), which was within the prespecified boundary for noninferiority criteria of 7.5 percentage points (90% CI) or 5 percentage points (95% CI).

The secondary outcomes of probable or possible treatment failures occurred in 6 of 506 participants (1.2%) in the intravenous group and 10 of 509 participants (2.0%) in the oral group, putting the combined difference of any treatment failure at −0.7 percentage points (90% CI,−4.4 to 3.1; 95% CI, −5.1 to 3.8).

Members of the intravenous group were more likely to discontinue treatment early than those receiving oral treatment (99/523 participants [18.9%] vs 67/523 [12.8%]; P = .006). In addition, complications associated with the intravenous catheter were more

common in the intravenous group (49/523 [9.4%] vs 5/523 [1.0%], $P < .001$).

Incidence of *Clostridium difficile*–associated diarrhea and/or serious adverse events did not differ between the groups. The median hospital stay was 14 days for the intravenous group compared with 11 days for the oral group. Rifampin use did not affect the groups differently.

Patient-reported hip pain improved with time and did not differ in the two groups, but knee pain was better in the oral antibiotic group.

Among patients administering their own medications, medium to high adherence to treatment (the Morisky score) at 42 days was reported from 75 of the 80 patients receiving intravenous antibiotics (93.8%) compared with 283 of 323 participants (87.6%) in the oral group. Among 62 patients in the oral group whose adherence was monitored with a medication event monitoring system, 56 (90.3%) had higher than 95% adherence, with only 3.8% of doses missed.

Helen W. Boucher, MD, from the Tufts Center for Integrated Management of Antimicrobial Resistance, points out limitations of the study in an accompanying editorial. These include the open-label design, infections by multiple pathogens, use of different treatment regimens, heterogeneous infections, and inclusion of few antibiotic-resistant organisms.

"It is noteworthy that oral therapy was associated with as many serious adverse events as intravenous therapy. Close monitoring of outpatients who are taking oral therapy may be warranted; indeed, it may be time to update outpatient parenteral antimicrobial therapy guidelines to include some oral antibiotic regimens," Boucher writes.

Bejon and Walker report support from NIHR Oxford Biomedical Research Center; Li, Briggs, Hemsley, and Romback from NIHR Health Technology Assessment; and Cooke from NIHR Imperial College Biomedical Research Center. Boucher serves as editor of Antimicrobial Agents and Chemotherapy *and* Infectious Disease Clinics of North America, *infectious diseases board member of the American Board of Internal Medicine, and treasurer of the Infectious Diseases Society of America.*

N Engl J Med. 2019;380:425-436, 487-489.

http://bit.ly/2G5xXqi

Fasting ramps up human metabolism, study shows

Research uncovers previously unknown effects of fasting, including notably increased metabolic activity and possible anti-aging effects.

Fasting may help people lose weight, but new research suggests going without food may also boost human metabolic activity, generate antioxidants, and help reverse some effects of aging. Scientists at the Okinawa Institute of Science and Technology Graduate University (OIST) and Kyoto University identified 30 previously-unreported substances whose quantity increases during fasting and indicate a variety of health benefits.

A study by the G0 Cell Unit and Kyoto University researchers suggests that fasting, which puts the body in 'starvation mode,' leads to fuel substitution, antioxidation, increased mitochondrial activation and altered signal transduction. **Credit: OIST**

"We have been researching aging and metabolism for many years and decided to search for unknown health effects in human fasting," said Dr. Takayuki Teruya, first author of the paper and a technician in the OIST G0 Cell Unit, led by Prof. Mitsuhiro Yanagida. "Contrary to the original expectation, it turned out that fasting induced metabolic activation rather actively."

The study, published January 29, 2019 in Scientific Reports, presents an analysis of whole human blood, plasma, and red blood cells drawn from four fasting individuals. The researchers monitored changing levels of metabolites -- substances formed during the chemical processes that grant organisms energy and allow them to grow. The results revealed 44 metabolites, including 30 that were previously

unrecognized, that increased universally among subjects between 1.5- to 60-fold within just 58 hours of fasting.

In previous research, the G0 Cell Unit identified various metabolites whose quantities decline with age, including three known as leucine, isoleucine, and ophthalmic acid. In fasting individuals, these metabolites increase in level, suggesting a mechanism by which fasting could help increase longevity. "These are very important metabolites for maintenance of muscle and antioxidant activity, respectively," said Teruya. "This result suggests the possibility of a rejuvenating effect by fasting, which was not known until now."

Metabolites Give Clues to Mechanism and Health Effects

The human body tends to utilize carbohydrates for quick energy -- when they're available. When starved of carbs, the body begins looting its alternate energy stores. The act of "energy substitution" leaves a trail of evidence, namely metabolites known as butyrates, carnitines, and branched-chain amino acids. These well-known markers of energy substitution have been shown to accumulate during fasting.

But fasting appears to elicit effects far beyond energy substitution. In their comprehensive analysis of human blood, the researchers noted both established fasting markers and many more. For example, they found a global increase in substances produced by the citric acid cycle, a process by which organisms release energy stored in the chemical bonds of carbohydrates, proteins and lipids. The marked increase suggests that, during fasting, the tiny powerhouses running every cell are thrown into overdrive.

Fasting also appeared to enhance the metabolism of purine and pyrimidine, chemical substances which play key roles in gene expression and protein synthesis. The finding suggests fasting may reprogram which proteins cells build at what time, thus altering their function. The change may promote homeostasis in cells, or serve to edit their gene expression in response to environmental influences.

When metabolized, purine and pyrimidine also boost the body's production of antioxidants. Several antioxidants, such as ergothioneine and carnosine, were found to increase significantly over the 58-hour study period. Antioxidants serve to protect cells from free radicals produced during metabolism. Products of a metabolic pathway called the "pentose phosphate pathway" also stay the harmful effects of oxidation, and were similarly seen to increase during fasting, but only in plasma.

Newfound Health Benefits of Fasting?

The authors suggest that these antioxidative effects may stand as the body's principal response to fasting, as starvation can foster a dangerously oxidative internal environment. Their exploratory study provides the first evidence of antioxidants as a fasting marker. In addition, the study introduces the novel notion that fasting might boost production of several age-related metabolites, abundant in young people, but depleted in old.

"Recent aging studies have shown that caloric restriction and fasting have a prolonging effect on lifespan in model animals...but the detailed mechanism has remained a mystery," said Teruya. "It might be possible to verify the anti-aging effect from various viewpoints by developing exercise programs or drugs capable of causing the metabolic reaction similar to fasting."

The findings expand on established ideas of what fasting could do for human health. The next step would be to replicate these results in a larger study, or investigate how the metabolic changes might be triggered by other means.

