http://www.eurekalert.org/pub_releases/2015-12/nsfc-rfm121715.php

Rare full moon on Christmas Day

Not since 1977 has a full moon dawned in the skies on Christmas. But this year, a bright full moon will be an added gift for the holidays.

December's full moon, the last of the year, is called the Full Cold Moon because it occurs during the beginning of winter. The moon's peak this year will occur at 20:11 p.m. Japan Standard Time. This rare event won't happen again until 2034. That's a long time to wait, so make sure to look up to the skies on Christmas Day.

As you gaze up at the Christmas moon, take note that NASA has a spacecraft currently orbiting Earth's moon. NASA's Lunar Reconnaissance Orbiter (LRO) mission has been investigating the lunar surface since 2009.

"As we look at the moon on such an occasion, it's worth remembering that the moon is more than just a celestial neighbor," said John Keller, NASA's Goddard Space Flight Center in Greenbelt, Maryland. "The geologic history of the moon and Earth are intimately tied together such that the Earth would be a dramatically different planet without the moon."

LRO has collected a treasure trove of data with its seven powerful instruments, making an invaluable contribution to our knowledge about the moon.

http://www.eurekalert.org/pub_releases/2015-12/cp-sla121015.php

Study links autism symptoms to change in brain chemistry

Researchers reporting in the Cell Press journal Current Biology on December 17 have uncovered a direct link between the behavioral symptoms of people with autism and reduced action of an inhibitory neurotransmitter called GABA.

GABA's primary responsibility is to dampen neural activity in the brain.

The findings suggest that drugs that increase brain concentrations of GABA might have potential for autism treatment, the researchers say. "These findings mark the first empirical link between a specific neurotransmitter measured in the brains of individuals with autism and an autistic behavioral symptom," says Caroline Robertson of Harvard University and MIT's McGovern Institute for Brain Research.

Earlier evidence from genetic studies and animals had suggested an important role of GABA signaling in autism, but direct empirical evidence in humans had been lacking. Studies also showed that people with autism spectrum disorders are slower at a phenomenon called binocular rivalry, which is known to involve inhibition in the brain.

In binocular rivalry, two conflicting images are presented simultaneously, one to each eye. To make out one image or the other, the brain must inhibit neural signals to push one out of visual awareness. Typically, developing individuals suppress a visual image from awareness for many seconds at a time. People with autism, on the other hand, struggle to suppress the visual images.

Robertson, senior author Nancy Kanwisher of MIT, and their colleagues wanted to find out whether this difficulty could be traced to differences in GABA levels in the autistic brain. They asked 21 people with autism and 20 typical control individuals to complete a binocular rivalry task. As expected, adults with autism were slower to suppress the visual images.

The researchers then used magnetic resonance spectroscopy to measure GABA concentrations in the brain while individuals completed the task. Those measurements showed a strong link in typical control participants between binocular rivalry dynamics and levels of GABA. That connection between perception and GABA brain chemistry was completely absent in the brains of people with autism.

"Individuals with autism are known to have detail-oriented visual perception--exhibiting remarkable attention to small details in the sensory environment and difficulty filtering out or suppressing irrelevant sensory information," Robertson says. "It's long been thought this might have something to do with inhibition in the brain, and our findings lend support to this notion." They note, however, that the GABA dysfunction that they've uncovered may vary substantially among people on the autism spectrum. There are also many other neurotransmitters that may play important roles in the behavioral manifestations of autism.

Further studies by the researchers will examine the genetic basis of the GABA imbalance. They are also examining binocular rivalry dynamics in children with autism and the potential of this phenomenon to serve as an early diagnostic marker.

This work was funded by a Harvard Milton Fund award, a NARSAD Young Investigator award, an MIT-MGH Strategic Partnership grant, and a grant from the Simons Center for the Social Brain.

Current Biology, Robertson et al.: "Reduced GABAergic Action in the Autistic Brain" http://dx.doi.org/10.1016/j.cub.2015.11.019

http://www.eurekalert.org/pub_releases/2015-12/uov-spa121715.php

Scientists peg Anthropocene to first farmers

Study shows 300-million-year natural pattern ended 6,000 years ago because of human activity

A new analysis of the fossil record shows that a deep pattern in nature remained the same for 300 million years. Then, 6,000 years ago, the pattern was disrupted -- at about the same time that agriculture spread across North America.

"When early humans started farming and became dominant in the terrestrial landscape, we see this dramatic restructuring of plant and animal communities,"

said University of Vermont biologist Nicholas Gotelli, an expert on statistics and the senior author on the new study.

In the hunt for the beginning of the much-debated "Anthropocene" -- a supposed new geologic era defined by human influence of the planet -- the new research suggests a need to look back farther in time than the arrival of human-caused climate change, atomic weapons, urbanization or the industrial revolution.

"This tells us that humans have been having a massive effect on the environment for a very long time," said S. Kathleen Lyons, a paleobiologist at the Smithsonian's National Museum of Natural History who led the new research.

The study was published Dec. 16 in the journal *Nature*.

Species split

Gotelli and Lyons were part of a team of 29 scientists, supported by the National Science Foundation, who studied plant and animal datasets from both modern ecosystems and the fossil record stretching back to the Carboniferous Period, well before the emergence of the dinosaurs.

Examining thousands of pairs of species, the scientists looked to see how often a particular pair of plant or animal species was found within the same community. Analyses of modern communities of plants and animals have shown that, for most pairs of species, the presence of one species within a community does not influence whether the other is present or absent. "We don't expect much interaction between, say, a woodpecker and an earthworm," Gotelli explains.

But some pairs of species appear to be "aggregated," meaning they tend to appear together in nature more often than one would expect by chance -- like cheetahs and giraffes who both depend on savannah habitats. Other species are "segregated," meaning that when one is found, it's unlikely to find the other there too -- "say two species of woodpecker that compete for insect prey," Gotelli says -- being driven apart by, perhaps, different habitat needs or fierce competition, so that they occur together less often than would be expected by chance.

For modern communities of plants and animals, recent studies show that segregated species pairs are more common than aggregated ones. But when the team investigated the composition of ancient communities using data from fossils, they were surprised to find the opposite pattern: from 307 million years ago to about 6,000 years ago, there was a higher frequency of aggregated species pairs. Then, from 6,000 years ago to the present, the pattern shifted to a predominance of segregated species pairs. An ancient rule had changed.

Humans were here

"We don't have direct evidence to show that this pattern change was caused by humans," Gotelli cautions, but the indirect evidence is compelling. The team's statistical analyses considered nearly 358,896 pairs of organisms in 80 plant or mammal communities on different continents, with data sets that collectively covered the last 300 million years of earth history -- including data sets that spanned the huge Permian-Triassic extinction (the "Great Dying" 252 million years ago), the Cretaceous-Paleogene extinction of the dinosaurs (66 million years ago), and a period of rapid global climate change around 56 million years ago.

The pattern of aggregated species occurrences remained the same across these massive disturbances and time spans, but then a dramatically new pattern started emerging about 6,000 years ago, during the great Neolithic revolution when humans developed agriculture and their populations grew and spread globally. From this time until the present, plant and animal communities exhibit less co-occurrence and a greater frequency of segregated species pairs.

The scientists explored -- and eliminated -- many possible reasons for why this new pattern appeared, including several kinds of statistical and sampling artifacts that might explain the shift they saw in the data. For example, Earth's climate became much more variable during modern times, and the team wondered whether this might explain the shift. But when they tracked climactic trends that occurred during the periods represented by their fossils, using data obtained from ancient ice and deep-sea cores, they found no evidence that ancient climate variability was responsible for the change in co-occurrence patterns.

"So we're left with human impacts," Lyons said. "We think it's something that humans do that causes barriers to dispersal for both plant and animal species." That idea is supported by data from modern island communities of plants and animals, which show even fewer co-occurring pairs than modern mainland communities. Island data sets, the authors note, are an extreme example of this phenomenon.

"If human activity has caused the terrestrial landscape to become more island-like, more fragmented," Gotelli said, "that would be consistent with this pattern of more segregated species pairs."

Difficult dispersal

Around the time these patterns changed, humans were becoming increasingly dependent on agriculture -- a cultural shift that physically altered the environment and would have introduced new barriers to dispersal of plants and animals. Even during the initial development of agriculture and expansion of human populations, the scientists could detect a shift in the structure of species co-occurrence, perhaps suggesting that species were not able to migrate as easily as they did for the previous 300 million years.

"The pattern of co-occurring species remained stable through the evolution of land organisms from the earliest tetrapods through dinosaurs, flowering plants and mammals," said Anna K. Behrensmeyer, a paleobiologist with the Smithsonian's

Museum of Natural History and a co-author of the study. "This pattern didn't change because of previous mass extinctions or ancient climate variability, but instead, early human activities 6,000 years ago suddenly began resetting a basic property of natural communities."

Climate considerations

And this change in an ancient natural pattern may have implications for modern conservation. "Isolating species has consequences -- it can catalyze evolutionary change over hundreds of thousands to millions of years," Behrensmeyer said, "but it also makes species more vulnerable to extinction."

"We humans have influenced the landscape, but perhaps for a lot longer than we had previously recognized," says Gotelli, a professor in UVM's biology department. "When we look at landscapes and say, 'this is pristine or unaltered,' that's not necessarily true. We may have changed the rules over a much larger scale than we appreciate."

Modern human-driven forces, like climate change and pollution, are "orders of magnitude more destructive than what early humans were doing," Lyons said, but even at the dawn of human civilizations, people were certainly having major -- and unprecedented -- ecological impacts, she said. "If we are thinking about how we're going to restore ecosystems, or how they're going to respond to climate change," UVM's Gotelli said, "we need to understand how they were organized before humans ever came on the scene."

http://www.eurekalert.org/pub_releases/2015-12/drnl-otc121715.php

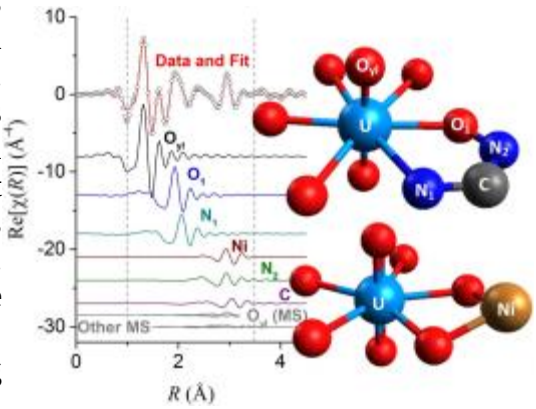
ORNL technique could set new course for extracting uranium from seawater

An ultra-high-resolution technique used for the first time to study polymer fibers that trap uranium in seawater may cause researchers to rethink the best methods to harvest this potential fuel for nuclear reactors.

OAK RIDGE, Tenn - The work of a team led by Carter Abney, a Wigner Fellow at the Department of Energy's Oak Ridge National Laboratory, shows that the polymeric adsorbent materials that bind uranium behave nothing like scientists had believed. The results, gained through collaboration with the University of Chicago and detailed in a paper published in Energy & Environmental Science, highlight data made possible with X-ray Absorption Fine Structure spectroscopy performed at the Advanced Photon Source. The APS is a DOE Office of Science User Facility at Argonne National Laboratory.

"Despite the low concentration of uranium and the presence of many other metals extracted from seawater, we were able to investigate the local atomic environment around uranium and better understand how it is bound by the polymer fibers," Abney said.

Surprisingly, the spectrum for the seawater-contacted polymer fibers was distinctly different from what was expected based on small molecule and computational investigations. Researchers concluded that for this system the approach of studying small molecule structures and assuming that they accurately represent what happens in a bulk material simply doesn't work. It is necessary to consider large-scale behavior to obtain the complete picture, highlighting the need for developing greater computational capabilities, according to Abney.



