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Scientists uncover marvel molecule that could lead to treatments for inflammatory diseases

Scientists from Trinity College Dublin believe that the marvel molecule - MCC950 - could one day be used to treat a myriad of these diseases

Dublin, Ireland, February 16th 2015 - Scientists at Trinity College Dublin have uncovered a marvel molecule that blocks a key driver of inflammatory diseases. The finding could meet a major unmet clinical need by inspiring new non-invasive treatments for arthritis, multiple sclerosis and Muckle-Wells syndrome, among a myriad of other inflammatory diseases.

In a study published this week in the world's leading preclinical medical journal Nature Medicine, the international research team led by Trinity and the University of Queensland Australia showed how the molecule MCC950 can suppress the 'NLRP3 inflammasome', which is an activator of the key process in inflammatory diseases.

Inflammasomes have been identified as promising therapeutic targets by researchers over the last decade. And now the discovery of MCC950's abilities represents a hugely significant development in the effort to find treatments for inflammatory diseases, for which current therapies are either highly ineffective or have major limitations.

Crucially, the finding also confirms that inflammatory diseases all share a common process, even though the part of the body becoming inflamed might differ.

Professor of Biochemistry at Trinity, Luke O'Neill, is the joint senior scientist behind the discovery. He said: "Drugs like aspirin or steroids can work in several diseases, but can have side effects or be ineffective. What we have found is a potentially transformative medicine, which targets what appears to be the common disease-causing process in a myriad of inflammatory diseases."

Dr Rebecca Coll, lead author on the paper, said: "MCC950 is blocking what was suspected to be a key process in inflammation. There is huge interest in NLRP3 both among medical researchers and pharmaceutical companies and we feel our work makes a significant contribution to the efforts to find new medicines to limit it."

Professor Matt Cooper, chemist and co-senior author from the University of Queensland's Institute for Molecular Bioscience (IMB), added: "MCC950 is able to be given orally and will be cheaper to produce than current protein-based treatments, which are given daily, weekly, or monthly by injection. Importantly, it will also have a shorter duration in the body, allowing clinicians to stop the anti-inflammatory action of the drug if the patient ever needed to switch their immune response back to 100% in order to clear an infection."

So far, the results have shown great promise for blocking multiple sclerosis in a model of that disease, as well as in sepsis, where in response to bacteria, potentially fatal blood poisoning occurs. However, the target for MCC950 is strongly implicated in diseases such as Alzheimer's disease, atherosclerosis, gout, Parkinson's disease and rheumatoid arthritis, which means it has the potential to treat all of these conditions.

Another disease where the new drug might have significant benefits is Muckle-Wells syndrome, which is a rare and severe auto-inflammatory disorder. Using blood samples from patients, the authors showed that MCC950 can block the rogue gene responsible for repeated inflammatory activation in sufferers.

Dr Dan Kastner of the National Institutes of Health USA, said: "MCC950 might well be a key addition to the options for treating Muckle-Wells syndrome and similar diseases."

Professor O'Neill added: "We are really excited about MCC950. We believe this has real potential to benefit patients suffering from several highly debilitating diseases, where there is currently a dire need for new medicines."

The study was a major collaboration between six institutions, including Trinity and the Universities of Queensland, Michigan, Massachusetts and Bonn.

The work in the O'Neill laboratory was supported by Science Foundation Ireland and the European Research Council. The research paper can be viewed here after the embargo has lifted: http://dx.doi.org/10.1038/nm.3806. A strictly embargoed copy can be viewed upon request.

http://www.eurekalert.org/pub_releases/2015-02/uow-ars021115.php

Ancient rocks show life could have flourished on Earth 3.2 billion years ago

A spark from a lightning bolt, interstellar dust, or a subsea volcano could have triggered the very first life on Earth. But what happened next?

Life can exist without oxygen, but without plentiful nitrogen to build genes - essential to viruses, bacteria and all other organisms - life on the early Earth would have been scarce.

The ability to use atmospheric nitrogen to support more widespread life was thought to have appeared roughly 2 billion years ago. Now research from the University of Washington looking at some of the planet's oldest rocks finds evidence that 3.2 billion years ago, life was already pulling nitrogen out of the air and converting it into a form that could support larger communities.