"People are interested in whether human beings can enjoy the effects of prevention of metabolic diseases and prolonging life span by fasting or caloric restriction, as with model animals," said Teruya. "Understanding the metabolic changes caused by fasting is expected to give us wisdom for maintaining health."

http://bit.ly/2BeID8c

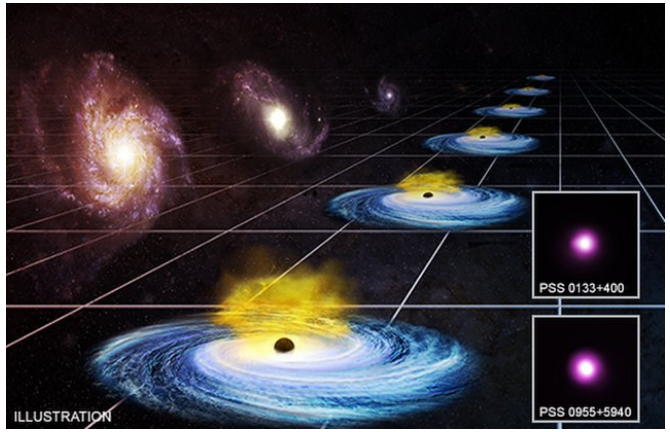
Dark Energy Gets Weirder: Mysterious Force May Vary Over Time

Dark energy is apparently even more mysterious than astronomers had thought.

By Mike Wall, Space.com Senior Writer

Scientists first proposed the existence of this invisible force two decades ago, to explain the surprising discovery that the universe's expansion is accelerating. (Surprising and incredibly important; the find netted three researchers the Nobel Prize in physics in 2011.)

The most-used astrophysical model of the universe's structure and evolution regards dark energy as a constant. Indeed, many astronomers believe it to be the cosmological constant, which Einstein posited in 1917 as part of his theory of general relativity.



Artist's illustration of quasars, along with observations of two of these superbright objects by NASA's Chandra X-ray Observatory (insets). **G.Risaliti & E.Lusso/Illustration: NASA/CXC/M.Weiss; X-ray: NASA/CXC/Univ. of Florence**

But a new study of enormous, superbright black holes known as quasars suggests that dark energy could be miscast as the cosmological constant, or any kind of constant; the force may have varied since the universe's birth 13.8 billion years ago, research team members said.

"We observed quasars back to just a billion years after the Big Bang, and found that the universe's expansion rate up to the present day was faster than we expected," study lead author Guido Risaliti, of the University of Florence in Italy, said in a statement. "This could mean dark energy is getting stronger as the cosmos grows older."

Quasars are fast-growing supermassive black holes at the hearts of galaxies. Quasars' incredible luminosity — they're the brightest objects in the universe — originates in the disks of material that swirl around the black holes. These fast-spinning disks generate huge amounts of ultraviolet (UV) light, some of which slams into electrons in nearby clouds of hot gas. Such interactions can ramp up the UV radiation to X-ray levels, producing a powerful glow across multiple wavelengths of high-energy light.

The correlation between these two types of light can reveal the distance to a quasar, Risaliti and co-author Elisabetta Lusso, of Durham University in England, determined. In the new study, the duo examined this relationship for nearly 1,600 quasars. They used NASA's Chandra X-ray Observatory and the European Space Agency's XMM-Newton spacecraft to observe the quasars' X-ray light, and the ground-based Sloan Digital Sky Survey to analyze the objects' UV output.

Risaliti and Lusso found many of the quasars to be incredibly distant. The most far-flung one, for example, was blasting out huge amounts of light into the cosmos just 1.1 billion years after the Big Bang.

Previous work on the universe's expansion rate — including the landmark late-1990s studies that introduced the concept of dark energy — have generally relied on observations of supernova explosions as "standard candles." Researchers determined the distances to these objects, whose intrinsic brightness is known, and figured out how fast they're moving relative to Earth by analyzing how much their light is "redshifted" (stretched to longer wavelengths).

Supernovas, while dramatic and powerful, are much less luminous than quasars and therefore cannot be observed from as far away. So,

the new study gives researchers another standard candle, which can be used to assess the universe's expansion across a broader stretch of time. But Risaliti and Lusso looked at some supernova measurements as well.

"Since this is a new technique, we took extra steps to show that this method gives us reliable results," Lusso said in the same statement. "We showed that results from our technique match up with those from supernova measurements over the last 9 billion years, giving us confidence that our results are reliable at even earlier times."

The new results are consistent with some earlier observations of relatively nearby supernovas. That previous work found an apparently accelerated expansion rate, compared to that of the early universe (as derived from measurements of the cosmic microwave background, the ancient light left over from the Big Bang).

"Some scientists suggested that new physics might be needed to explain this discrepancy, including the possibility that dark energy is growing in strength," Risaliti said. "Our new results agree with this suggestion."

The new study was published online Monday (Jan. 28) in the journal Nature Astronomy. You can read it for free at the online preprint site arXiv.org.

http://bit.ly/2DQCv7y

Experimental Brain-Computer Interface Translates Brain Signals into Recognizable Speech

Advance marks critical step toward brain-computer interface systems that hold immense promise for those with limited or no ability to speak.

A team of researchers at Columbia University has developed a speech brain-computer interface system that translates brain signals into intelligible, recognizable speech. By monitoring someone's brain activity, the system can reconstruct the words a person hears with unprecedented clarity. The **breakthrough**, reported in the journal ***Scientific Reports***, could lead to new ways for computers to communicate directly with the brain, and lays the groundwork for helping people who cannot speak.

"Our voices help connect us to our friends, family and the world around us, which is why losing the power of one's voice due to injury or disease is so devastating. With today's study, we have a potential way to restore that power. We've shown that, with the right technology, these people's thoughts could be decoded and understood by any listener," said senior author Dr. Nima Mesgarani, principal investigator in the Mortimer B. Zuckerman Mind Brain Behavior Institute at Columbia University.

Early efforts to decode brain signals by Dr. Mesgarani and colleagues focused on simple computer models that analyzed spectrograms, which are visual representations of sound frequencies.

But because this approach has failed to produce anything resembling intelligible speech, the team turned instead to a vocoder, a computer algorithm that can synthesize speech after being trained on recordings of people talking.

"This is the same technology used by Amazon Echo and Apple Siri to give verbal responses to our questions," Dr. Mesgarani said.

"We asked epilepsy patients already undergoing brain surgery to listen to sentences spoken by different people, while we measured patterns of brain activity. These neural patterns trained the vocoder."

Next, the researchers asked those same patients to listen to speakers reciting digits between 0 to 9, while recording brain signals that could then be run through the vocoder.

The sound produced by the vocoder in response to those signals was analyzed and cleaned up by neural networks, a type of artificial intelligence that mimics the structure of neurons in the biological brain. The end result was a robotic-sounding voice reciting a sequence of numbers.

To test the accuracy of the recording, the scientists tasked individuals to listen to the recording and report what they heard.

“We found that people could understand and repeat the sounds about 75% of the time, which is well above and beyond any previous attempts,” Dr. Mesgarani said.

“The improvement in intelligibility was especially evident when comparing the new recordings to the earlier, spectrogram-based attempts. The sensitive vocoder and powerful neural networks represented the sounds the patients had originally listened to with surprising accuracy.”

The study authors now plan to test more complicated words and sentences next, and they want to run the same tests on brain signals emitted when a person speaks or imagines speaking.

Ultimately, they hope their system could be part of an implant, similar to those worn by some epilepsy patients, that translates the wearer’s thoughts directly into words.