Using high-energy X-rays, researchers discovered uranium is bound by adsorbent fibers in an unanticipated fashion. **ORNL**

"This challenges the long-held assumption regarding the validity of using simple molecular-scale approaches to determine how these complex adsorbents bind metals," Abney said. "Rather than interacting with just one amidoxime, we determined multiple amidoximes would have to cooperate to bind each uranium molecule and that a second metal that isn't uranium also participates in forming this binding site."

An amidoxime is the chemical group attached to the polymer fiber responsible for binding uranium. Abney and colleagues plan to use this knowledge to design adsorbents that can harness the vast reserves of uranium dissolved in seawater. The payoff promises to be significant.

"Nuclear power production is anticipated to increase with a growing global population, but estimates predict only 100 years of uranium reserves in terrestrial ores," Abney said. "There is approximately 1,000 times that amount dissolved in the ocean, which would meet global demands for the foreseeable future."

Other authors of the paper, titled "XAFS investigation of polyamidoxime-bound uranyl contests the paradigm from small molecule studies," are Richard Mayes, Vyacheslav Bryantsev, Gabriel Veith and Sheng Dai of ORNL and Marek Piechowicz, Zekai Lin and Wenbin Lin of the University of Chicago.

Research at ORNL was supported by DOE's Office of Nuclear Energy while work at the University of Chicago was supported by NE's Nuclear Energy University Program. Experiments were performed at the Advanced Photon Source and the National Energy Research Scientific Computing Centre, DOE Office of Science user facilities.

http://www.eurekalert.org/pub_releases/2015-12/ucl-leo121615.php

Life exploded on Earth after slow rise of oxygen

It took 100 million years for the amount of oxygen in the atmosphere to climb from less than 1% to over 10% of today's current level

It took 100 million years for oxygen levels in the oceans and atmosphere to increase to the level that allowed the explosion of animal life on Earth about 600 million years ago, according to a UCL-led study funded by the Natural Environment Research Council.

Before now it was not known how quickly Earth's oceans and atmosphere became oxygenated and if animal life expanded before or after oxygen levels rose. The new study, published today in Nature Communications, shows the increase began significantly earlier than previously thought and occurred in fits and starts spread over a vast period. It is therefore likely that early animal evolution was kick-started by increased amounts of oxygen, rather than a change in animal behaviour leading to oxygenation.

Lead researcher, Dr Philip Pogge von Strandmann (UCL Earth Sciences), said: "We want to find out how the evolution of life links to the evolution of our climate. The question on how strongly life has actively modified Earth's climate, and why the Earth has been habitable for so long is extremely important for understanding both the climate system, and why life is on Earth in the first place."

Researchers from UCL, Birkbeck, Bristol University, University of Washington, University of Leeds, Utah State University and University of Southern Denmark tracked what was happening with oxygen levels globally 770 - 520 million years ago (Ma) using new tracers in rocks across the US, Canada and China.

Samples of rocks that were laid down under the sea at different times were taken from different locations to piece together the global picture of the oxygen levels of Earth's oceans and atmosphere. By measuring selenium isotopes in the rocks, the team revealed that it took 100 million years for the amount of oxygen in the atmosphere to climb from less than 1% to over 10% of today's current level. This was arguably the most significant oxygenation event in Earth history because it ushered in an age of animal life that continues to this day.

Dr Pogge von Strandmann, said: "We took a new approach by using selenium isotope tracers to analyse marine shales which gave us more information about the gradual changes in oxygen levels than is possible using the more conventional techniques used previously. We were surprised to see how long it took Earth to produce oxygen and our findings dispel theories that it was a quick process caused by a change in animal behaviour."

During the period studied, three big 'snowball Earth' glaciations - Sturtian (~716Ma), Marinoan (~635Ma) and Gaskiers (~580Ma) - occurred whereby the Earth's land was covered in ice and most of the oceans were frozen from the poles to the tropics. During these periods, temperatures plummeted and rose again, causing glacial melting and an influx of nutrients into the ocean, which researchers think caused oxygen levels to rise deep in the oceans.

Increased nutrients means more ocean plankton, which will bury organic carbon in seafloor sediments when they die. Burying carbon results in oxygen increasing, dramatically changing conditions on Earth. Until now, oxygenation was thought to have occurred after the relatively small Gaskiers glaciation melted. The findings from this study pushes it much earlier, to the Marinoan glaciation, after which animals began to flourish in the improved conditions, leading to the first big expansion of animal life.

Co-author Professor David Catling (University of Washington Earth and Space Sciences), added: "Oxygen was like a slow fuse to the explosion of animal life. Around 635 Ma, enough oxygen probably existed to support tiny sponges. Then, after 580 Ma, strange creatures, as thin as crêpes, lived on a lightly oxygenated seafloor.

Fifty million years later, vertebrate ancestors were gliding through oxygen-rich seawater. Tracking how oxygen increased is the first step towards understanding why it took so long.

Ultimately, a grasp of geologic controls on oxygen levels can help us understand whether animal-like life might exist or not on Earth-like planets elsewhere."

http://www.eurekalert.org/pub_releases/2015-12/r-mt121815.php

Multiplying teeth

A way to literally multiply teeth

Researchers from the RIKEN Center for Developmental Biology, working with colleagues from the Tokyo Medical and Dental University, have found a way to -- literally -- multiply teeth. In mice, they were able to extract teeth germs -- groups of cells formed early in life that later develop into teeth, split them into two, and then implant the teeth into the mice's jaws, where they developed into two fully functional teeth.

Teeth are a major target of regenerative medicine. According to Takashi Tsuji, the leader of the team, approximately 10 percent of people are born with some missing teeth, and in addition, virtually all people lose some teeth to either accidents or disease as they age.

Remedies such as implants and bridges are available, but they do not restore the full functionality of the teeth. Growing new teeth would be beneficial, but unfortunately humans only develop a limited number of teeth germs -- the rudimentary cell groups from which teeth grow. "We wondered," says Tsuji, "about whether we might be able to make more teeth from a single germ."

To demonstrate that it might be feasible, the group focused on the fact that teeth development takes place through a wavelike pattern of gene expression involving Lef1, an activator, and Ectodin, an inhibitor.

To manipulate the process, they removed teeth germs from mice and grew them in culture. At an appropriate point in the development process, which turned out from their experiments to be 14.5 days, they nearly sliced the germs into two with nylon thread, leaving just a small portion attached, and continued to culture them. The hope was that signaling centers -- which control the wave of molecules that regulate the development of the tooth -- would arise in each part, and indeed this turned out to be true

The ligated germs developed naturally into two teeth, which the team transplanted into holes drilled into the jaws of the mice. The teeth ended up being fully functional, allowing the mice to chew and feel stimulus, though they were only half the size of normal teeth, with half the number of crowns -- a result that could be expected given that the researchers were using already developed germs.

Significantly, they were able to manipulate the teeth using orthodontic methods, equivalent to braces, and the bone properly remodeled to accommodate the movement of the teeth.

Looking to the future, Tsuji says, "Our method could be used for pediatric patients who have not properly developed teeth as a result of conditions such as cleft lip or Down syndrome, since the germs of permanent teeth or wisdom teeth could be split and implanted. In the future, we could also consider using stem cells to grow more germs, but today there are barriers to culturing such cells, which will need to be overcome."

The research was published in the Dec. 17, 2015(London time) edition of Scientific Reports, an online journal of the publishers of Nature.

http://bit.ly/1O6kzEM

Magnetic Mystery of Earth's Early Core Explained

Competing ideas suggest how sloshing motions could maintain a primordial magnetic field

By Alexandra Witze, Nature magazine on December 18, 2015

Geophysicists call it the new core paradox: They can't quite explain how the ancient Earth could have sustained a magnetic field billions of years ago, as it was cooling from its fiery birth.

Now, two scientists have proposed two different ways to solve the paradox. Each relies on minerals crystallizing out of the molten Earth, a process that would have generated a magnetic field by churning the young planet's core. The difference between the two explanations comes in which particular mineral does the crystallizing.

Silicon dioxide is the choice of Kei Hirose, a geophysicist at the Tokyo Institute of Technology who runs high-pressure experiments to simulate conditions deep within the Earth. “I'm very confident in this,” he reported on December 17 at a meeting of the American Geophysical Union in San Francisco, California.

But David Stevenson, a geophysicist at the California Institute of Technology in Pasadena, says that magnesium oxide — not silicon dioxide—is the key to solving the problem. In unpublished work, Stevenson proposes that magnesium oxide, settling out of the molten early Earth, could have set up the buoyancy differences that would drive an ancient geodynamo.

The core paradox arose in 2012, when several research teams reported that Earth's core loses heat at a faster rate than once thought. More heat conducting away from the core means less heat available to churn the core’s liquid. That's important because some studies suggest Earth could have had a magnetic field more than 4 billion years ago—just half a billion years after it coalesced from fiery debris swirling around the newborn Sun. “We need a dynamo more or less continuously,” Peter Driscoll, a geophysicist at the Carnegie Institution for Science in Washington DC, said at the meeting.

In his Tokyo laboratory, Hirose put different combinations of iron, silicon and oxygen into a diamond anvil cell and squeezed them to produce extraordinarily high pressures and temperatures—sometimes above 4,000 ºC—to simulate the hellish conditions of Earth’s interior. He found that silicon and oxygen crystallized out together, as silicon dioxide, whenever both were present.

When silicon dioxide precipitated in the early Earth, it would have made the remaining melt buoyant enough to continue rising, thus setting up the churning motion needed to sustain the dynamo, Hirose reported. “As far as I know, this is the most feasible mechanism to drive the geodynamo,” he said.

Stevenson, in contrast, plumps for magnesium, saying it “makes much more sense” than silicon dioxide because magnesium oxide would precipitate out of a molten Earth first. Hirose, he says, “is telling you something that can happen, not what did happen.”

http://nyti.ms/1Yu6Z4U

‘Run, Hide, Fight’ Is Not How Our Brains Work

IN this age of terror, we struggle to figure out how to protect ourselves — especially, of late, from active shooters.

By JOSEPH LEDOUX DEC. 18, 2015

One suggestion, promoted by the Federal Bureau of Investigation and Department of Homeland Security, and now widely disseminated, is “run, hide, fight.” The idea is: Run if you can; hide if you can’t run; and fight if all else fails. This three-

step program appeals to common sense, but whether it makes scientific sense is another question.

Underlying the idea of "run, hide, fight" is the presumption that volitional choices are readily available in situations of danger. But the fact is, when you are in danger, whether it is a bicyclist speeding at you or a shooter locked and loaded, you may well find yourself frozen, unable to act and think clearly.

Freezing is not a choice. It is a built-in impulse controlled by ancient circuits in the brain involving the amygdala and its neural partners, and is automatically set into motion by external threats. By contrast, the kinds of intentional actions implied by "run, hide, fight" require newer circuits in the neocortex.

Contemporary science has refined the old "fight or flight" concept — the idea that those are the two hard-wired options when in mortal danger — to the updated "freeze, flee, fight." While "freeze, flee, fight" is superficially similar to "run, hide, fight," the two expressions make fundamentally different assumptions about how and why we do what we do, when in danger.

Why do we freeze? It's part of a predatory defense system that is wired to keep the organism alive. Not only do we do it, but so do other mammals and other vertebrates. Even invertebrates — like flies — freeze. If you are freezing, you are less likely to be detected if the predator is far away, and if the predator is close by, you can postpone the attack (movement by the prey is a trigger for attack).

The freezing reaction is accompanied by a hormonal surge that helps mobilize your energy and focus your attention. While the hormonal and other physiological responses that accompany freezing are there for good reason, in highly stressful situations the secretions can be excessive and create impediments to making informed choices.

A vivid example of freezing was captured in a video of the Centennial Olympic Park bombing during the 1996 Summer Olympics in Atlanta. After the bomb went off, many people froze. Then, some began to try to escape (run), while others were slower on the uptake.

This variation in response is typical. Sometimes freezing is brief and sometimes it persists. This can reflect the particular situation you are in, but also your individual predisposition. Some people naturally have the ability to think through a stressful situation, or to even be motivated by it, and will more readily run, hide or fight as required. But for others, additional help is needed.