"People always had the idea that the really ancient biosphere was just tenuously clinging on to this inhospitable planet, and it wasn't until the emergence of

nitrogen fixation that suddenly the biosphere become large and robust and diverse," said co-author Roger Buick, a UW professor of Earth and space sciences. "Our work shows that there was no nitrogen crisis on the early Earth, and therefore it could have supported a fairly large and diverse biosphere."

The results were published Feb. 16 in Nature.

The authors analyzed 52 samples ranging in age from 2.75 to 3.2 billion years old, collected in South Africa and northwestern Australia. These are some of the oldest and best-preserved rocks on the planet. The rocks were formed from sediment deposited on continental margins, so are free of chemical irregularities that would occur near a subsea volcano. They also formed before the atmosphere gained oxygen, roughly 2.3 to 2.4 billion years ago, and so preserve chemical clues that have disappeared in modern rocks.

Even the oldest samples, 3.2 billion years old - three-quarters of the way back to the birth of the planet - showed chemical evidence that life was pulling nitrogen out of the air. The ratio of heavier to lighter nitrogen atoms fits the pattern of nitrogen-fixing enzymes contained in single-celled organisms, and does not match any chemical reactions that occur in the absence of life.

"Imagining that this really complicated process is so old, and has operated in the same way for 3.2 billion years, I think is fascinating," said lead author Eva Stüeken, who did the work as part of her UW doctoral research. "It suggests that these really complicated enzymes apparently formed really early, so maybe it's not so difficult for these enzymes to evolve."

Genetic analysis of nitrogen-fixing enzymes have placed their origin at between 1.5 and 2.2 billion years ago.

"This is hard evidence that pushes it back a further billion years," Buick said.

Fixing nitrogen means breaking a tenacious triple bond that holds nitrogen atoms in pairs in the atmosphere and joining a single nitrogen to a molecule that is easier for living things to use. The chemical signature of the rocks suggests that nitrogen was being broken by an enzyme based on molybdenum, the most common of the three types of nitrogen-fixing enzymes that exist now. Molybdenum is now abundant because oxygen reacts with rocks to wash it into the ocean, but its source on the ancient Earth - before the atmosphere contained oxygen to weather rocks - is more mysterious.

The authors hypothesize that this may be further evidence that some early life may have existed in single-celled layers on land, exhaling small amounts of oxygen that reacted with the rock to release molybdenum to the water.

"We'll never find any direct evidence of land scum one cell thick, but this might be giving us indirect evidence that the land was inhabited," Buick said. "Microbes could have crawled out of the ocean and lived in a slime layer on the rocks on land, even before 3.2 billion years ago."

Future work will look at what else could have limited the growth of life on the early Earth. Stüeken has begun a UW postdoctoral position funded by NASA to look at trace metals such as zinc, copper and cobalt to see if one of them controlled the growth of ancient life.

Other co-authors are Bradley Guy at the University of Johannesburg in South Africa, who provided some samples from gold mines, and UW graduate student Matthew Koehler. The research was funded by NASA, the UW's Virtual Planetary Laboratory, the Geological Society of America and the Agouron Institute.

http://nyti.ms/17SKjTQ

Research Finds a Reason Leprosy Has Persisted

Mycobacterium leprae bacteria can survive for months inside common amoebae

The bacteria that cause leprosy can survive for months inside amoebae that are common in water and soil, and even in human eyes and noses, scientists at Colorado State University have found.

The discovery may help answer a question that has puzzled tropical disease experts for years: Why does the number of new leprosy cases around the world not decrease even though thousands of victims are now on drugs that make them less infectious and eventually will cure them?

There are about 200,000 new infections each year in Brazil, India, Angola, Madagascar, Myanmar, Indonesia, the Philippines and a few other countries.

The study was published in December in PLOS Neglected Tropical Diseases.

Leprosy is caused by Mycobacterium leprae, slow-growing bacteria related to tuberculosis that target nerve cells beneath the skin. They cannot be cultured in the laboratory, and exactly how they infect is unclear.

Because leprosy spreads in families and among people in prolonged contact, researchers have long assumed that it always moves between human hosts.