Hassan Akbari et al. *2019. Towards reconstructing intelligible speech from the human auditory cortex.* Scientific Reports *9, article number: 874; doi: 10.1038/s41598-018-37359-z*

http://bit.ly/2MKGDZG

Ancient pandas weren't exclusive bamboo eaters, bone evidence suggests

Extinct and ancient panda species most likely had a more varied and complex diet

The giant pandas we know and love today live only in the understory of particular mountains in southwestern China, where they subsist on bamboo alone. In support of their tough and fibrous bamboo diet, they've got distinctive teeth, skull, and muscle characteristics along with a special pseudo-thumb, the better to grasp and hold bamboo stems, leaves, and shoots with. But according to new evidence reported in Current Biology on January 31, extinct and ancient panda species most likely had a more varied and complex diet.

"It has been widely accepted that giant pandas have exclusively fed on bamboo for the last two million years," says Fuwen Wei of Chinese Academy of Sciences. But, "our results showed the opposite."

It's impossible to know exactly what extinct animals ate. But researchers can get clues by analyzing the composition of stable isotopes (different forms of the same element that contain equal numbers of protons but different numbers of neutrons) in animal teeth, hair, and bones, including fossil remains. In the new study, the researchers first analyzed bone collagen of modern pandas (1970s-2000s) and other mammals from the same mountains.

The stable isotopic composition of carbon and nitrogen from modern panda and other modern mammal bone samples indicated three obvious groups: carnivores, herbivores, and giant pandas. The giant pandas were clearly unique, on account of their habit of eating bamboo. Next, Wei's team measured bone collagen isotopes of 12 ancient pandas collected from seven archaeological sites in southern and southwestern China and compared them to the patterns they observed in modern giant pandas.

The data comparison showed that ancient and modern pandas are isotopically distinct from one another, suggesting differences in their dietary habits. There was also more variation among ancient panda species, suggesting that the niche they occupied was about three times wider than that of modern pandas. That is, ancient pandas most likely had a varied diet, similar to that of other mammalian species that lived alongside them. They were, the researchers write, "probably not exclusive bamboo feeders."

The researchers suggest that pandas' dietary habits have evolved in two phases. First, the pandas went from being meat eaters or omnivores to becoming dedicated plant eaters. Only later did they specialize on bamboo.

The researchers say they would now like to figure out when exactly pandas shifted to the specialized diet they have today. To find out, they plan to collect and study more panda samples from different historical times over the last 5,000 years.

This work was supported by the Chinese Academy of Sciences, the National Key Program of Research and Development of the Ministry of Science and Technology, and the Key Project and Creative Research Group Project of the National Natural Science Foundation of China.

Current Biology, Han et al.: "Diet Evolution and Habitat Contraction of Giant Pandas via Stable Isotope Analysis" https://www.cell.com/current-biology/fulltext/S0960-9822(19)30004-1

http://bit.ly/2t4bRSM

Earth's largest extinction event likely took plants first

Plants may have suffered the wrath of the Great Dying long before many animal counterparts

Little life could endure the Earth-spanning cataclysm known as the Great Dying, but plants may have suffered its wrath long before many animal counterparts, says new research led by the University of Nebraska-Lincoln.

About 252 million years ago, with the planet's continental crust mashed into the supercontinent called Pangaea, volcanoes in modern-day Siberia began erupting. Spewing carbon and methane into the atmosphere for roughly 2 million years, the eruption helped extinguish about 96 percent of oceanic life and 70 percent of land-based vertebrates - the largest extinction event in Earth's history.

Yet the new study suggests that a byproduct of the eruption - nickel - may have driven some Australian plant life to extinction nearly 400,000 years before most marine species perished.

"That's big news," said lead author Christopher Fielding, professor of Earth and atmospheric sciences. "People have hinted at that, but nobody's previously pinned it down. Now we have a timeline."

The researchers reached the conclusion by studying fossilized pollen, the chemical composition and age of rock, and the layering of sediment on the southeastern cliffsides of Australia. There they discovered surprisingly high concentrations of nickel in the Sydney Basin's mud-rock - surprising because there are no local sources of the element.

Tracy Frank, professor and chair of Earth and atmospheric sciences, said the finding points to the eruption of lava through nickel deposits in Siberia. That volcanism could have converted the nickel into an aerosol that drifted thousands of miles southward before descending on, and poisoning, much of the plant life there. Similar spikes in nickel have been recorded in other parts of the world, she said.

"So it was a combination of circumstances," Fielding said. "And that's a recurring theme through all five of the major mass extinctions in Earth's history."

If true, the phenomenon may have triggered a series of others: herbivores dying from the lack of plants, carnivores dying from a lack of herbivores, and toxic sediment eventually flushing into seas already reeling from rising carbon dioxide, acidification and temperatures.

'It Lets Us See What's Possible'

One of three married couples on the research team, Fielding and Frank also found evidence for another surprise. Much of the previous research into the Great Dying - often conducted at sites now near the equator - has unearthed abrupt coloration changes in sediment deposited during that span.

Shifts from grey to red sediment generally indicate that the volcanism's ejection of ash and greenhouse gases altered the world's climate in major ways, the researchers said. Yet that grey-red gradient is much more gradual at the Sydney Basin, Fielding said, suggesting that its distance from the eruption initially helped buffer it against the intense rises in temperature and aridity found elsewhere.

Though the time scale and magnitude of the Great Dying exceeded the planet's current ecological crises, Frank said the emerging

similarities - especially the spikes in greenhouse gases and continuous disappearance of species - make it a lesson worth studying.

"Looking back at these events in Earth's history is useful because it lets us see what's possible," she said. "How has the Earth's system been perturbed in the past? What happened where? How fast were the changes? It gives us a foundation to work from - a context for what's happening now."

The researchers detailed their findings in the journal Nature Communications. Fielding and Frank authored the study with Allen Tevyaw, graduate student in geosciences at Nebraska; Stephen McLoughlin, Vivi Vajda and Chris Mays from the Swedish Museum of Natural History; Arne Winguth and Cornelia Winguth from the University of Texas at Arlington; Robert Nicoll of Geoscience Australia; Malcolm Bocking of Bocking Associates; and James Crowley of Boise State University.

The National Science Foundation and the Swedish Research Council funded the team's work.

http://bit.ly/2D69fs9

More die after surgery than from HIV, TB, and malaria combined -- study

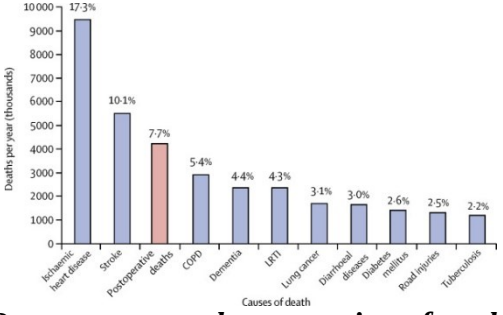
Around the world 4.2 million people die every year within 30 days after surgery - with half of these deaths occurring in low- and middle-income countries (LMICs), a new study reveals.

There is also a significant unmet need for surgery in LMICs and researchers believe that if operations were provided for all patients who need them the number of global post-operative deaths would increase to 6.1 million.

Researchers at the University of Birmingham published their analysis on the numbers of people dying within 30 days of surgery in a research letter to *The Lancet*. They estimate that more people die each year within 30 days after surgery than from HIV, tuberculosis, and malaria combined (2.97 million).