In my lab at New York University, we have created a version of this predicament using rats. The animals have been trained, through trial and error, to "know" how to escape in a certain dangerous situation.

But when they are actually placed in the dangerous situation, some rats simply cannot execute the response — they stay frozen. If, however, we artificially shut down a key subregion of the amygdala in these rats, they are able to overcome the built-in impulse to freeze and use their "knowledge" about what to do.

We can learn a great deal about the basic mechanisms of how the brain detects and responds to threats through studies of rats. But people are not rats. We have additional cognitive resources, such as the ability to conceptualize our situation and re-evaluate it.

Every weekday, get thought-provoking commentary from Op-Ed columnists, The Times editorial board and contributing writers from around the world.

Studies by the psychologists James Gross at Stanford, Kevin Ochsner at Columbia and Elizabeth Phelps and me at New York University have shown that if people cognitively reappraise a situation, it can dampen their amygdala activity. This dampening may open the way for conceptually based actions, like "run, hide, fight," to replace freezing and other hard-wired impulses.

How to encourage this kind of cognitive reappraisal? Perhaps we could harness the power of social media to conduct a kind of collective cultural training in which we learn to reappraise the freezing that occurs in dangerous situations. In most of us, freezing will occur no matter what. It's just a matter of how long it will last.

If we could come to use the fact that we are freezing to trigger a reappraisal in a moment of danger, we might just be able to dampen the amygdala enough to accelerate our ability to shift into the action mode required for "run, hide, fight." Even if this cut only a few seconds off our freezing, it might be the difference between life and death.

Joseph LeDoux, a professor of science at New York University, directs the Emotional Brain Institute. He is the author of "Anxious: Using the Brain to Understand and Treat Fear and Anxiety."

http://www.bbc.com/news/magazine-35131678

Does going into hospital make you sick?

Unpublished research suggests that a stay in hospital weakens us so much that, far from restoring us to health, we are more likely to get sick again after discharge.

By William Kremer BBC World Service

A professor at Yale says enough is enough - it's time to completely rethink patient care. When a hospital discharges someone, both patient and doctor are usually united in a hope that they will not see one another again soon.

But for some time it's been known that about a fifth of patients who leave US hospitals are back within a month. In England the number is lower - about 7% - but readmissions still cost the NHS £2.4bn in the 2012-2013 financial year.

In both countries, and many others, re-admission rates are taken as a measure of the quality of care a hospital provides. However when Dr Harlan Krumholz at the Center for Outcomes Research and Evaluation at Yale School of Medicine asked doctors about re-admissions, he got a rather curious response.

"They would say, 'How can you blame me when they come back with pneumonia after they were in for heart failure? We took care of the heart failure, it's not our fault that they came back with pneumonia!'" Krumholz recalls. "Or they would say, 'Why are you blaming us when they fall over - it's not our fault.'"

Krumholz learned that only about a third of patient readmissions were related to the original cause of hospitalisation. Patients' reasons for returning to hospital were diverse and linked to their immune systems, balance, cognitive functioning, strength, metabolism and respiratory systems. It was as though they were mentally and physically below par, off-kilter, out of whack.

Could it be, Krumholz wondered, that the very experience of going to hospital had made patients more vulnerable to disease and accidents? In a series of opinion pieces in top medical journals, he has developed the concept of "post-hospital syndrome" (PHS), which he defines as "an acquired, transient period of generalised risk".

"My premise is it's the cumulative effect of a lot of insults to the body, of all the stress coming from all different directions," he says. "What do we do to them? We sleep-deprive them, we malnourish them, we stress them, we disturb their circadian [sleep] rhythms, we put them at bed rest and de-condition them, we confuse them with lots of different people and new routines - we don't give them any control."

A recent, yet-to-be-published study lends support to Krumholz's theory. Dr Paul Kuo, chairman of surgery at Loyola University Medical Center in Illinois, supervised research in which records from about 58,000 patients who had gone in for a hernia operation in California were carefully analysed. The research team identified a sub-group of 1,332 patients who had been in hospital in the 90 days leading up to the operation.

They found that in the 30 days following the hernia operation, this subgroup was roughly twice as likely to visit the emergency department, and five times as likely to have to be admitted to the hospital as an in-patient. It seemed their previous stay in hospital had "de-tuned" them, making them more vulnerable to complications arising from the hernia operation, even though it is a very straightforward, same-day procedure.

One clear implication of the research is that hospital doctors should resist the urge to fix a patient's health problems in quick succession, but leave time between operations for recuperation. "These findings are hypothesis-generating," says Kuo. Clinical trials are required, he suggests, to understand what is causing PHS and to confirm any link with readmission rates.

But Harlan Krumholz thinks hospitals need to fix the problem rather than study it. Improving the patient's experience of hospital is as urgent in his view as tackling a hospital infection. In an article co-authored with Dr Allan Detsky at the University of Toronto, he lists dozens of ways in which hospitals could reduce stress. Why are hospitals so impersonal? Why can't wards look more cheerful, like they do in children's hospitals? Why do patients have their blood taken so frequently nowadays? And why is hospital food so unappetising?

Instead of thinking of the hospital as a place of healing, Krumholz says his profession sees it as a battlefield. Medical staff come to work to "fight" disease and injury, and everyday niceties fall by the wayside. For example, it's not unheard of for patients to miss four meals in six, if they fast for an evening operation, which then gets postponed to the following evening. It's not very good for the patient, but it gets chalked up as collateral damage in the bigger fight.

But Krumholz says it's also true that hospital systems have developed to serve the people who work there, not the clients. He gives the example - which will be familiar to many - of doctors telling patients on their morning rounds that they will stop by that afternoon to examine them, give test results or have a proper conversation. But because this promise of an appointment is not attached to a specified time, the patient - and sometimes, his or her family - is left waiting all afternoon, afraid to leave the bedside in case the doctor is missed. "It serves us so well to say, 'Well I'll be there when I'll be there'," says Krumholz. "And it's kind of an abuse of power, quite honestly."

Eventually, most doctors and nurses find out what it's like to be in-patients too. That time came much earlier than anyone would have hoped for Dr Kate Granger, who was diagnosed with a rare form of cancer as a 29-year-old trainee in Yorkshire, England. She was told she would probably die in about 12 to 18 months. "Sometimes I had amazing care, and sometimes I felt very lonely in hospital," she says. "And I felt quite faceless at times, like I was this girl-with-a-rare-cancer, and I didn't really have any other meaning to my life."

She found herself at the receiving end of ward rounds in which large groups of staff and students gathered around her bed - "and how vulnerable that feels when you're not looking your best, you're in your pyjamas and you've got all these people standing over you," she says.

But the real "eye-opener" came one day when she arrived at hospital through Accident and Emergency, with post-operative sepsis. A couple of days after she had been admitted, a porter introduced himself to her, and she realised that of the dozens of doctors and nurses she had seen, very few had shown her the same

courtesy. "It just felt really wrong," she says, "who are these people doing things to your body?"

She wrote a tweet about the experience with the hashtag #hellomynameis and very soon a big campaign had started to get NHS staff to introduce themselves. It went on to be endorsed by just about every senior figure in British medicine.

"It's a stepping-stone to compassion, really, in the sense that if you introduce yourself, you see a human being in front of you," she says. "You make a connection with them, and then you start a relationship. If you don't introduce yourself you're hiding behind the anonymity of healthcare."

In defiance of her prognosis, Granger is still campaigning four years after she found she had cancer, and has just started her first post as consultant, or senior doctor. Even though she works in hospitals every day she confesses that she can't stay there as a patient for longer than about three days because, as she puts it, "I start to go a bit crazy."

One of the main reasons is that she simply doesn't get enough sleep in hospital. She says she is woken through the night to have observations performed and fluids changed, and then not allowed to sleep during the day. As a doctor, she says she doesn't really understand why a patient who is sleeping soundly and breathing normally would ever really need to be woken.

"Anyone who's in healthcare, when they themselves get sick, is usually rather shocked at what it's like to be on the other side," says Harlan Krumholz, who has often cited disruption to sleep patterns as a cause of concern in hospitals.

At his own hospital, Yale-New Haven, all non-essential observations are now banned at the hospital between 23:00 and 06:00. And during the day, staff perform hourly rounds to check patients are comfortable, help them to the toilet or just say "hello". The hospital's other innovations include "patient excellence awards" for staff and a bulk procurement of folding chairs, to encourage doctors and nurses to sit at the bedside.

Overseeing these changes is Dr Michael Bennick, the hospital's Associate Chief of Medicine. He says that PHS is a particular problem for the elderly. "When older patients are discharged from the hospital, almost 30% may never fully get back to their prior functional status and recover their ability to wash, dress or feed themselves, even six months after leaving the hospital."

The Oxfordshire-based doctor and writer Druin Burch says the concept of PHS may go some way to persuade National Health Service bosses of the need to improve the patient's experience of hospital, but real change will only come once they are convinced that Harlan Krumholz's ideas improve clinical outcomes and save money in the long run.

"The NHS - we try and run it efficiently, which is another way of saying we try and run it on the cheap," he says. "A lot of the things that Harlan talks about would be expensive, so you don't just need to know they work but you need to know they work enough to be worth the money."

But there are other things on Krumholz's long list of suggestions, he says, that cost very little, and that any hospital should be acting on now. "The trolleys that get wheeled past patients at 3am - they shouldn't clatter so that they wake everyone up," he says. "The bins when a nurse throws away a pair of gloves shouldn't crash so they wake everyone up. "Those sorts of simple things we should be getting right and I think most people would feel we're not doing those things well enough." And who knows, they could result in hospitals not only curing us of one illness, but also leaving us in better shape to resist the next one.

http://nyti.ms/1PoYNxe

Drink to Your Health (in Moderation), the Science Says

Clearing up the misconceptions about alcohol

Aaron E. Carroll THE NEW HEALTH CARE DEC. 21, 2015

Over the past year, I've tried to clear up a lot of the misconceptions on food and drink: about salt, artificial sweeteners, among others, even water.

Now let me take on alcohol: wine, beer and cocktails. Although I have written about the dangerous effects of alcohol abuse and misuse, that doesn't mean it's always bad. A part of many complex and delicious adult beverages, alcohol is linked to a number of health benefits in medical studies.

That doesn't mean the studies provide only good news, either, or that the evidence in its favor is a slam dunk. You won't be surprised to hear that, once again, my watchword — moderation — applies.

Research into how alcohol consumption affects health has been going on for a long time. A 1990 prospective cohort study included results of more than 275,000 men followed since 1959. Compared with those who never drank alcohol, those who consumed one to two drinks a day had a significantly reduced mortality rate from both coronary heart disease and "all causes." Those who consumed three or more drinks a day still had a lower risk of death from coronary heart disease, but had a higher mortality rate over all.

A 2004 study came to similar conclusions. It followed about 6,600 men and 8,000 women for five years and found that compared with those who drank about one drink a day on average, those who didn't drink at all and those who drank more than two drinks a day had higher rates of death. Results like these have been consistent across a number of studies in different populations. Even studies published in the journal Alcoholism: Clinical and Experimental Research agree

that moderate drinking seems to be associated with a decreased risk of death over all.

However, alcohol seems to have different effects on different diseases. Almost all of the major benefits of drinking are seen in cardiovascular illnesses. In fact, with men, even consumption of a surprisingly large amount can seem protective.

When it comes to cancer, the picture isn't as rosy. For instance, a 2007 study involving the Women's Health Study cohort found that increased alcohol consumption was associated with an increased risk of breast cancer. More broadly, a 2014 systematic review of epidemiologic and experimental studies looking at alcohol and breast cancer found that the overall consensus is that each additional drink per day increases the relative risk (comparing the risk in two groups) of breast cancer by a statistically significant, but small, 2 percent — although not the absolute risk.

A meta-analysis of colorectal cancer and alcohol found that heavy drinkers, but not light or moderate drinkers, were at increased risk of the disease. No relationship is seen with respect to bladder cancer or ovarian cancer. A study that included all cancers found that light drinking was protective; moderate drinking had no effect; and heavy drinking was detrimental.