“But we do get novel cases that don’t seem to be related to others," said William H. Wheat, a microbiologist at Colorado State University and one of the study’s authors.

M. leprae are engulfed by five kinds of common amoebae, including some that can live in mucus and eye fluids and can resist being digested. When the amoebae form cysts to avoid drying out, the study found, the bacteria can survive inside them for months and then still infect laboratory mice.

That, Dr. Wheat said, may explain how the bacteria persist and turn up even where no infected humans are found.

http://bit.ly/1LcJLGw

Mystery cloud-like blobs over Mars baffle astronomers

Astronomers around the world noticed a strange blob rising out of the planet's southern hemisphere

16:03 16 February 2015 by Jacob Aron

For space watchers, Mars is like a second home. Astronomers have been studying the Red Planet for centuries – the first map of the Martian surface was sketched 500 years ago. Since then, it has become the most surveyed planet in the solar system, besides Earth. We have sent over 50 robot explorers to patrol its surface and watch it from orbit, seven of which are operational on and around the Red Planet right this minute. It's not for nothing that space aficionados quip that Mars is the only planet known to be inhabited solely by robots.

So it was that much more surprising when, on 12 March 2012, amateur astronomers around the world noticed a strange blob rising out of the planet's southern hemisphere, soaring to 250 kilometres above the surface.

They watched for 11 days as it grew to around 1000 kilometres across, even stretching a "finger" out into space. "I was really quite amazed that it was sticking out the side of the planet quite prominently," says Damian Peach, who lives in Selsey, UK, and was one of the first to spot it.

Poor weather and other issues meant no one had their eye on Mars the following week, and by 2 April it seemed to have disappeared. Then on 6 April a second object of the same type emerged from the same spot and lasted another 10 days. It, too, has not been seen since.

Nearly three years later, the sighting still defies explanation. In an attempt to pin down the blobs' origins, Agustin Sánchez-Lavega of the University of the Basque Country, Spain, and colleagues, including Peach, sought out images of Mars from that period. They wound up collecting pictures from 18 observers equipped with a variety of small telescopes. The team also searched through old images taken by the Hubble Space Telescope and identified a similar object in 1997.

Exotic theories

The team considered several possible explanations, each more exotic than the last. Despite their best efforts, though, they couldn't come up with any that were consistent with known processes – and neither can anyone else. "Frankly, I'm puzzled by the observations," says Bruce Jakosky of the University of Colorado, Boulder, who leads NASA's Mars-atmosphere-observing MAVEN mission. "I don't understand how material can get that high and stay there for so long."

One clue is that the blobs seemed to appear at Mars's terminator, the fuzzy line where night turns into day. That suggests a change in atmospheric temperature due to the morning sun may be responsible. The team's best guess is that the object is a cloud of frozen carbon dioxide and water particles condensing in the upper atmosphere.

If that's the case, it would be unlike any cloud seen anywhere on Mars, or on Earth. Clouds on both planets are only ever seen at altitudes below 100 kilometres, which on Earth is the accepted height for the beginning of outer space. "If the phenomenon is a cloud, then the most similar phenomena on Earth will be the mesospheric clouds that form at 80 kilometres altitude on polar regions," says Sánchez-Lavega.

Auroras

With that in mind, thoughts have turned to other potential explanations. Charged particles from the sun interact with the Earth's magnetic field to make the upper atmosphere glow – the phenomenon we call auroras. Mars's magnetic field is weak and patchy in comparison, meaning auroras were only seen there for the first time in 2005. That sighting was over a region tantalising close to the unexplained blobs.

The team calculate that the blobs could be auroras, but only if it is more than 1000 times brighter than Earth's. That seems unlikely, especially since the sun wasn't particularly active in March 2012. "The fact that you might see a visible aurora is not completely out of the realm of possibility," says Nicholas Heavens of Hampton University in Virginia. "But they don't really come to visible brightness anywhere near what this thing would be."

What about something like a massive volcano pumping material into the atmosphere? The blobs seemed to extend upwards from the surface of Mars, though it's hard to determine this exactly given the quality of the images we have. But that wouldn't explain why the blobs have only appeared in the morning says Sánchez-Lavega, and in any case we don't know of any active volcanoes on Mars. "You would think that something large enough to dump that much vapour in the atmosphere would be picked up," says Heavens. A massive dust storm is also ruled out, as they normally don't reach above 60 kilometres and the blob doesn't carry Mars's signature dusty red.