The Lancet Commission on Global Surgery identified that 313 million surgical procedures are performed each year, but little is known about the quality of surgery globally, as robust postoperative death rates are available for only 29 countries.

Researchers at the University's NIHR Global Health Research Unit on Global Surgery analysed available information to estimate how many people around the world die after operations - based on surgical volume, case-mix and post-operative death rates adjusted for country income.



Top ten global causes of death, 2016 Percentages are the proportion of total global deaths attributable to each cause. Data, except those on postoperative deaths, are from the Global Burden of Disease Study 2016.4

COPD=chronic obstructive pulmonary disease. LRTI=lower respiratory tract infections. Dr Dmitri Nepogodiev, Research Fellow at the University of Birmingham, commented: "Surgery has been the 'neglected stepchild' of global health and has received a fraction of the investment put in to treating infectious diseases such as malaria.

"Although not all postoperative deaths are avoidable, many can be prevented by increasing investment in research, staff training, equipment, and better hospital facilities. To avoid millions more people dying after surgery, planned expansion of access to surgery must be complemented by investment in to improving the quality of surgery around the world."

Professor Dion Morton, Barling Chair of Surgery at the University of Birmingham and Director of Clinical Research at the Royal College of Surgeons of England, commented: "Surgery saves lives and can transform patients' quality of life, but this study shows that a large number of patients die in the immediate postoperative period. As efforts continue to increase access to surgery around the world, there is also an urgent need for research to improve the quality and safety of surgery."

The researchers project that expanding surgical services to address unmet need would add another 1.9 million post-operative deaths in LMICs each year. Based on 4.2 million deaths, 7.7% of all deaths globally occur within 30 days of surgery. This figure is greater than that attributed to any other cause of death globally except ischaemic heart disease and stroke .

At present, around 4.8 billion people worldwide lack timely access to safe and affordable surgery and it is estimated that there is an annual unmet need for 143 million procedures in LMICs.

http://bit.ly/2DPz4Ot

Introducing nemuri, a protein that induces sleep and fights infection

Bacteria-fighting peptide also promotes sleep after sleep deprivation or infection

日本のニュース

Researchers have discovered a bacteria-fighting peptide in fruit flies that also promotes sleep after sleep deprivation or infection, according to a new study. The protein, encoded by a gene the authors dubbed nemuri (nur), after the Japanese word for sleep, is secreted more heavily in scenarios of sleep loss.

According to the study's results, it may be particularly important in situations where sleep is critical, including recovering from illness, and its two-pronged activity demonstrates a link between sleep and immune function.

Despite spending a large portion of our lives sleeping, why we sleep and the mechanisms underlying what makes us sleepy are largely unknown.

Previous research has suggested that being awake promotes a buildup of sleep-promoting signals in the nervous system, cumulatively increasing our drive to fall asleep. This drive has also been found to increase during sickness.

However, whether there is a relationship between being tired from a lack of sleep and being under the weather, remains unknown.

Hirofumi Toda and colleagues performed a genetic screen of over 12,000 Drosophila and found a single gene that constantly increased the amount of sleep when overexpressed. According to Toda et al., the nemuri (nur) gene, which encodes the sleep-promoting NUR peptide, is involved in the flies' innate homeostatic need for sleep.

Overexpression of the gene created sleepier flies; by contrast, flies in which nur was mutated woke easily and had difficulty falling asleep.

What's more, in addition to increasing sleep, nur was also shown to increase the ability of the flies to survive bacterial infection.

The study revealed that the NUR peptide, secreted by neurons in the brain, serves a dual purpose - to promote sleep and kill bacteria.

This suggests that NUR is relevant in driving sickness- or stress-induced sleep. Since sleep during illness promotes survival, the sleep promotion of NUR is likely closely linked to its immune function, according to the authors.

While peptides with some similarity have been detected in vertebrates (fish and frogs), they have not yet been detected in mammals.

"The idea that increased sleep during infection is somehow protective is very appealing," write Grigorios Oikonomou and David Prober in a related Perspective. "It agrees with the common experience on the recuperative properties of a good night's sleep..."

http://bit.ly/2TvhxRo

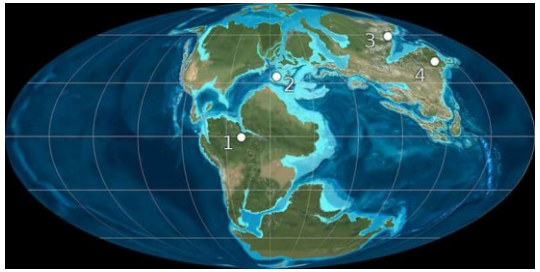
Study finds billion-year superocean cycles in Earth's history

Ancient supercontinents formed and then fell apart through alternating cycles spanning hundreds of millions of years

Curtin researchers believe that ancient supercontinents formed and then fell apart through alternating cycles spanning hundreds of

millions of years that involved superoceans being swallowed and the restructuring of the Earth's mantle.

The research, published in science journal *Precambrian Research*, found the supercontinents assembled and broke up through alternating processes of 'introversion' and 'extroversion.'



Research found that ancient supercontinents formed and then fell apart through alternating cycles spanning hundreds of millions of years. **Curtin University**

The latter process caused supercontinent Rodinia to be turned inside out by tectonic forces, thereby consuming the surrounding superocean and leading to the creation of Pangea, the supercontinent that incorporated almost all of the Earth's landmasses.

Rodinia had formed via 'introversion' where the internal oceans formed during the break-up of previous supercontinent Nuna were consumed.

Lead researcher John Curtin Distinguished Professor Zheng-Xiang Li, from the School of Earth and Planetary Sciences at Curtin University, said the assembly and break-up of supercontinents occurred in alternating cycles of about 600 million years.

"In the past 30 years, researchers have discovered that Pangea-like supercontinents existed at least twice before Pangea, occurring roughly every 600 million years in what is known as the supercontinent cycle," Professor Li said.

"More recently, researchers studying Earth's geochemical records and formation of mineral deposits identified even longer-term variations in these cycles but it was not known why."

Professor Li and his team of Curtin researchers, funded by the Australian Research Council's Laureate Fellowship grant, recently discovered that the answer to this question could be found in the history of some of Earth's deepest oceans.

"We found that supercontinents appear to assemble through two alternating processes of extroversion and introversion," Professor Li said.

"More intriguingly, these two alternating processes determine not only whether the superocean survives, but also whether the circum-superocean Ring of Fire—like the present-day Pacific Ring of Fire – survives.

"If the Ring of Fire survives along with the superocean, then the Earth's mantle structure maintains a similar pattern to the previous supercontinent. If not, then the mantle gets completely reorganised.

"Such alternating ways of supercontinent assembly, along with the survival or regeneration of the superocean and the Ring of Fire, led to the presence of an Earth cycle twice as long as the 600-million-year supercontinent cycle and influenced the formation of some of the planet's resources."

Z.X. Li et al. Decoding Earth's rhythms: Modulation of supercontinent cycles by longer superocean episodes, Precambrian Research (2019). DOI: 10.1016/j.precamres.2019.01.009

http://bit.ly/2DRPZA8

More mysterious brain injuries in Cuba; Canada halves staff after new case

Cuba fumes that Canada's actions "do not help find answers."