Moderate alcohol consumption has been found to be associated with other benefits, though. A cohort of about 6,000 people followed in Britain found that those who consumed alcohol at least once a week had significantly better cognitive function in middle age than those who did not drink at all. This protective effect on cognition was seen in people who drank up to 30 drinks a week.

A 2004 systematic review found that moderate drinking was associated with up to 56 percent lower rates of diabetes compared with nondrinkers. Heavy drinkers, though, had an increased incidence of diabetes. This is where savvy readers should be asking: What about randomized controlled trials? After all, epidemiologic evidence and associations only go so far; they cannot get us to causation.

Recently, in Annals of Internal Medicine, such a trial was published. Patients with well-controlled Type 2 diabetes were randomized to drink 150 milliliters of water, white wine or red wine with dinner for two years. The beverages were provided to patients free of charge. They were all placed on a Mediterranean diet with no calorie restrictions.

Researchers found that those who drank the wine, most notably red wine, had a reduction in cardiometabolic risk factors, or those for heart disease, diabetes or stroke. This was especially true in patients who had certain genotypes. Further, no one had any significant adverse effects from being randomized to drink the alcohol.

In another analysis of that randomized control trial published this year, the most interesting finding was about blood pressure. In this study, some people saw a reduction in systolic blood pressure. Again, the alcohol was not associated with significant adverse effects. This contradicts the findings from systematic reviews of epidemiologic studies that show alcohol intake may be associated with a small but significant increase in blood pressure.

Adding further complications was a shorter-term trial looking at red wine consumption that found it had no effect, positive or negative, on blood pressure in patients with atherosclerosis. A different analysis of that study found that it did result in improved cholesterol levels, even though many patients were already being treated with statins.

A 2011 meta-analysis examined 63 controlled trials of wine, beer and spirits, and found that all of those beverages increased levels of HDL cholesterol (the good cholesterol). There was even a dose-response, with more alcohol consumed having more of an effect.

Synthesizing all this, there seems to be a sizable amount of evidence that moderate alcohol consumption is associated with decreased rates of cardiovascular disease, diabetes and death. It also seems to be associated with increased rates, perhaps to a lesser extent, of some cancers, especially breast cancer, as well as some other diseases or conditions. The gains from improved cardiovascular disease deaths seem to outweigh all of the losses in other diseases combined. The most recent report of the U.S.D.A. Scientific Advisory Panel agrees with that assessment.

But alcohol isn't harmless. Many people with certain diseases or disorders, and women who are pregnant, need to avoid it. Others who can't keep their consumption to acceptable levels need to abstain. Alcohol is very harmful when abused, so much so that it's difficult for me to tell people to start drinking for their health. That's rarely the conclusion of any studies about alcohol, no matter how positive the results. Nor is it the advice any doctors I know give.

However, the evidence does seem to say that moderate consumption is safe, and that it may even be healthy for many people. If you're enjoying some drinks this holiday season, it's nice to know that they may be doing more than just bringing you cheer.

Correction: December 21, 2015

An earlier version of this article misstated the effect that alcohol was shown to have on HDL cholesterol in a 2011 meta-analysis. The meta-analysis found that wine, beer and spirits increased levels of HDL cholesterol (the good cholesterol), not decreased them.

http://www.eurekalert.org/pub_releases/2015-12/esfm-ec-121815.php

Asian women with endocrine-resistant breast cancer benefit from combination therapy

Promising results of PALOMA3 trial confirmed in Asian patients

Singapore/Lugano - Data collected in Japanese and Korean patients included in the global PALOMA3 trial provides evidence that combining palbociclib with fulvestrant is an effective strategy to overcome endocrine resistance in women with hormone receptor positive (HR+), HER2 negative (HER2-) advanced breast cancer. The analysis of efficacy and safety of the combined therapy in an Asian population was presented (1) at the first ESMO Asia 2015 Congress in Singapore, and results are in line with those reported in all patients (both Asian and non-Asian) earlier this year.

Endocrine resistance is a major clinical issue that makes advanced breast cancer more difficult to treat. Hormone therapy is generally well tolerated and an easy-to-administer option for breast cancer, with demonstrated benefits in patients whose tumours express hormone receptors (HR), particularly the HR+/HER2- subgroup. The ideal option for patients is to be on one endocrine therapy after another, as long as the disease responds or remains unchanged. "However, unavoidably, resistance develops in almost all advanced patients a median ten months after the first-line hormonal agent is administered, and a much shorter median time after the second- or third-line hormonal agents, eventually driving patients to switch to the more toxic chemotherapy," one of the study authors, Dr. Jungsil Ro, Center for Breast Cancer at the National Cancer Center, Goyang, Korea, said.

Palbociclib is an orally active selective inhibitor of the CDK 4/6 growth signal that blocks cell proliferation and cellular division. It has high activity in HR+ breast cancer cell lines and is synergistic in combination with different endocrine therapies.

The PALOMA3 trial assessed the safety and efficacy of the combination of palbociclib and fulvestrant in premenopausal and postmenopausal women with HR+/HER2- advanced breast cancer that progressed during prior endocrine therapy. By March 2015, 105 Asian patients in Korea and Japan were randomised, 74 to receive palbociclib plus fulvestrant and 31 to placebo plus fulvestrant. "For postmenopausal women, the study definitely showed positive results --- progression-free survival more than doubled. Patients suffered from more adverse events in the palbociclib arm, specifically haematologic toxicity, which was easily manageable. "For premenopausal women, the outcome looks as promising as in postmenopausal women, although the numbers are quite small for definitive conclusions," Ro said.

The analysis containing Asian patients nicely confirms that combining palbociclib with fulvestrant is a promising therapeutic approach. "Although median progression-free survival in Asian patients was not reached for the drug combination, it is a reasonable therapeutic option in this population," ESMO spokesperson, Dr. Fabrice André, Institut de Cancérologie Gustave Roussy, Villejuif, France, said. "Palbociclib shows clinical activity with modest toxicity. Although the difference in toxicity profile between Asian and non-Asian populations is really interesting, no clear explanation could be made from this study because of the existing differences reported in non-Asian and Asian patients."

To support the superiority of this drug combination over the hormonal agent alone, a longer follow-up for the overall survival result is needed, Ro said. "So far, we do not have predictive biomarkers to select patients for palbociclib in addition to fulvestrant other than the subtype itself, HR+/HER2- breast cancer. We also need to see that other results from the first-line hormone therapy with palbociclib clinical trial verify the efficacy of the drug, but a longer time is needed to have these results."

Commenting on the results, ESMO spokesperson Dr. Evandro de Azambuja, medical director of the Br.E.A.S.T. Data Centre, Jules Bordet Institute in Brussels, Belgium, not involved in the study, said: "Targeting CDK4/6 represents a further promising option to address endocrine resistance. Other mechanisms of resistance to endocrine therapy include the activation of tyrosine kinase signalling, the up-regulation of the PI3 kinase mammalian target of rapamycin (mTOR) signalling and, lastly, the mutation of ESR1." On the basis of the impressive results from the phase II PALOMA-1 trial, the combination of palbociclib plus letrozole has been approved by U.S. Food and Drug Administration (FDA) for the treatment of postmenopausal women with ER+, HER2- advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

Information contained in this press release was provided by the abstracts authors and reflects the content of the studies. It does not necessarily express ESMO's point of view.

(1) Abstract 53O_PR, Efficacy and safety of palbociclib plus fulvestrant in Asian women with hormone receptor-positive (HR+)/human epidermal growth factor-2 negative (HER2-) metastatic breast cancer (MBC) that progressed on prior endocrine therapy (ET) J. Ro, S.-A. Im, N. Masuda, Y.-H. Im, K. Inoue, Y. Rai, R. Nakamura, J.H. Kim, K. Zhang, C. Giorgetti, P. Schnell, C. Huang Bartlett, H. Iwata, will be presented during Breast Cancer session on Saturday 19th December, h. 16:30 Abstract will be available online on 18th December 2015, 23:55 hours (SGT) https://cslide.ctimeetingtech.com/library/esmo/browse/itinerary/5225

http://www.eurekalert.org/pub_releases/2015-12/dgo-lft122115.php

Looking for the next superfood? When in Europe, search no further than black raspberries

Antioxidant properties of raspberry and blackberry fruits grown in Central Europe

As far as healthy foods go, berries make the top of the list. They contain potent antioxidants, which decrease or reverse the effects of free radicals - natural byproducts of energy production that can play havoc on the body and that are closely linked with heart disease, cancer, arthritis, stroke or respiratory diseases.

Unsurprisingly, the benefits of berries are extoled in one study after another. It is usually the exotic Goji, Acerola or Acai berries that make the headlines as Superfoods, but for the health-savvy European consumer the native homegrown species could be even more alluring.

The current study from the University of Agriculture in Krakow shows what's in store for Old Continent foodies in the berries department. The research published now in Open Chemistry suggests that black raspberries grown in Central Europe show greater health benefits than their better known cousins - raspberries or blackberries.

A group of researchers led by Anna Ma?gorzata Kostecka-Guga?a measured the content of phenolics and anthocyanins in black raspberries, red raspberries and blackberries, assessing their antioxidant potential and health benefits. They were able to confirm that the antioxidant activity of natural products correlates directly with their health promoting properties.

It turns out that the amount of antioxidants in black raspberries was three times higher than the other fruits under investigation. Remarkably, the number was even higher for phenolics or the amount of anthocyanines - with black raspberries topping their humble cousins by over 1000%.

But most interestingly, black raspberries seem to be characterized by a higher content of secondary metabolites, which have been proved beneficial for human health.

The Central Europe-grown variety of black raspberries showed greater health benefits than raspberries and blackberries.

As there is no significant difference fruits collected in either summer or autumn they should remain a solid staple on our diet throughout the seasons.

The original article is available to read, download and share in full open access on De Gruyter Online.

http://www.eurekalert.org/pub_releases/2015-12/acop-sca121515.php

Sudden cardiac arrest may not be so sudden

Warning signs are common, but are often ignored, in the weeks preceding a heart attack

According to an article published in Annals of Internal Medicine, sudden cardiac arrest may not be an entirely unexpected event. Warning signs are common in the days and weeks leading up to a heart attack, but those symptoms are often ignored. Attention to symptoms and early interventions may improve survival.

Sudden cardiac arrest is almost always fatal, so finding ways to prevent it is important. Researchers hypothesized that the presence of and response to warning symptoms that occur in the hours, days, and weeks preceding heart attack may be associated with better survival. They collected information about the 4 weeks before sudden cardiac arrest from survivors, family members, friends, medical records, and emergency response records to determine what symptoms, if any, were present. Symptoms were classified as chest pain (typical or atypical), difficulty breathing, palpitations, sudden drop in blood pressure/loss of consciousness, and other (including abdominal pain, nausea or vomiting, back pain).

The researchers found that about one half of patients with available information had warning symptoms in those 4 weeks that often recurred during the 24 hours before sudden cardiac arrest. Most patients ignored their symptoms, but the patients who called 911 significantly increased chances for survival. The authors suggest that these findings highlight the potential importance of developing new community-based strategies for short-term prevention of sudden cardiac arrest.

Note: For an embargoed PDF, please contact Cara Graeff. To interview the lead author, please contact Sally Stewart at Sally.Stewart@cshs.org or 310-248-6566.

Abstract: http://www.annals.org/article.aspx?doi=10.7326/M14-2342

URL live when embargo lifts

http://www.eurekalert.org/pub_releases/2015-12/nion-sub121815.php

Speeding up brain's waste disposal may slow down neurodegenerative diseases

NIH-funded mouse study identifies therapeutic target for clearing out toxic proteins damaged during neurodegenerative disorders

A study of mice shows how proteasomes, a cell's waste disposal system, may break down during Alzheimer's disease (AD), creating a cycle in which increased levels of damaged proteins become toxic, clog proteasomes, and kill neurons. The study, published in Nature Medicine and supported by the National Institutes of Health, suggests that enhancing proteasome activity with drugs during the early stages of AD may prevent dementia and reduce damage to the brain.