Aliens at work?

OK, now we're getting desperate. Could the explanation be biological? Whether there is life on Mars is one of the planet's major mysteries (see box), but any alien hunters excited by the blobs should calm down, says Sánchez-Lavega: "No life past or present [has been] detected so far on Mars, so it cannot be." Heavens says there isn't really enough data to rule either way, but it's better to be cautious. "If there is no positive evidence, you should probably exclude something biological."

It seems that all we can do is wait and hope the object turns up again, although Peach thinks that the favourable conditions that occurred in 2012 may not happen

for some time. "The season on Mars is very cloudy around that time of year, and that just happened to occur at opposition," he says, referring to when Mars and Earth are aligned on the same side of the sun. That particular combination won't happen again for over a decade, he says.

Perhaps instead it will be observed by one of our robot minions. MAVEN is on an orbit that would have allowed it to fly through the blob, but the probe only reached Mars last year. "MAVEN should see something like this very easily if it occurred again, if we were at the right place at the right time," says Jakosky. "I've given a heads-up to our science team, so they'll be keeping an eye out for it."

Journal reference: Nature, DOI: 10.1038/nature14162

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Humans off the Hook for Alaskan Mastodon Extinction

A reexamination of museum mastodon specimens provides evidence that that last ones were gone from what's called the Beringia region well before any humans showed up. Emily Schwing reports

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It's long been thought mammoths and mastodons rambled over North America's arctic and subarctic realms between 75,000 and 100,000 years ago, and were made extinct by hungry new arrivals on the scene: human beings. But new evidence indicates mastodons probably roamed the region as far back as 120,000 years ago - and they were gone before the first people showed up.

"For at the least the story of the mastodon, we now know for what we call Beringia - Alaska, parts of Yukon and over into northeastern Asia - they were wiped out in those areas for things that had nothing to do with humans, because they all died out before there were humans there." Pat Druckenmiller is the Curator of Earth Science at the University of Alaska Museum of the North. "Humans could not have been part of the story and that's pretty interesting."

The research is in the Proceedings of the National Academy of Sciences. [Grant D. Zazula et al, American mastodon extirpation in the Arctic and Subarctic predates human colonization and terminal Pleistocene climate change]

Druckenmiller and co-authors were led to these conclusions after colleagues at the Yukon Paleontology Program in Canada decided to redate nearly 40 specimens, because American mastodons are often mistaken for their much hairier wooly mammoth cousins, who hung around the area later.

"A mammoth and a mastodon can be immediately distinguished on the basis of their teeth, their big cheek teeth." The surface of a mammoth tooth looks like a washboard, perfect for grinding grasses that grew during the last ice age. But mastodon teeth have much lumpier, bumpier cusps: ideal for chewing twigs and leaves.

"People in the past when they found these teeth and bones, they put glue and other kinds of strange things on them, and that glue can mess up the dates, gives you a wrong date. In fact, it gives you a date that's too young."

The new dates corroborate what mastodon teeth show: They ambled over Beringia when the region was warmer and forested, long before mammoths and earlier than humans. So, if humans didn't wipe out the mastodon, what did? That mystery remains for scientists to sink their teeth into.

http://www.eurekalert.org/pub_releases/2015-02/luhs-it021615.php

In the short run, a high-fat diet may help minimize heart attack damage

High-fat diet one day to two weeks before a heart attack reduced heart attack damage by about 50

MAYWOOD, Il. - It's well known that over the long run, a high-fat diet increases the risk of heart attack and stroke. But a new study has found that a high-fat diet, eaten one day to two weeks days before a heart attack, actually reduced heart attack damage in mice by about 50 percent.

The finding by a team led by W. Keith Jones, PhD, of Loyola University Chicago Stritch School of Medicine, is published in the American Journal of Physiology - Heart and Circulatory Physiology.

"The study improves our understanding of the relationship between diet and health," Dr. Jones said. "Learning about how fat, in the short run, protects against heart attacks could help in the development of better therapies." Dr. Jones emphasized the study is not a license to eat a lot of cheeseburgers and ice cream.