Beth Mole

The Canadian government announced Wednesday that it will halve the number of diplomats at its embassy in Cuba after a 14th Canadian has mysteriously fallen ill with brain injuries there.

The latest case from December suggests that the enigmatic incidents—which began in late 2016 and have been considered by the US government to be attacks—are still ongoing, straining relations between Cuba and the US, and now Cuba and Canada.

Josefina Vidal, Cuba's ambassador to Canada, called the decision Wednesday "incomprehensible."

"This behavior favors those who in the United States use this issue to attack and denigrate Cuba," she wrote in a statement. "It is well known that some individuals with high-level positions within US foreign policy are trying very hard to create a climate of bilateral tension seeking to portray our country as a threat."

The latest confirmed Canadian case concerns a senior government official who arrived in Cuba over the summer and reported symptoms on December 29, officials said. Symptoms generally include nausea, dizziness, trouble concentrating, and headaches. Medical experts in the US with access to affected US cases confirmed the presences of mild traumatic brain injuries and described "injury to widespread brain networks without an associated history of head trauma."

US officials have confirmed 26 American cases, many of which were associated with episodes involving unexplained, irritating sounds, pressure, and vibrations.

International tension

In September of 2017 and March of 2018, the US government announced pull-backs of diplomates from its embassy in Cuba, which is operating only with a skeleton crew.

Canada had not issued such draw-downs until now, working collaboratively with the Cuban government to try to identify the cause of the injuries. However, in April of 2018, the government designated Cuba as an "unaccompanied" post, meaning diplomats were not allowed to bring their families. With Wednesday's announcement, staff at the Canadian embassy will go from about 16 positions to no more than eight.

Cuba is a popular tourist destination for Canadians, and the Canadian government noted that "[t]here is no evidence that Canadian travelers to Cuba are at risk." The US government, on the other hand, has issued a level 2 travel advisory, urging travelers to "exercise increased caution."

Conspiracies and crickets

Meanwhile, the three governments seem no closer to determining the cause of the injuries and illnesses, despite a wide range of ideas being floated. Scientists and experts have discussed the possibility that microwave assaults, sonic weapons, malfunctioning surveillance equipment, chemical agents, viruses, and mass delusions may be the cause.

In late 2017, a panel of Cuban scientists speculated that the noise associated with some of the injuries may have simply been crickets—the Jamaican field cricket (*Gryllus assimilis*) to be exact. This month, a US biologist and a British entomologist released a paper speculating that a different cricket—the Indies short-tailed cricket (*Anurogryllus celerinictus*)—may explain the noise. Neither theory provides an explanation for the brain injuries, however.

Cuba's Vidal added in her statement that Canada's decision to remove staff won't help clear the air. "Cutting Canada's staff at its Embassy in Cuba and adjusting the mission's programs are actions that do not help find answers," she wrote.

Since the reports of the mysterious incidents and ailments came to light in Cuba, US diplomats in China have reported similar experiences and injuries.

http://bit.ly/2GkYipV

Molecules Found in Ginger Remodel the Microbiome

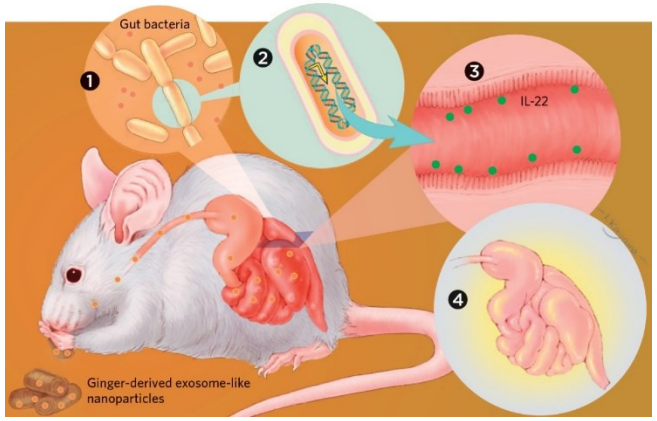
Small RNA-containing particles in ginger root are found to promote the growth of beneficial bacteria and alleviate colitis in mouse guts.

Katarina Zimmer

When Huang-Ge Zhang was younger, his parents would often make him ginger tea when he was ill. Now, as a microbiologist at the University of Louisville in Kentucky, Zhang investigates the

mechanisms through which ginger and other edible plants might affect health.

In previous studies, he had found that exosome-like nanoparticles (ELNs)—small extracellular vesicles that often contain RNA—derived from plants such as broccoli and ginger can help prevent alcohol-induced liver damage and artificially induced colitis in mouse models. Recently, when he sequenced ginger-derived ELNs (GELNs), he found that they contained many microRNAs. This made him wonder whether the edible plant RNA could be taken up by gut bacteria and drive expression of bacterial genes—something that human fecal microRNAs have been shown to do in mice.



***GINGER FEAST: Using a mouse model of colitis, researchers studied the effects of ginger-derived exosome-like nanoparticles (GELNs) on gut flora. The team found that GELNs are preferentially taken up by* Lactobacillus *gut bacteria, and boost their abundance (1). The particles contain microRNAs, which stimulate a suite of bacterial genes (2). In particular, they activate a pathway that results in the expression of interleukin-22 in colon mucus (3). This is believed to promote tissue repair and antimicrobial immunity, ultimately improving colitis symptoms in the mice (4). See full infographic:* WEB | PDF © Ikumi Kayama, Studio Kayama**

To find out, Zhang and his colleagues fed purified GELNs to mice, and analyzed the makeup of their gut microbes by sequencing the 16S rRNA gene. The researchers found a substantial increase in *Lactobacillaceae*—a family of beneficial bacteria often used as probiotics—in GELN-treated mice compared to mice given a neutral medium.

In vitro cultures also showed that GELNs promoted the growth of *Lactobacillus rhamnosus* and several other *Lactobacillus* species—but ELNs from grapefruit had the opposite effect.

To see if the GELN mechanism could translate to beneficial health effects, Zhang and his collaborators induced colitis in mice using the chemical dextran sulfate sodium, which causes ulcers and lesions in the gut lining similar to human colitis. After consuming GELN RNAs, the mice showed improvements in their colitis symptoms. By contrast, control mice that had been given particles of scrambled RNA encapsulated in GELN-derived lipid did not.

Further experiments suggested that the microRNAs contained in GELNs activate a suite of bacterial genes, including an enzyme in *L. rhamnosus* that activates a pathway that triggers the expression of the cytokine IL-22 in colon mucus. IL-22 has been shown in other studies to promote tissue repair at the gut lining, and is therefore thought to ameliorate colitis symptoms.

Zhang says the results are a proof of concept that plant-derived ELNs can affect microbiome composition and health, and present "a new avenue for future studies." He is in the process of constructing a library of other ELNs derived from vegetables and fruit—"not just ginger," he says—so that he can test how they affect the microbiome.

For University of Minnesota geneticist Ran Blekhman, who was not involved in the study, the findings illustrate "a remarkable mechanism of these interactions between the diet, the microbes, and the host."