"This exciting research advances our understanding of the role of the proteasomes in neurodegeneration and provides a potential way to alleviate symptoms of neurodegenerative disorders," said Roderick Corriveau, Ph.D., program director at the NIH's National Institute of Neurological Disorders and Stroke (NINDS), which provided funding for the study.

The proteasome is a hollow, cylindrical structure which chews up defective proteins into smaller, pieces that can be recycled into new proteins needed by a cell. To understand how neurodegenerative disorders affect proteasomes, Natura Myeku, Ph.D., a postdoctoral fellow working with Karen E. Duff, Ph.D., professor of pathology and cell biology at Columbia University, New York City, focused on tau, a structural protein that accumulates into clumps called tangles in the brain cells of patients with AD and several other neurodegenerative disorders known as tauopathies.

Using a genetically engineered mouse model of tauopathy, as well as looking at cells in a dish, the scientists discovered that as levels of abnormal tau increased, the proteasome activity slowed down.

Treating the mice at the early stages of tauopathy with the drug rolipram increased proteasome activity, decreased tau accumulations and prevented memory problems. They found that the drug worked exclusively during the early stages degeneration, which began around four months of age. It helped four-month old tauopathy mice remember the location of hidden swimming platforms as well as control mice, and better than tauopathy mice that received placebos. Treating mice at later stages of the disease was not effective.

"These results show, for the first time, that you can activate the proteasome in the brain using a drug and effectively slow down the disease, or prevent it from taking a hold," said Dr. Duff, senior author of the study.

Rolipram was initially developed as an antidepressant but is not used clinically due to its side effects. It increases the levels of cyclic AMP, a compound that triggers many reactions inside brain cells. Rolipram works by blocking cyclic AMP phosphodiesterase four (PDE4), an enzyme that degrades cyclic AMP. The scientists found that cyclic AMP levels are critical for controlling proteasome activity. Treating brain slices from tauopathy mice with rolipram, or a version of cyclic AMP that PDE4 cannot degrade, reduced the accumulation of tau and sped proteasome activity. "We were hoping to show, using rolipram, that increasing cyclic AMP is a pharmaceutical strategy worth pursuing. The suggestion is not that rolipram should immediately go into the clinic but that drugs with mechanisms similar to rolipram should be investigated further," said Dr. Myeku.

Drs. Myeku and Duff plan to further investigate proteasome activity and the impact of tau and other disease-related proteins on this system for chewing up and clearing out damaged proteins. In addition, they want to search libraries of FDA-approved compounds or new molecules for drugs that work in a similar way to rolipram or activate proteasomes by different pathways.

"The proteasome system we are studying also degrades proteins associated with a number of other neurodegenerative diseases such as Parkinson's, Huntington's, frontotemporal degeneration and amyotrophic lateral sclerosis. We may be able to apply these findings to other disorders that accumulate proteins," said Dr. Duff.

This work was supported by the NINDS (NS074593) and the CurePSP Foundation.

Myeku N et al. 'Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling,' Nature Medicine, Dec. 21, 2015.

http://s.nikkei.com/1IvpGy8

At Samsung, biologics are the new semiconductors

The Samsung group is set to double its capacity for producing biopharmaceuticals, seeking to build up its presence in the fast-expanding market.

KENTARO OGURA, Nikkei staff writer

SEOUL -- The South Korean conglomerate believes its expertise in the chip business gives it a significant edge.

The group is to invest 850 billion won ($729 million) in a new plant in Incheon, near Seoul, that will produce the drugs on behalf of other companies. The facility will raise Samsung BioLogics' capacity to 360,000 liters -- enough to make the company the world's largest contract biopharmaceutical producer.

The company, 97% owned by Samsung Electronics and Samsung C&T, will become a "champion" in contract production of biological drugs, or biologics, by 2020, chief executive Kim Tae-han said at a groundbreaking ceremony for the new plant on Monday. The factory will be Samsung BioLogics' third.

The market for biologics is forecast to grow to more than $280 billion by 2020. The Samsung group will not only seek to make them for clients but also accelerate development of biological generics.

Now that Samsung is losing momentum in the smartphone business, analysts are closely watching whether biologics can pick up the slack. The conglomerate -- and the government -- clearly see the drugs as important for the future. South Korean President Park Geun-hye attended Monday's ceremony and said the country would become a major player in the biologics business, currently led by U.S. and European companies.

Aggressive recruiting

Samsung BioLogics, established in 2011, is a joint venture between the Samsung group and Quintiles Transnational, a U.S. company that assists in the development

of new drugs. The venture already has two plants in Incheon, which turn out biologics on behalf of companies such as Roche of Switzerland and Bristol-Myers Squibb of the U.S.

The third plant is expected to help Samsung BioLogics boost annual sales to 2 trillion won by 2025, from 100 billion won at present. The company also envisions an increase in operating profit to 1 trillion won by 2025. Assuming it hits its targets, the company is poised to surpass Lonza of Switzerland and Boehringer Ingelheim of Germany in production capacity, sales and profit.

Samsung has spared no expense when it comes to biologics. The unit's workforce now numbers 1,000; 10% of the employees are foreign nationals. It has been aggressive in recruiting overseas; Executive Vice President Lee Kyusung was brought over from Bristol-Myers Squibb. Rivals admit that Samsung BioLogics has hired a considerable number of workers away from them.

The group appears to be taking an approach similar to its successful microchip strategy. The semiconductor department at Sungkyunkwan University, an elite private school, was funded by Samsung; the conglomerate hires many of its graduates. Now the university has set up a new global biomedical engineering department. This, too, could prove to be a valuable source of human resources.

Built-in advantage

Semiconductor know-how is useful in the production of biologics. As with computer chips, the drugs are made in clean rooms, which minimize dust and other contaminants. Kim said Samsung BioLogics can build a plant comparable in size to those of its rivals for 40% less money, and in half the time.

Samsung BioLogics expects to have an operating profit margin of 50% in 2025. Wide margins are possible because producing biopharmaceuticals is more difficult than regular drugs, so newcomers to the market face high hurdles.

In the semiconductor industry, foundries that make chips for other companies have spread. Samsung expects the same thing to happen in the biologics business, resulting in a division of development and production.

Today, pharmaceutical companies produce 70-80% of their products on their own. Biological generics represent another promising segment. Samsung Bioepis, founded with an investment from American biotechnology company Biogen, earlier this month began selling a generic drug for treating rheumatism and other causes of joint inflammation in South Korea. It plans to release the drug in Europe in the first half of 2016.

South Korean brokerage SK Securities projects Samsung Bioepis' operating profit at 540 billion won in 2022, on sales of 1.2 trillion won. The combination of Samsung BioLogics and Samsung Bioepis could generate 1.54 trillion won of operating profit. That would make the biologics business the Samsung group's No. 3 source of earnings, after information technology equipment -- including smartphones -- and semiconductors.

http://www.eurekalert.org/pub_releases/2015-12/tjnj-rec121815.php

Researchers examine cases in California of neurological illness affecting limbs

Nearly 60 cases of acute flaccid myelitis - a rare polio-like illness

There have been nearly 60 cases identified in California from 2012 - 2015 of acute flaccid myelitis, a rare syndrome described as polio-like, with most patients being children and young adults, according to a study in the December 22/29 issue of JAMA. The cause of the condition in these cases remains unknown.

With the elimination of wild poliovirus in populations throughout most of the world, the clinical syndrome of acute flaccid paralysis (characterized by weakness or paralysis and reduced muscle tone) due to spinal motor neuron injury has largely disappeared from North America. Despite occasional case reports, the absence of centralized public health surveillance for non-polio acute flaccid paralysis in the United States has precluded accurate incidence estimates. In the fall of 2012, the California Department of Public Health (CDPH) received 3 separate reports of acute flaccid paralysis cases with evidence of spinal motor neuron injury. No such cases had been reported to the program during the preceding 14 years. In response to these unusual case reports, the CDPH implemented enhanced surveillance for similar cases with the goal of characterizing observed cases and identifying possible causes.

Keith Van Haren, M.D., of Stanford University, Palo Alto, Calif., and colleagues summarized reported cases of acute flaccid myelitis, which encompasses a subset of acute flaccid paralysis cases, in patients with radiological or neurophysiological findings suggestive of spinal motor neuron involvement reported to the CDPH with symptom onset between June 2012 and July 2015. Cerebrospinal fluid, serum samples, nasopharyngeal swab specimens, and stool specimens were submitted to the state laboratory for infectious agent testing.

Fifty-nine cases were identified. Median age was 9 years (50 of the cases were younger than 21 years). Symptoms that preceded or were concurrent included respiratory or gastrointestinal illness (n = 54), fever (n = 47), and limb myalgia (n = 41; muscle pain). Among 45 patients with follow-up data, 38 had persistent weakness at a median follow-up of 9 months. Two patients, both immunocompromised adults, died within 60 days of symptom onset. Enteroviruses were the most frequently detected pathogen in either nasopharynx swab specimens, stool specimens, serum samples (15 of 45 patients tested). No pathogens were isolated from the cerebrospinal fluid. The incidence of reported

cases was significantly higher during a national enterovirus D68 outbreak occurring from August 2014 through January 2015 compared with other monitoring periods.

"The etiology of acute flaccid myelitis cases in our series remains undetermined. Although the syndrome described is largely indistinguishable from poliomyelitis on clinical grounds, epidemiological and laboratory studies have effectively excluded poliovirus as an etiology," the authors write.

The researchers note that "ongoing surveillance efforts are required to understand the full and potentially evolving levels of infectious agent-associated morbidity and mortality." "To our knowledge, the California surveillance program for acute flaccid paralysis is the first to use specific case criteria and report subsequent incidence data for the subset of paralysis cases attributable solely to acute flaccid myelitis and may serve as a guide for similar surveillance efforts in the future."

(doi:10.1001/jama.2015.17275; Available pre-embargo to the media at http://media.jamanetwork.com)

http://www.eurekalert.org/pub_releases/2015-12/wuso-sui122115.php

Study uncovers inherited genetic susceptibility across 12 cancer types

Researchers long have known that some portion of the risk of developing cancer is hereditary and that inherited genetic errors are very important in some tumors but much less so in others.

In a new analysis, researchers have shed light on these hereditary elements across 12 cancer types -- showing a surprising inherited component to stomach cancer and providing some needed clarity on the consequences of certain types of mutations in well-known breast cancer susceptibility genes, BRCA1 and BRCA2.

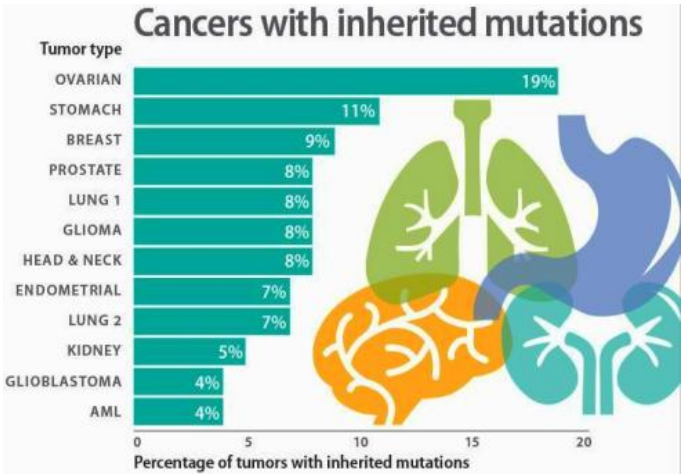
The study, from Washington University School of Medicine in St. Louis, appears Dec. 22 in the journal Nature Communications.

The investigators analyzed genetic information from more than 4,000 cancer cases included in The Cancer Genome Atlas project, an initiative funded by the National Institutes of Health (NIH) to unravel the genetic basis of cancer.