The study may provide new insight into the "obesity paradox": Obesity is a major risk factor for heart disease. But once a heart attack or heart failure does occur, moderately obese patients tend to live longer.

In the study, mice were given a high-fat diet (60 percent of calories from animal fat) before experiencing heart attacks. Mice that consumed a high-fat diet for either one day, one week or two weeks before the heart attack experienced about half as much heart damage as mice that ate a control diet. The benefit was greatest among mice that ate a high-fat diet for one week before the heart attack. But in mice that ate a high-fat diet for six weeks, the protective effect disappeared.

Further research is needed to understand why this is so; the reason may be due to the bad effects of a persistent high-fat diet, Dr. Jones said.

Dr. Jones said that in the short-term, a high-fat diet protects the heart through a mechanism called autophagy, which works somewhat like a garbage truck. Proteins damaged by the heart attack are removed from heart cells as if they were garbage, thus increasing the chances the cells will survive. Acutely, a high-fat diet

increases levels of a molecule in the blood that activates protective pathways in heart muscle. This increases the readiness of the "garbage trucks," which means that the cell becomes resistant to damage when the heart attack occurs. As a result, more heart muscle survives. Dr. Jones's team is studying the nature of the blood-borne molecule and will report results of this research in a later publication.

The current study "opens a new perspective on the acute effects of a high-fat diet," first author Lauren Haar, PhD and colleagues wrote. "Future work will determine whether these effects are linked to the obesity paradox and whether studying the mechanism can identify therapeutic targets for cardioprotection."

The authors added that, given the increasing number of obese people in both developed and developing countries, understanding the relationship between fat intake and heart health is "critically important."

Dr. Jones is professor and chair of the Department of Molecular Pharmacology and Therapeutics of Loyola University Chicago Stritch School of Medicine. In addition to Dr. Jones and Dr. Haar, co-authors from Loyola University Chicago and the University of Cincinnati are Xiaoping Ren, Yong Liu, Sheryl E. Koch, Jillian Goines, Michael Tranter, Melinda A. Engevik, Michelle Nieman and Jack Rubenstein.

http://www.eurekalert.org/pub_releases/2015-02/uom-sha021615.php

Sex has another benefit: It makes humans less prone to disease over time

Mixing our genes through sex helps purge us of disease mutations

For decades, theories on the genetic advantage of sexual reproduction had been put forward, but none had ever been proven in humans, until now. Researchers at the University of Montreal and the Sainte-Justine University Hospital Research Centre in Montreal, Canada have just shown how humanity's predispositions to disease gradually decrease the more we mix our genetic material together. This discovery was finally made possible by the availability in recent years of repositories of biological samples and genetic data from different populations around the globe.

What we already knew

As humans procreate, generation after generation, the exchange of genetic material between man and woman causes our species to evolve little by little. Chromosomes from the mother and the father recombine to create the chromosomes of their child (chromosomes are the larger building blocks of genomes). Scientists have known for some time, however, that the parents' genomes don't mix together in a uniform way. Chromosomes recombine frequently in some segments of the genome, while recombination is less frequent in others. These segments of low-frequency recombination will eventually recombine like others do but it will take many, many generations.

The findings

More specifically, the team of Canadian researchers led by Dr. Philip Awadalla discovered the following: the segments of the human genome that don't recombine as often as others also tend to carry a significantly greater proportion of the more disease-enabling genetic mutations*. Until chromosome recombination eventually occurs, these segments accumulate more and more bad mutations. In other words, as far as susceptibility to disease is concerned, our genetic material actually worsens, before it gets better. Thankfully, disease-enabling mutations are eventually shuffled off our genetic code through sexual reproduction. "But since these mutations rest on less dynamic segments of our genome, the process can potentially take many hundreds of generations," explains Dr. Awadalla.

Why these findings are significant

"This discovery gives us a better understanding of how we, as humans, become more or less at risk of developing or contracting diseases," says Dr. Awadalla. It also tells scientists more precisely where to look in the human genome to find disease-enabling mutations, he adds, which should speed up the discovery and identification of mutations associated with specific diseases. Researchers and health authorities will in turn be able to apply this new information to develop more effective treatments and prevention programs.