Many studies establish correlations between dietary interventions and changes in the microbiome, whereas very few examine the molecular mechanisms involved, he notes. "In general, there should be a lot more studies like this."

EDITOR'S CHOICE IN Microbiology

The paper: Y. Teng et al., "Plant-derived exosomal microRNAs shape the gut microbiota," Cell Host Microbe, 24:637–52, 2018.

https://wb.md/2D53yuo

Updated Beers Criteria Guide Drug Use in Elders

The American Geriatrics Society (AGS) has released the 2019 update to the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

Ricki Lewis, PhD

The update was published online January 29 in the *Journal of the American Geriatrics Society*.

"Medications play an important role in health and well-being for many older people," Donna M. Fick, PhD, RN, FGSA, FAAN, a co-chair of the expert panel responsible for the 2019 AGS Beers Criteria, said in a news release. "With this new update, we hope the latest information on what makes medications appropriate for older people can play an equally important role in decisions about treatment options that meet the needs of older adults while also keeping them as safe as possible."

The Beers Criteria are intended to improve medication selection, reduce adverse drug events, and provide a tool to assess cost, patterns, and quality of care of drugs used for people aged 65 years or older. It lists drugs that should be avoided in the treatment of older adults, either generally or in patients with specific diseases or conditions. Clinicians, researchers, educators, healthcare administrators, and regulators use the criteria, which were first published in 1991 and have been updated every 3 years since 2011.

The 2019 criteria include 30 medications or medication classes to be avoided in older adults in general and 40 medications or medication classes that should be used with caution or avoided in certain patients with certain diseases or conditions. Two criteria were added in response to the worsening opioid crisis — not prescribing opioids with benzodiazepines or gabapentinoids.

The criteria dropped eight seizure medications, eight drugs for insomnia, and vasodilators for syncope. Some of these drugs were dropped because the problems associated with their use are not unique to older patients. Two — ticlopidine and pentazocine — were dropped because they are no longer available in the United States.

Removed From the Criteria

H2-receptor antagonists were removed from the criteria because the evidence that they harm people with dementia is weak. The drugs, which relieve gastric reflux, can continue to be used in patients with delirium.

The chemotherapeutic drugs carboplatin, cisplatin, vincristine, and cyclophosphamide were removed from the criteria because the panel considered them to be "highly specialized" and outside the scope of the criteria.

"Use With Caution"

Dextromethorphan/quinidine should be used with caution because it has limited efficacy in alleviating behavioral symptoms of dementia in patients without pseudobulbar affect and because it potentially increases the risk for falls and drug-drug interactions.

Rivaroxaban is to be used with caution for venous thromboembolism or atrial fibrillation in patients older than 75 years because of the risk for gastrointestinal bleeding.

Trimethoprim and sulfamethoxazole can elevate risk for hyperkalemia in patients with decreased kidney function who are taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Carbamazepine, mirtazapine, oxcarbazepine, serotonin, norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, and tramadol should be used with caution because they may exacerbate or cause SIADH (syndrome of inappropriate antidiuretic hormone secretion). Sodium levels should be monitored closely when using these drugs.

Aspirin should be used with caution for primary protection against cardiovascular disease or colorectal cancer in patients older than 70

years, not 80 years, because new data show that the age at which the risk for bleeding is elevated has fallen.

Serotonin and norepinephrine reuptake inhibitors should be prescribed with caution for patients at risk of falling or sustaining fractures.

Also New

For Parkinson's disease, the general advice to avoid all antipsychotics has been revised to accept quetiapine, clozapine, and pimavanserin.

For heart failure, nondihydropyridine and calcium channel blockers should not be prescribed for patients with low ejection fractions, and nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, thiazolidinediones, and dronedarone should be prescribed with caution in patients who have no symptoms of heart failure.

Macrolides (except azithromycin) or ciprofloxacin should not be prescribed with warfarin owing to bleeding risk.

Ciprofloxacin and theophylline should not be prescribed owing to increased theophylline toxicity.

For patients with reduced kidney function, use of ciprofloxacin is associated with increased risk for tendon rupture and increased central nervous system effects. Use of trimethoprim-sulfamethoxazole is associated with worsening renal failure and hyperkalemia.

"The AGS Beers Criteria are an essential evidence-based tool that should be used as a guide for drugs to avoid in older adults. However, they are not meant to supplant clinical judgment or an individual patient's preferences, values, care goals, and needs, nor should they be used punitively or to excessively restrict access to medications," the authors conclude.

Limitations of the criteria are that consideration was given only to studies published in English, including observational studies, and consideration was not given to subpopulations of patients.

In an accompanying editorial, panel members Michael A. Steinman, MD, Division of Geriatrics, the University of California, San Francisco, and Donna Fick, PhD, RN, the College of Nursing and the College of Medicine, Pennsylvania State University, Hershey, remind readers that the drugs that were deemed unsafe for older patients in the 2019 criteria are potentially inappropriate, not definitely inappropriate, and advise close reading of the details.

"Optimal application of the AGS Beers Criteria involves identifying potentially inappropriate medications and where appropriate offering safer nonpharmacologic and pharmacologic therapies," they write. Clinicians should view the criteria as a starting point for individual prescribing.

"Assuring the safe and effective use of medications by older adults is a cornerstone of high-quality medical care and a superb arena for interprofessional practice. Use the AGS Beers Criteria well, and use them wisely," Steinman and Fick conclude.

For the 2019 update, an expert panel reviewed evidence published since the last update to evaluate whether to add, remove, or change specific criteria. The 13 members of the panel were physicians, pharmacists, or nurses who had participated in the 2015 update.

The panel fully reviewed 1422 articles. Of those, 377 were abstracted into evidence tables; these articles included 29 controlled clinical trials, 281 observational studies, and 67 systematic meta-analyses and/or reviews. Comments were collected from August 13, 2018, to September 4, 2018, and included 79 comments from 47 individuals, 10 comments from six pharmaceutical companies, and 155 comments from 22 peer organizations.

Beizer consults for Wolters-Klewer. Brandt consults for Institute for HealthCare Improvement, is section editor for SLACK, Inc, and received a grant from IMPAQ on MTM. Fick consults for SLACK Inc and Precision Health Economics. Hollmann reviews physicians for CVS/Caremark. Linnebur consults for the Colorado Access Pharmacy and Therapeutics Committee. Semla is an editor for Lexi-Comp. Steinman consulted for iodine.com. The remaining authors have disclosed no relevant financial relationships.

J Am Geriatr Soc. Published online January 29, 2019. Abstract, Editorial

http://bit.ly/2DQtvQ2

Suicide can't be predicted by asking about suicidal thoughts, major Australian study shows

The majority of people who die by suicide deny having suicidal thoughts when asked by doctors in the weeks and months leading up to their death, a ground-breaking UNSW Sydney study has found.

The research questions a widely held belief that suicide can be accurately predicted by psychiatrists and clinicians by assessing a patient's risk, especially in the short-term.

The meta-analysis, co-authored by clinical psychiatrist and Conjoint Professor Matthew Large from UNSW's School of Psychiatry, is published today in the journal *BJPsych Open*.