"In general, we have known that ovarian and breast cancers have a significant inherited component, and others, such as acute myeloid leukemia and lung cancer, have a much smaller inherited genetic contribution," said senior author Li Ding, PhD, associate professor of medicine and assistant director of the McDonnell Genome Institute at Washington University. "But this is the first time on a large scale that we've been able to pinpoint gene culprits or even the actual mutations responsible for cancer susceptibility."

The new information has implications for improving the accuracy of existing genetic tests for cancer risk and eventually expanding the available tests to include a wider variety of tumors.

Past genomic studies of cancer compared sequencing data from patients' healthy tissue and the same patients' tumors. These studies uncovered mutations present in the tumors, helping researchers identify important genes that likely play roles in cancer. But this type of analysis can't distinguish between inherited mutations present at birth and mutations acquired over the lifespan.



Sara Dickherber

To help tease out cancer's inherited components, the new study adds analysis of the sequencing data from the patients' normal cells that contain the "germline" information. A patient's germline is the genetic information inherited from both parents. This new layer of information gives a genetic baseline of a patient's genes at birth and can reveal whether cancer-associated mutations were already present.

In all the cancer cases they analyzed, the investigators looked for rare germline mutations in genes known to be associated with cancer. If one copy of one of these genes from one parent is already mutated at birth, the second normal copy from the other parent often can compensate for the defect. But individuals with such mutations are more susceptible to a so-called "second hit." As they age, they are at higher risk of developing mutations in the remaining normal copy of the gene.

"We looked for germline mutations in the tumor," Ding said. "But it was not enough for the mutations simply to be present; they needed to be enriched in the tumor -- present at higher frequency. If a mutation is present in the germline and amplified in the tumor, there is a high likelihood it is playing a role in the cancer."

In 114 genes known to be associated with cancer, they found rare germline mutations in all 12 cancer types, but in varying frequencies depending on the type. They focused on a type of mutation called a truncation because most truncated genes can't function at all.

Of the ovarian cancer cases the investigators studied, 19 percent of them carried rare germline truncations. In contrast, only 4 percent of the acute myeloid leukemia cases in the analysis carried these truncations in the germline. They also found that 11 percent of the stomach cancer cases included such germline truncations, which was a surprise, according to the researchers, because that number is on par with the percentage for breast cancer.

"We also found a significant number of germline truncations in the BRCA1 and BRCA2 genes present in tumor types other than breast cancer, including stomach and prostate cancers, for example," Ding said. "This suggests we should pay attention to the potential involvement of these two genes in other cancer types."

The BRCA1 and BRCA2 genes are important for DNA repair. While they are primarily associated with risk of breast cancer, this analysis supports the growing body of evidence that they have a broader impact.

"Of the patients with BRCA1 truncations in the germline, 90 percent have this BRCA1 truncation enriched in the tumor, regardless of cancer type," Ding said.

Genetic testing of the BRCA1 and BRCA2 genes in women at risk of breast cancer can reveal extremely useful information for prevention. When, for example, the genes are shown to be normal, there is no elevated genetic risk of breast cancer. But if either of these genes is mutated in ways that are known to disable either gene, breast cancer risk is dramatically increased. In this situation, doctors and genetic counselors can help women navigate the options available for reducing that risk. But mutations come in a number of varieties. Genetic testing also can reveal many that have unknown consequences for the function of these genes, so their influence on cancer risk can't be predicted.

To help clarify this gray area in clinical practice, Ding and her colleagues Jeffrey Parvin, MD, PhD, professor and director of the division of computational biology and bioinformatics at The Ohio State University, and Feng Chen, PhD, associate professor of medicine at Washington University, investigated 68 germline non-truncation mutations of unknown significance in the BRCA1 gene. For each mutation, they tested how well the BRCA1 protein could perform one of its key DNA-repair functions. The researchers found that six of the mutations behaved like truncations, disabling the gene completely. These mutations also were enriched in the tumors, supporting a likely role in cancer.

"It is important to be able to show that these six mutations of unknown clinical significance are, in fact, loss-of-function mutations," Ding said. "But I also want to emphasize the contrasting point. Many more show normal function, at least according to our analysis. Many of these types of mutations are neutral, and we would like to identify them so that health-care providers can better counsel their patients."

Ding said more research is needed to confirm these results before they can be used to advise patients making health-care decisions. "Our strategy of investigating germline-tumor interactions provides a good way to prioritize important mutations that we should focus on," she said. "For the information to eventually be used in the clinic, we will need to perform this type of analysis on even larger numbers of patients."

Other key contributors to the study include Charles Lu, PhD; Mingchao Xie; Mike Wendl, PhD; Mike McLellan; Jiayin Wang, PhD; and Kim Johnson, PhD, from Washington University; and Mark Lerseison from Brown University.

This work was supported by the National Institutes of Health (NIH), including the National Cancer Institute (NCI), grants R01CA180006, R01CA178383, R01CA141090 and PO1CA101937; the National Human Genome Research Institute (NHGRI), grants U01HG006517, R01HG007069, U54HG003079 and T32 HG000045; the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), grant R01DK087960; the Department of Defense, grant PC130118; a Ministry of Education in Taiwan Fellowship, and CMB training grant GM 007067. The Cancer Genome Atlas (cancergenome.nih.gov) was the source of primary data.

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http://www.eurekalert.org/pub_releases/2015-12/cwru-sso122215.php

Simple shell of plant virus sparks immune response against cancer

Mice tumor free and protected from metastases after treatment

The shells of a common plant virus, inhaled into a lung tumor or injected into ovarian, colon or breast tumors, not only triggered the immune system in mice to wipe out the tumors, but provided systemic protection against metastases, researchers from Case Western Reserve University and Dartmouth University report.

The scientists tested a 100-year-old idea called in-situ vaccination. The idea is to put something inside a tumor and disrupt the environment that suppresses the immune system, thus allowing the natural defense system to attack the malignancy. That something--the hard coating of cowpea mosaic virus--caused no detectible side effects, which are a common problem with traditional therapies and some immunotherapies. The team's research is published in the journal Nature Nanotechnology.

"The cowpea virus-based nanoparticles act like a switch that turns on the immune system to recognize and fight against the tumor - as well as to remember it," said

Nicole Steinmetz, an assistant professor of biomedical engineering at Case Western Reserve, appointed by the Case Western Reserve School of Medicine.

"The particles are shockingly potent," said Steven Fiering, professor of microbiology and immunology at Dartmouth's Geisel School of Medicine. "They're easy to make and don't need to carry antigens, drugs or other immunostimmulatory agents on their surface or inside."

The professors studied the nanoparticles with Dartmouth's Pat Lizotte, a molecular and cellular biology PhD student; Mee Rie Sheen, a postdoctoral fellow; and Pakdee Rojanasopondist, an undergraduate student; and Case Western Reserve's Amy Wen, a biomedical engineering PhD student.

Taking another shot

The immune system's ability to detect and destroy abnormal cells is thought to prevent many cancers, according to the National Cancer Institute. But when tumors start to develop, they can shut down the system, allowing tumors to grow and spread.

To restart immune defenses, the scientists used the tumor itself as if it were the antigen in a vaccine--that is, the target for antibodies produced by the immune system. The cowpea virus shell, with its infectious components removed, acts as the adjuvant--a substance that triggers and may enhance or prolong antigen-specific immune responses.

The process and results

The researchers first switched on the immune system in mice to attack B16F10 lung melanoma or skin melanoma, leaving the mice tumor-free. When the treated mice were later injected with B16F10 skin melanoma (to re-challenge the cured mice), four out of five mice were soon cancer free and one had a slow-growing tumor.

The nanoparticles proved effective against ovarian, breast and colon tumor models. Most of the tumors deteriorated from the center and collapsed. The systemic response prevented or attacked metastatic disease, which is the deadliest form of cancer.

"You get benefits against disease you don't even know is there yet," Fiering said.

"Because everything we do is local, the side effects are limited," despite the strength and extent of the immune response, Fiering said. No toxicity was found.

Harsh side effects, such as fatigue, pain, flu-like symptoms and more are common with chemo and radiation therapies and with some immunostimulation drugs.

The researchers are now trying to understand how the virus shell stimulates the immune system. "It's not cytotoxic, there's no RNA involved or lipopolysaccharides that may be used as adjuvants, and it's not simply an irritant," Steinmetz said. "We see a specific immune response."

Unlike most other adjuvants, Fiering said, the virus shells stimulate neutrophils, a type of white blood cell. What role that plays is not yet known.

The researchers are seeking grants to study whether the shell's physical traits or something virus-specific causes the immune response.

They are also seeking grants to test the therapy in animal models that have immune systems closer to humans. If the virus shell continues to prove effective, the researchers believe it could eventually be used in combination with other therapies tailored to individual patients.

http://www.bbc.com/news/health-35154713

How to spot dementia in a loved one

As families meet up for the festive season, the Alzheimer's Society is offering advice on recognising early signs of dementia in a loved one.

By Michelle Roberts Health editor, BBC News online

It says it typically sees a rise in people seeking out such information and support at this time of year. While many realise that repeatedly forgetting names can be a red flag for dementia, few know that using repetitive phrases can also be a sign.

Stuttering or mispronouncing words is another warning.

There are around 850,000 people living with dementia in the UK. And 225,000 more people will develop dementia this year - that's one every three minutes.

A YouGov survey of more than 4,000 adults reveals many people are confused about what are and are not signs of dementia. Many people thought that forgetting why you have walked into a room (39%) might be a sign, which could happen to anyone. For a person with dementia, it is not so much why they walked into a room that is troubling, but the room itself seeming unfamiliar.

Warning signs

Seek medical advice if your memory loss is affecting daily life and especially if you:

struggle to remember recent events, although you can easily recall things that happened in the past

find it hard to follow conversations or programmes on TV

forget the names of friends or everyday objects

cannot recall things you have heard, seen or read

lose the thread of what you are saying

have problems thinking and reasoning

feel anxious, depressed or angry

feel confused even when in a familiar environment or get lost on familiar journeys

find that other people start to notice or comment on your memory loss

The risk of dementia increases with age with one-in-six of those over 80 having the degenerative disease. But it can strike even in middle-age.

While a diagnosis of dementia can be daunting, it can be a sense of relief, as Dianne Wilkinson, 57 and from Folkestone, knows first-hand.

"I've always been a positive person, so it was odd when I started to feel low and withdrawn. I just put it down to one of those things that people go through from time to time and would eventually shift. I certainly didn't think it could be a sign of dementia.

"After a couple of months some family members encouraged me to visit my GP, but it was only after my dementia diagnosis that others came forward and told me that they had noticed changes in my behaviour, such as repeating myself constantly, being unable to recall where I'd put things like my phone and feeling confused about the day of the week.

"I feel a sense of relief because now that I know I have dementia there's an explanation for why I was behaving strangely. "It's so important people seek help early after noticing signs so that they can make sense of what is happening to them and get help to stay connected and get the most out of their life."

Jeremy Hughes, Chief Executive of Alzheimer's Society, said: "We know dementia is the most feared illness for many, and there's no question that it can have a devastating impact on people, their family and friends.

"It's important we tackle confusion around what are and aren't signs of dementia, and help give people confidence in approaching loved ones about their concerns so people don't delay getting help. "Dementia can strip you of connections to the people you love, but we have many services that can help stop that and support you."

http://www.eurekalert.org/pub_releases/2015-12/uog-uef122315.php

UGA ecologist finds another cause of antibiotic resistance

Environmental contaminants may be partly to blame for the rise in bacterial resistance

Aiken, S.C. - While the rapid emergence of antibiotic-resistant bacteria has prompted the medical community, non-profit organizations, public health officials and the national media to educate the public to the dangers of misusing and overusing antibiotics, the University of Georgia's J. Vaun McArthur is concerned that there's more to the problem than the misuse of common medications.

McArthur, a senior research ecologist with the Savannah River Ecology Laboratory and Odum School of Ecology, believes environmental contaminants may be partly to blame for the rise in bacterial resistance, and he tested this hypothesis in streams on the U.S. Department of Energy's Savannah River Site.

The 310-square mile site near Aiken, South Carolina, east of the Savannah River, was closed to the public in the early 1950s to produce materials used in nuclear weapons. This production led to legacy waste, or contamination, in limited areas of the site. This waste impacted some of the streams in the industrial areas.

"The site was constructed and closed to the public before antibiotics were used in medical practices and agriculture," McArthur said. "The streams have not had inputs from wastewater, so we know the observed patterns are from something other than antibiotics."

McArthur tested five antibiotics on 427 strains of E. coli bacteria in the streams. His research team collected samples from 11 locations in nine streams, which included sediment as well as water samples. The level of metal contamination among these locations varied from little to high.

The results, published in the journal Environmental Microbiology, revealed high levels of antibiotic resistance in eight of the 11 water samples. The highest levels were found at the northern location of Upper Three Runs Creek, where the stream system enters the site, and on two tributaries located in the industrial area, U4 and U8. The level of antibiotic resistance was high in both water and sediment samples from these streams.

McArthur said Upper Three Runs Creek flows through residential, agricultural and industrial areas before it enters the SRS, so the bacteria in this stream have been exposed to antibiotics. In contrast, U4 and U8 are completely contained within the site and have no known input from antibiotics. However, they have a long history of inputs from the legacy waste.

McArthur conducted a second screening using 23 antibiotics on U4, U8 and U10, a nearby stream with little to no industrial impact.

"More than 95 percent of the bacteria samples from these streams were resistant to 10 or more of the 23 antibiotics," McArthur said. These included front-line antibiotics -- gatifloxacin and ciprofloxacin, which are used to treat basic bacterial infections from pink eye to urinary tract and sinus infections.

The contaminated streams U4 and U8 had the highest level of antibiotic resistance. "These streams have no source of antibiotic input, thus the only explanation for the high level of antibiotic resistance is the environmental contaminants in these streams -- the metals, including cadmium and mercury," McArthur said.

McArthur said the three tributaries of Upper Three Runs Creek, U4, U8 and U10 vary in the level of contamination respectively, from highly impacted and impacted to not as impacted.

It is possible that antibiotic-exposed wildlife may have dumped waste into these streams, MacArthur said, but only streams with a history of industrial input had

antibiotic-resistant bacteria. Bacteria in the six streams in the pristine areas of the site were susceptible to the antibiotics.

McArthur said it is concerning that these antibiotic-resistant streams drain into the Savannah River, a large body of water bordering Georgia and South Carolina. The Savannah River shares at least two major characteristics with many large bodies of water in the U.S. It is in close proximity to residential communities, and it receives industrially contaminated water--prone to antibiotic resistance.

"The findings of this study may very well explain why resistant bacteria are so widely distributed," McArthur said.

Additional researchers on this study include R. Cary Tuckfield, Ecostatys, LLC, Aiken, S.C.; Craig Baker-Austin, Centre for Environment, Fisheries and Aquaculture Science, Lowestoft, U.K.; and Dean E. Fletcher, UGA Savannah River Ecology Laboratory, Aiken, S.C.

The study, 'Patterns of Multi-Antibiotic-Resistant Escherichia Coli from Streams with No History of Antimicrobial Inputs,' is available at http://link.springer.com/article/10.1007/s00248-015-0678-4/fulltext.html.

http://www.eurekalert.org/pub_releases/2015-12/jhm-uth122115.php

Unsynching the heartbeat a bit each day halts worsening heart failure

Short daily exposure to 'asynchrony' using a pacemaker may jump-start a suite of recovery mechanisms, experiments suggest

Johns Hopkins has demonstrated in animals that applying a pacemaker's mild electrical shocks to push the heart in and out of normal synchronized contraction for part of each day may be an effective way to slow down the progression of heart failure, a disorder that afflicts millions of Americans.

In the study published online in the Dec. 23 issue of Science Translational Medicine, the researchers say recent experiments in dogs show that the therapy, called Pacemaker Induced Transient Asynchrony, or PITA, reverses cellular damage to the heart's response to hormones, like adrenaline, and fixes the damage to the motor proteins in the heart muscle that generate force. Essentially, the therapy uses a pacemaker over several hours to alternately "zap" a region of heart muscle with electrical shocks so it beats out of synch, and then reverses this so the heart beats again in synchrony for the rest of the day.

"It's the process of going back and forth that is important. In a way, we've attached a light-switch timer to a pacemaker -- like the automatic timers used in homes to turn lights on and off -- but here it flips the pacemaker between synchronous and out-of-synch states each day," says David Kass, M.D., a professor of medicine and biomedical engineering at the Johns Hopkins University School of Medicine. "We're very excited about prospects for this therapy because if further research confirms its effectiveness and safety, it's relatively easy to implement. The pacemaker hardware already exists, and with some software upgrades, we may have a treatment that would benefit many, many people."

According to Kass, congestive heart failure, marked by enlargement and weakness of the heart muscle, affects tens of millions of people worldwide and remains a leading cause of hospitalization and death. In approximately 25 percent of patients, the disease is worsened by so-called dyssynchronous contraction resulting from delays in electrical activation between the two sides of the heart.

"For heart failure patients who develop dyssynchrony, the heart ends up out of tune, like a car with a broken timing belt," says Kass. A decade ago, his team pioneered cardiac resynchronization therapy, which uses a pacemaker to deliver electric pulses to both sides of the heart so it's retuned, or synchronized. Over the years, they discovered that resynchronization therapy also improves the heart's tissue, including changes in the way that calcium flows through heart muscle cells, the way that receptors on the heart respond to hormones, like adrenaline, and the way that the heart's force-generating fibers performed. "We discovered that this wasn't just tuning the engine -- the engine itself wasn't the same anymore," says Kass. "At a very basic level, the molecular processes that control heart contraction had improved."

These observations led Kass and his colleagues to develop PITA and begin their latest animal experiments. They would ultimately be aimed at the 75 percent of heart failure patients who do not have dyssynchrony and so are not eligible for a resynchronizing pacemaker.

In the new experiments with dogs, the researchers first induced heart failure in the animals -- 10 received PITA, and 13 served as heart failure controls -- by delivering atrial pacing, or small electrical pulses to the right atrium of the heart, 200 times per minute, 24 hours a day for four weeks. After four weeks, the PITA treatment group received six hours of electrical pulses per day to the right ventricle at the same 200-times-per-minute rate and then atrial pacing for the remaining 18 hours of the day. The control group received an additional four weeks of continuous atrial pacing. An additional eight dogs received no atrial pacing at all and were kept as controls.

The investigators found that, relative to the heart failure control group, four weeks of PITA treatment reduced progressive enlargement of the heart, boosted its response to adrenaline stimulation by 38 percent, reversed dysfunction and structural damage of motor proteins that occurred in about 40 percent of the heart failure group, and increased the force-generating ability of the muscle also by about 40 percent. There were no apparent adverse side effects from PITA.

"We liken PITA to immunization, where you're given just a bit of a bug to help you mount a robust immune response that protects you against a more serious infection. Too much dyssynchrony exposure is also bad for the heart; we knew that, but here we show that a little bit each day can stimulate beneficial effects," says Kass.

Kass speculates that the ideal patient for PITA, if further research affirms its value, would be one with heart failure who has normal synchronous heart contractions and is a candidate for an internal defibrillator; this covers about 75 percent of heart failure patients.

A defibrillator is an insurance policy that is only helpful if you have a lethal arrhythmia, but by itself, it does not change heart function or symptoms. Used in conjunction with PITA, though, the defibrillator has the potential to improve symptoms now as well. PITA was not compared to any drug therapies in this animal study, and long-term risks remain to be determined.

Additional authors on the study include Khalid Chakir, Richard Tunin, Iraklis Pozios, Theodore Abraham and Jennifer Van Eyk of Johns Hopkins Medicine; Jonathan Kirk and Pieter de Tombe of Loyola University; Kyoung Hwan Lee and Roger Craig of the University of Massachusetts Medical School; Edward Karst and Taraneh Farazi of St. Jude Medical; Ronald Holewinski of Cedars-Sinai Medical Center; and Gianluigi Pironti and Howard Rockman of Duke University.

The study was funded by grants from the National Heart, Lung, and Blood Institute (P01-HL077180, T32-HL007227, P01-HL059408, NHLBI-HV-10-05(2), P01-HL75443); Abraham and Virginia Weiss and Michael and Janet Huff Endowments; the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01-AR034711); the Department of Health and Human Services (HHSN268201000032C); the American Heart Association (14SDG20380148); and the Burroughs Wellcome Fund.

Kass, who has a patent pending for PITA in accordance with Johns Hopkins University policies, says clinical trials with PITA could begin in 2017 in selected patients.

http://www.eurekalert.org/pub_releases/2015-12/nlmc-mdr122315.php

Marijuana derivative reduces seizures in people with treatment-resistant epilepsy

New open-label trial of prescription cannabidiol shows overall safety and efficacy

NEW YORK, NY - Cannabidiol (CBD), a medical marijuana derivative, was effective in reducing seizure frequency and well-tolerated and safe for most children and young adults enrolled in a year-long study led by epilepsy specialists at NYU Langone Medical Center.

These latest findings provide the first estimates of safety, tolerability and efficacy of prescription CBD in children and adults with severe, highly treatment-resistant epilepsy. Led by Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry and director of the Comprehensive Epilepsy Center at NYU Langone, the study is published in the December 23 issue of Lancet Neurology. While early findings have been released at medical meetings -- including the 2015 American Academy of Neurology conference -- these are the first findings from the trial to be published in a peer-reviewed journal.

The study took place at 11 epilepsy centers across the country. Patients were given the oral CBD treatment Epidiolex over a 12-week treatment period. Results showed a median 36.5 percent reduction in monthly motor seizures, with the median monthly frequency of motor seizures falling from 30 motor seizures a month at the study's start to 15.8 over the 12 weeks. Equally important, CBD was shown to have a sufficient safety profile and was well-tolerated by many patients, despite some isolated adverse events.

"We are very encouraged by our trial results showing that CBD was safe and well-tolerated for most patients, and that seizures dropped significantly," says Devinsky. "But before we raise hopes for families who regularly deal with the devastation of treatment-resistant epilepsy, more research, including further studies through our ongoing randomized controlled trial, are needed to definitively recommend CBD as a treatment to patients with uncontrolled seizures."

How the Research Was Conducted

The study was an open-labeled trial, meaning that both the researchers and participants' families knew they were receiving CBD, a compound in medical marijuana that does not contain psychoactive properties. Between January 15, 2014, and January 15, 2015, 214 patients between 1 and 30 years of age with intractable, or treatment-resistant, epilepsy were enrolled in the trial. Of that cohort, 162 (76 percent) had at least 12 weeks of follow-up after the first dose of CBD and were included in the safety and tolerability analysis. In addition, 137 of the original study cohort (64 percent) were included in the analysis to determine the drug's efficacy.

Patients were given an oral CBD regimen from 2-5 mg/kg per day, with a dose up-titrated until intolerance occurred or to a maximum dose of 25 mg/kg or 50 mg/kg per day, depending on the trial site. Seizures were recorded by parents or caregivers in diaries and reviewed by the study team at each visit.

Lab screenings also were conducted at baseline, and after 4, 8 and 12 weeks of CBD treatment. The study showed variability in responses of individual seizure types to cannabidiol treatment. For example, the median change in total seizures was 34.6 percent , with the greatest reduction occurring in patients with focal and atonic seizures followed by tonic or tonic-clonic seizures. Two patients were free of all seizure types over the entire 12 weeks.

Adverse events were reported among participants, including drowsiness, decreased appetite, diarrhea, fatigue and convulsion. Most were mild to moderate and transient, but 20 patients had serious adverse events related to CBD use -most commonly status epilepticus, or seizures that last too long or too close together. Five patients had to discontinue treatment due to these adverse events.

Devinsky is currently leading a randomized, controlled trial - considered the gold standard of scientific research -in which CBD or a placebo is randomly assigned to patients to better tease out the drug's effects and better eliminate research bias.