The review of data from 70 major studies of suicidal thoughts shows that, as a stand-alone test, only 1.7% of people with suicidal ideas died by suicide. About 60% of people who died by suicide had denied having suicidal thoughts when asked by a psychiatrist or GP.

"We know that suicide ideas are pretty common and that suicide is actually a rare event, even among people with severe mental illness," said Professor Large, an international expert on suicide risk assessment who also works in the emergency department of a major Sydney hospital. "But what we didn't know was how frequently people who go on to suicide have denied having suicidal thoughts when asked directly," he said.

The study showed that 80% of patients who were not undergoing psychiatric treatment and who died of suicide reported not to have suicidal thoughts when asked by a GP.

"This study proves we can no longer ration psychiatric care based on the presence of suicidal thoughts alone. Hospital and community care teams in Australia are extremely under-resourced, and this needs to change. We need to provide high-quality, patient-centred care for everyone experiencing mental illness, whether or not they reveal they are experiencing suicidal thoughts."

Professor Large said that clinicians should not assume that patients experiencing mental distress without reporting suicidal ideas were not at elevated risk of suicide. Asking about suicidal thoughts was a central skill for health professionals, he said, but clinicians should be not be persuaded into false confidence generated by a lack of ideation.

"Doctors sometimes rely on what is known as suicidal ideation - being preoccupied with thoughts and planning suicide - as a crucial test for short-term suicide risk, and it has been argued it could form part of a screening test for suicide," said the study's lead author, Dr Catherine McHugh, a registrar psychiatrist. "Our results show that this is not in the best interests of patients.

"Some people will try to hide their suicidal feelings from their doctor, either out of shame or because they don't want to be stopped. We also know that suicidal feelings can fluctuate rapidly, and people may suicide very impulsively after only a short period of suicidal thoughts."

The main message, said Professor Large, was that clinicians should give less weight to suicidal ideation than had been the case. "It means trying to better understand the patient's distress and not making patients wait weeks for treatment or denying treatment in the absence of suicidal thoughts."

There was also an important message for people bereaved of a loved one after a suicide, said Professor Large. "Even if they knew their relative was suicidal, the risk of death was low. And it was not their fault if they did not know someone was suicidal."

http://bit.ly/2G8d8R8

Watching brains on acid using an MRI

Acid may limit the brain's ability to tell internal ideas from external events.

John Timmer

What exactly happens in a brain when it is hit by a hallucinogen? Lots of drugs have effects that are obvious extensions of our normal body processes; they raise moods, dull pain, or boost our energy. But hallucinogens are notable for giving their users experiences that are anything but normal.

***Enlarge* / LSD blotter paper campusdrugprevention.gov**

Now, a team of Swiss researchers has used MRI imaging to follow the brain as it's under the influence of acid. And their results support the idea that hallucinogens cause the breakdown of the system that helps the brain keep track of which information is coming from the real world and which is generated by the brain itself.

Cortex overload

The brain receives a steady flow of information, some from the outside world, some from the body, and some generated by its internal thought processes. Your brain has to essentially decide which of it to take seriously and raise to the level of consciousness, which to monitor subconsciously, and which to discard. Hallucinations, whether due to drugs or mental disorders, appear to involve a breakdown in this information processing.

We have some idea of the different brain structures responsible for this processing. The cerebral cortex appears critical for consciousness, perception, and attention, for example. The thalamus also appears to be involved in consciousness and helps relay sensory signals to other areas of the brain. Based on this and additional research, neuroscientists have proposed that the thalamus acts as a gatekeeper for sensory information flowing into the cortex.

In this model, hallucinogens suppress this gatekeeping function. As a consequence, the cortex gets overwhelmed by information and starts losing track of information, leading to a flood of intense sensations and other cognitive disruptions. The idea is consistent with a lot of data we have, but it's an extremely difficult idea to test. After all, people using hallucinogens aren't reliable witnesses to anything, much less their internal brain state.

To get at this question, the researchers behind the new work got ahold of a healthy supply of LSD and an MRI machine. These were combined with a technique that was developed relatively recently called dynamic causal modeling.

Functional meets causal

Normally, functional MRI (fMRI) imaging involves getting someone to perform a task and then comparing the brain's activity during the task to its resting activity. This method is great if you want to isolate a specific process, but it's not especially useful if you want to identify global changes in brain activity, like those caused by LSD.

In this work, however, the researchers focused on the brain's activity in two resting states: with and without acid. Even when seemingly doing nothing, our brain experiences waves of activity. Some brain regions signal independently of each other, while others have linked activity—one region's firing triggers another's. Since there's so much going on in the brain, it's tough to tell these situations apart.

That's where dynamic causal modeling comes in. It involves researchers making a predictive model and then having an algorithm see whether real-world data can fit the model by tweaking the strength of the connections in it.

While it's a complicated process, you can think of it as a way of checking whether the firing we see during normal brain activity is consistent with the connections we think are present in the brain.

To do the comparison, the researchers used three different conditions: a group of control subjects, a group that had taken LSD, and a group that took both LSD and a second drug. LSD, as it turns out, binds to a lot of proteins in the brain, including multiple

receptors for serotonin and dopamine.The additional drug in these experiments, called Ketanserin, blocks just one of the serotonin receptors. But that's enough to block most of the subjective experiences of being on acid. So while we might expect LSD to change a lot of activity that isn't relevant to its hallucinogenic effects, the combination of the two drugs should help us identify which of these changes is most relevant to the issue at hand.

The researchers' model testing identified a number of changes driven by LSD that aren't altered by Ketanserin, suggesting they're not central to the hallucinations. And it identified another set of connections that appeared to be critical to the hallucinogenic effects.

Gatekeeper or organizer?

Overall, these effects were consistent with the model, in which the thalamus acts as a gatekeeper for the cerebral cortex. But instead of a general flooding of the cortex, they found that a limited number of specific regions saw increased activity. This suggests the states induced by hallucinogens are distinct from states like anesthesia and sleep, which lead to widespread changes in the cortex. To some extent, this is a "duh!" finding, given that you can hold conversations with people on acid. But it's an important finding for future studies that want to further tease out how hallucinogens work.

Of course, LSD isn't the only hallucinogen out there; other studies have looked at ayahuasca and psilocybin. These results are generally consistent with the ones reported here but have also suggested that psychedelic drugs may simply lead to a disorganization of signaling within the brain. And at our current level of understanding, it's not possible to distinguish between these two models.

Which of course means that the folks in Zurich are going to be lining up additional volunteers to take some acid and find out if it makes sitting in an MRI tube entertaining.

PNAS, 2019. DOI: 10.1073/pnas.1815129116 (About DOIs).

http://bit.ly/2G7Bfzu

Unusual sugar from cyanobacteria acts as natural herbicide

Natural substance that could compete with the controversial herbicide glyphosate

Researchers at the University of Tübingen have discovered a natural substance that could compete with the controversial herbicide glyphosate: a newly discovered sugar molecule synthesized from cyanobacteria that inhibits the growth of various microorganisms and plants but is harmless to humans and animals. The joint study was led by Dr. Klaus Brilisauer, Professor Stephanie Grond (Institute of Organic Chemistry) and Professor Karl Forchhammer (Interfaculty Institute of Microbiology and Infection Medicine). It was published in the journal *Nature Communications* on Friday.

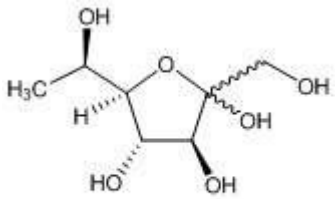
Active ingredients for pharmaceutical or agricultural use often originate from natural substances. These substances can consist of complex chemical structures, but can also be relatively simple. The ingenuity of such active ingredients often lies in their simplicity: Antimetabolites interact with vital processes in the cell by mimicking metabolic products. This disrupts the biological process, which can inhibit cell growth or even kill the cell.

Chemists and microbiologists at the University of Tübingen discovered an unusual antimetabolite with a simple chemical structure: a sugar molecule with the scientific name 7-deoxy-sedoheptulose (7dSh). Unlike ordinary carbohydrates, which usually serve as an energy source for growth, this substance inhibits the growth of plants and microorganisms, such as bacteria and yeasts. The sugar molecule blocks a key enzyme of the shikimate pathway, a metabolic pathway that occurs only in microorganisms and plants. For this reason, the scientists classify the substance as harmless for humans and animals, and have already demonstrated this in initial studies.

The rare deoxy sugar was isolated from cultures of the freshwater cyanobacterium Synechococcus elongatus, which is able to inhibit the growth of related bacterial strains.

While searching for the cause of this growth inhibition, scientists deciphered the structure of the natural compound.

Through a newly developed method for the production of 7dSh – a chemoenzymatic synthesis – the scientists were able to conduct extensive studies to determine the molecular mechanism of 7dSh.



7-desoxy-Sedoheptulose

Chemical structure of 7dSh. **Klaus Brilisauer**

The scientists used coupled high-resolution mass spectrometry to obtain precise insights into the inhibition mechanism and discovered that 7dSh blocks Dehydroquinatesynthase (DHQS), an enzyme of the shikimate pathway. One of the best-known inhibitors of this metabolic pathway to date is the controversial herbicide glyphosate.

"In contrast to glyphosate, the newly discovered deoxy sugar is an entirely natural product that is believed to have good degradability and low ecotoxicity," says Dr. Klaus Brilisauer. So far, 7dSh inhibits plant growth promisingly.

"We see an excellent opportunity here to use it as a natural herbicide."

Scientists hope to replace controversial herbicides in the long term and thus reduce herbicide metabolites, which pose a health risk. However, effectiveness in the field, degradability in the soil and harmlessness to livestock and humans would have to be further investigated in comprehensive long-term studies for 7dSh.

More information: *Klaus Brilisauer et al. Cyanobacterial antimetabolite 7-deoxy-sedoheptulose blocks the shikimate pathway to inhibit the growth of prototrophic organisms, Nature Communications (2019).* *DOI: 10.1038/s41467-019-08476-8*

https://wb.md/2D4bUm4

Top Hope Among Advanced Cancer Patients Is Not Cure

Caveat: Survey Pre-dates Immunotherapy Whirlwind

Nick Mulcahy

What do American metastatic cancer patients hope for from their cancer treatment? Most commonly, they desire a good quality of life, according to a rare large survey on the subject in this patient population.

Cure was not even in the top five responses among the 216 participating patients, report Jeremy DeMartini, MD, Department of Psychiatry, University of California, Davis, and colleagues in a new study published in the January issue of the *Journal of Pain and Symptom Management*.

The most prevalent hope (42% of the total responses) was maintaining quality of life.

Life extension (32%) ranked second, followed by tumor stabilization (26%), remission (20%), reaching a milestone (such as seeing a child married; 14%), and "unqualified" cure (12%). Another 5% had hope for a cure that was "tempered by realism" (such as hoping for a cure, but admitting it was not possible). Thus, even if both cure categories were combined, they still only accounted for 17% of the patients' expressed hopes.

However, the new study has an important caveat: the survey was part of a trial conducted from 2012 to 2014, before immunotherapy received widespread publicity — and hype — about improving survival and potentially curing some patients with advanced cancer.

In short, the survey data may be dated, to some extent.

Times have changed, acknowledged DeMartini in an email to *Medscape Medical News*.

"Immunotherapy and the promise of other new treatments for many types of cancer bring hope to patients and physicians alike," he said.

Clinicians who want to put the survey results into practice may struggle, suggested Bishal Gyawali, MD, PhD, of Brigham and Women's Hospital in Boston, in a comment posted on his Twitter feed about the new results.

That's because, in terms of drug treatment, quality of life is not well reported, said Gyawali, who was not involved in the study.

"Unfortunately nearly half of cancer drug trials don't even include QoL as an endpoint and, those that do, a quarter won't report it," he tweeted, citing a 2018 study.

However, the study authors do not discuss this failing.

DeMartini said that cancer drugs "are not side-effect free" and that advanced cancer patients and their physicians must balance the related risks and benefits. The authors say that "little is known" about advanced cancer patients' hopes for their treatment.

Other studies on the subject have had shortcomings, they say, citing small sample sizes, inclusion of patients with serious illnesses other than advanced cancer, andinclusion of small subsets of cancer types. Asked if the lack of substantial data was a surprise given the importance of the matter, DeMartini responded: "Yes!"

Authors Concerned About Hopes for Cure

The new study comes from the VOICE trial, a patient communication study. The investigators surveyed 265 patients at the University of Rochester and University of California, Davis; these patients had a variety of advanced cancers, including 50% that were categorized as "aggressive." After 3 months, 45 patients died and four dropped out of the study, leaving 216 patients for the final results.

At baseline, patients' hopes were elicited in interviews by investigators, who asked the open-ended question, "What are you hoping for…in your cancer treatment?"

Subsequent interviews at 3 months yielded another set of answers, but the relative prevalence of the responses "did not change substantially" from baseline, say the authors.

In other words, quality of life was still the top hope in the second interview. And cure was still toward the bottom.

The study locations are one of its limitations. The authors explain: "Our results may not be generalizable to the entire population of advanced cancer patients because patients were recruited from only two geographic areas, and the sample was predominately white, Christian, and well educated."

The study used open-ended interviewing, which the team transcribed and analyzed. This resulted in eight categories of hopes, as noted above, into which 95% of patients' responses could be categorized at both the baseline and 3 months.

The study also asked patients about the discussions they had concerning their hopes for cancer treatment, and with whom they discussed these hopes.

Most patients reported discussing treatment hopes with partners, family/friends, and oncologists. A minority reported discussing hopes with nurses, primary care physicians, clergy, or support groups.

In logistic regression analysis, unqualified hopes for cure were more likely in younger patients and those who did not discuss their hopes with primary care physicians, write the authors.

DeMartini explained: "While primary care physicians don't typically directly treat cancer itself, they may have a longstanding and holistic relationship with the patient that is helpful in focusing or reframing hopes."

The study authors hope clinicians ask patients about their hopes for treatment — in order to address probable reality. The authors repeatedly state their concern about the "sizeable minority" of patients who express hope for a cure, despite having metastatic disease.

The study was supported by the National Cancer Institute.DeMartini, his coauthors, and Gyawali have disclosed no relevant financial relationships.

Journal of Pain and Symptom Management. Published online January 2019. Full text