"I empathize with parents who are looking for answers and will try anything to help their children suffering the devastating effects of intractable epilepsy. But we must let the science, and not anecdotal success stories and high media interest, lead this national discussion," cautions Devinsky. "Taking CBD in a controlled medical setting is vastly different from going to a state where medical marijuana is legal and experimenting with dosing and CBD strains."

The 11 sites included in the trial are NYU Langone Medical Center; Children's Hospital of Philadelphia; Massachusetts General Hospital for Children; Ann & Robert H Lurie Children's Hospital of Chicago; Benioff Children's Hospital, University of California, San Francisco; Miami Children's Hospital; Pediatric and Adolescent Neurodevelopmental Associates in Atlanta; Texas Children's Hospital; University of Utah Medical Center and Primary Children's Hospital; Wake Forest School of Medicine; and Nationwide Children's Hospital.

GW Pharmaceuticals in the U.K. supplied the cannabidiol but had no role in the study design, data analysis, data interpretation, writing of the study or publication submission. The study was also funded by the Epilepsy Therapy Project of the Epilepsy Foundation, and Finding A Cure for Epilepsy and Seizures (FACES).

In addition to Devinsky, the authors of this study are Eric Marsh and Daniel Friedman (who were equal contributors with Devinsky), Elizabeth Thiele, Linda Laux, Joseph Sullivan, Ian Miller, Robert Flamini, Angus Wilfong, Francis Filloux, Matthew Wong, Nicole Tilton, Patricia Bruno, Judith Bluvstein, Julie Hedlund, Rebecca Kamens, Jane Maclean, Srishti Nangia, Nilika Shah Singhal, Carey A Wilson, Anup Patel, and Maria Roberta Cilio.

http://bit.ly/1YI7QK8

Flu Season Will Likely Peak in February, Model Suggests

This flu season will likely peak in February and could be a mild one, according to a new model that aims to forecast the flu in the United States this winter.

by Rachael Rettner, Senior Writer | December 21, 2015 05:13pm ET

The model uses information from past flu seasons, along with a mathematical representation of how influenza spreads through a population and the latest data on the current flu season, to predict how seasonal flu will pan out in the coming months.

According to the new model, there's a less than 1 percent chance that the flu season will peak before January in most of the country, and a less than 20 percent chance that it will peak in January.

On the other hand, there's a 57 percent chance that flu season will peak in February. That would be relatively late — the last three flu seasons have all peaked in December, said Dave Osthus, a researcher at Los Alamos National Laboratory who leads the flu forecast project.

The new model also predicts that this flu season will be mild, meaning there will be fewer flu cases than in a typical flu season.

The main reason for this prediction is that "historically, earlier-peaking flu seasons have tended to be more intense... [and] later-peaking seasons tend to be more mild," Osthus told Live Science.

But Osthus cautioned that there is still a lot that scientists don't know about predicting flu seasons — factors such as holiday travel and the rate at which people get flu shots could change the predictions. The researchers plan to update their predictions every two weeks during the 2015-2016 flu season and, at the end of the flu season, assess how well their model did, Osthus said.

The researchers will also continue to tweak their model to improve the predictions. For example, they plan to update the model to take into account how well the flu shot matches the strains of flu in circulation. The model will also incorporate Wikipedia searches for flu, which has been shown in previous research to help predict flu outbreaks.

Dr. Amesh Adalja, an infectious-disease specialist and a senior associate at the University of Pittsburgh Medical Center's Center for Health Security, who was not involved with the study, said that predictions for flu season can help people plan for the coming season.

For example, a later start to flu season means there is more time for people to get vaccinated before flu activity picks up.

"A prediction [of a late flu season] could sway somebody that's been delaying" vaccination, Adalja said.

However, Adalja said that mild flu seasons can still cause a substantial number of illnesses. "Even a mild season of influenza is still a substantial burden," Adalja said. "Every season … kills thousands of Americans."

Osthus agreed. "Even though we're anticipating a milder flu season, we still highly recommend that everyone go and get their flu shot," Osthus said. He also noted that the term "mild season" refers to how many people get sick with the illness, and not how severe the flu will be for an individual person.

http://www.eurekalert.org/pub_releases/2015-12/usmc-lhr122315.php

Liver hormone reduces preference for sweets, alcohol, via brain's reward pathway

A liver hormone works via the brain's reward pathway to reduce cravings for sweets and alcohol in mammals, UT Southwestern Medical Center researchers have found.

DALLAS - "This is the first time a hormone made in the liver has been shown to affect sugar and alcohol preference in mammals," said Dr. Steven Kliewer, Professor of Molecular Biology and Pharmacology at UT Southwestern and co-senior author of the study, published online today in Cell Metabolism.

The hormone - fibroblast growth factor 21, or FGF21 - is associated with environmental stress such as extreme dietary changes or cold temperature exposure. It is also produced when mammals consume carbohydrates. Because of FGF21's unique effects, forms of the protein are being evaluated as drugs for the treatment of obesity and type 2 diabetes.

"Our findings raise the possibility that FGF21 administration could affect nutrient preference and other reward behaviors in humans, and that the hormone could potentially be used to treat alcoholism," said Dr. Kliewer, who holds the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research.

The researchers report that mice with elevated levels of FGF21 showed reduced preference for sweetener- and alcohol-laced water as well as a marked decrease in levels of dopamine, a neurotransmitter that plays a central role in reward behavior.

"We found that FGF21 administration markedly reduces sweet and alcohol preference in mice, and sweet preference in larger animal models," said co-senior author Dr. David Mangelsdorf, Chair of the Department of Pharmacology and a Howard Hughes Medical Institute Investigator, who runs a joint laboratory with Dr. Kliewer. Dr. Mangelsdorf holds the Alfred G. Gilman Distinguished Chair in Pharmacology, and the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D.

To confirm that FGF21 acts via a brain pathway, the researchers took advantage of the fact that FGF21 requires the co-receptor β-Klotho in order to function. When FGF21 levels were increased in mice genetically unable to make β-Klotho in the central nervous system, the effect on taste preference disappeared.

This marks the fourth study from the Mangelsdorf-Kliewer laboratory to show that FGF21 directly affects the central nervous system. First, in two studies in Nature Medicine in 2013, they reported on FGF21's ability to regulate metabolism, circadian (body clock) behavior, and female reproduction. In 2014, they reported in Cell Metabolism that FGF21 acts on the brain to cause weight loss.

"The finding that FGF21 acts via the brain was completely unexpected when we started down this path of investigation a dozen years ago," Dr. Kliewer said. "These findings suggest that additional studies are warranted to assess the effects of FGF21 on sweet and alcohol preference and other reward behavior in humans."

The study was supported by the National Institutes of Health, the Robert A. Welch Foundation, the Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society, the Ford Foundation Fellowship, the German National Science Foundation, and the Howard Hughes Medical Institute. Novo Nordisk provided the recombinant FGF21 used in the experiments.

UT Southwestern co-authors from Pharmacology included Dr. Bryn Owen, a former postdoctoral researcher now at Imperial College, London; Dr. Parkyong Song, a postdoctoral researcher; graduate student Genaro Hernandez; Dr. Yuan Zhang, Instructor in Pharmacology; and summer intern William T. Scott. Also contributing was Dr. Hao Tang, Assistant Professor of Clinical Sciences.

UT Southwestern collaborated on the study with researchers from Friedrich-Alexander University Erlangen-Nuremberg in Germany, King's College London in England, and Pfizer in the United States.

http://www.eurekalert.org/pub_releases/2015-12/osu-res122315.php

River ecosystems show 'incredible' initial recovery after dam removal

Fate of one songbird species indicates fast rebound

Written by Misti Crane

COLUMBUS, Ohio - A songbird species that flourishes on the salmon-rich side of dams in the western United States struggles when it tries to nest on the side closed off from the fish and the nutrients they leave behind.

But the songbird and the rest of the divided ecosystem rebounds, faster than some experts expected, when dams come down and rivers are allowed to resume their natural flow.

Two new studies led by Christopher Tonra, assistant professor of avian wildlife ecology at The Ohio State University, illustrate the stress dams impose on species that rely on salmon and the impact of dam removal on the well-being of that wildlife.

The areas previously depleted of salmon are on a fast track to recovery in a shorter time than he ever expected after the dam removal, Tonra said.

"It's exciting to be able to show a real positive outcome in conservation. We don't always get that," he said. "That these rivers can come back within our own generation is a really exciting thing."

During his time conducting the studies in Washington, Tonra watched reservoir beds that looked like moonscapes return to vibrant, rich habitat and cascades emerge where none had been, at least for the last century.

"Watching that happen was just incredible," he said.

Tonra and his colleagues studied the American dipper, a bird set apart by its unusual feeding style. Dippers, which are equipped with a transparent second eyelid (think water goggles for birds), dive below the river's surface and walk the riverbed scouring the rocky floor for meals, mostly aquatic insects in their larval stage. They also eat some small fish, including juvenile salmon when they're available.

The studies are the first to examine the effects of dams, and dam removal, on the dipper, considered an indicator species and the only bird of its type found in North America. Dippers that are faring well point to a strong ecosystem in and around the river.

"These birds are right where aquatic and terrestrial ecosystems meet," Tonra said.

Tonra and his colleagues spent four years in Washington's Olympic National Park and surrounding tribal, federal and private lands. The Elwha River winds through the park and is the site of the largest dam removal in history. Crews started tearing down the Elwha and Glines Canyon dams in 2011 and concluded in 2014, freeing the path for migratory fish for the first time in a century.

Salmon, which do most of their growing in the ocean, carry marine-derived nitrogen and carbon back into freshwater systems when they return to spawn and die. They benefit animals and plants, whether through direct consumption or because nutrients find their way into plants and other food, including larval mayflies and other insects for which the dipper dives.

"They're truly fertilizing the river and so that makes its way all the way up through the food chain," Tonra said.

In one study, the researchers documented that American dippers with access to salmon were in better physical condition and more likely to attempt multiple broods of offspring in a season. They also produced larger female offspring and were more likely to stay in breeding territories year-round. The research, published early online, will appear in an upcoming issue of the journal Ecography.

Tonra and his colleagues worked along four streams, three of which were blocked to salmon either by waterfalls or dams. They banded the birds, weighed them and collected blood samples. They looked at carbon and nitrogen in the birds' blood to determine their level of marine-derived nutrient intake.

The research team watched for multiple attempts to breed and an inclination to stay in the nesting area year-round, and tracked what type of food was delivered to nestlings.

The birds with salmon access had more marine-derived nutrients and were 20 times more likely to attempt multiple broods. They were 13 times more likely to stay year-round and had an annual adult survival rate that was 11 percent higher than their salmon-deprived peers.

The female birds with access to salmon had larger body mass, suggesting they were healthier. Fledgling females raised in areas with salmon also were larger.

The birds without access to salmon and food enriched by their presence "weren't in very good condition and it looked like they weren't attempting to breed as much," Tonra said.

And they took off after they fledged a single brood, presumably for salmon-rich waters.

"Within the same river you basically have two different populations," Tonra said.

There's good news in the team's second dipper study, published in the December 2015 issue of the journal Biological Conservation: Within a year of the Elwha Dam removal, Tonra and his colleagues were able to document an increase in salmon-derived nutrients in American dippers.

Tonra was surprised, and delighted, by how quickly the salmon returned.

"It was pretty much as soon as the first dam came out and fish were beating up against the second, wanting to go." Tonra, previously with the Smithsonian Migratory Bird Center, worked with Kimberly Sager-Fradkin of the Lower Elwha Klallam Tribe and Peter Marra of the Smithsonian on both studies. Sara Morley of the Northwest Fisheries Science Center and Jeffrey Duda of the Western Fisheries Research Center contributed to the study published in Biological Conservation.

Tonra said he'd like to return to the Pacific Northwest soon to measure changes in the birds' patterns and health since the dam removal. He's hopeful that other birds and bats that feast on insects in the air and on the trees near the river will become stronger as well.

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