The science behind the findings

Dr. Awadalla and his team studied the sequenced genomes of hundreds of individuals from Canada's CARTaGENE genetic data repository and the multinational 1000 Genomes Project. They found that the proportion of mutations associated with disease was significantly higher in low recombining segments known as "coldspots" relative to highly recombining regions, and that the bad mutations in these coldspots were generally more damaging than the mutations in the highly recombining segments.

Through the 1000 Genomes and CARTaGENE programs, the team was able to compare this phenomenon across four present-day population basins: Africans, Asians, Europeans and Canadians of French descent. Each of these genetic groups exhibit the above behaviour to varying degrees. African individuals showed the smallest relative proportion of disease-associated mutations on their genome's coldspots, with Western Europeans showing the largest.

The complete scientific paper was published by Nature Genetics and can be found online at http://www.nature.com/articles/doi:10.1038/ng.3216.

Research partners

This study was made possible by the financial support of Fonds de la Recherche en Santé du Québec (FRSQ), Genome Québec, Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT) and the Canadian Partnership Against Cancer. The CARTaGENE biobank, of which Dr. Awadalla is also the scientific director, receives funding from the

Canadian Partnership Against Cancer, Genome Québec, Genome Canada and the Canadian Institutes of Health Research. Dr. Awadalla is also a Professor of Medical and Population Genetics at the University of Montreal and at the Ontario Institute for Cancer Research.

http://www.eurekalert.org/pub_releases/2015-02/mc-mcm021615.php

Mayo Clinic: Molecule that provides cellular energy found key to aggressive thyroid cancer

Molecule important to survival of anaplastic thyroid carcinoma seems to play a role in a wide range of cancers

JACKSONVILLE, Fla. - Cancer researchers at Mayo Clinic's campus in Jacksonville, Florida, have identified a molecule they say is important to survival of anaplastic thyroid carcinoma (ATC) -- a lethal tumor with no effective therapies. The molecule also seems to play a role in a wide range of cancers.

In an online issue of The Journal of Clinical Endocrinology and Metabolism, they identify Stearoyl-CoA desaturase 1 (SCD1) as an oncogenic enzyme that when inhibited and paired with another targeted drug effectively shuts down ATC cell growth and induces cell death.

Investigators think that ATC relies on SCD1 to provide the fuel the cancer cells need to rapidly duplicate. The molecule provides this energy by promoting the cancer cell's ability to generate certain fatty acids that are important for several biological processes such as cell division, survival, drug resistance and migration.

"We now have some hope for treatment of this cancer, which is arguably the most lethal solid tumor known to medicine," says John Copland, Ph.D., a cancer biologist and the study's senior author. "Although ATC is rare -- accounting for only 1 to 2 percent of thyroid cancers, it is responsible for up to 39 percent of all thyroid cancer-related deaths."

"Currently, there are no therapies for ATC that lead to prolonged survival, but I think combining an SCD1 inhibitor with a cocktail of other agents, all of which have dramatically different targets and approaches, may work," says co-author Robert Smallridge, M.D., an endocrinologist who treats thyroid cancer.

The Mayo researchers have already developed SCD1 inhibitors and are testing the agents in different tumor models.

Cells normally take the fatty acids they need from the bloodstream, instead of making them internally, says lead author Christina von Roemeling, a graduate student and cancer researcher. "But we have found this very unique switch in tumors that makes them very dependent on this method of fatty acid synthesis," she says.

"Given the work we have done in the past several years, it is becoming really clear to us that fatty acid metabolism is quite possibly a crutch used by many cancers," von Roemeling says. "An SCD1 inhibitor might be a therapeutic target that is multipotent for several cancers -- not just a one-hit wonder in a single cancer but very useful as a generic therapy."

"We have seen activity of SCD1 in a number of cancer cell lines -- everything from melanoma to ovarian and breast cancer to prostate and pancreatic cancer," says Dr. Copland. "We now have a new area of cancer therapy to explore that has not been looked at yet in anaplastic thyroid cancer," adds Dr. Smallridge.

Other study co-authors include Laura Marlow, Angela Crist, James Miller and Han Tun, M.D., from Mayo Clinic; and Anthony Pinkerton from the Conrad Prebys Center for Chemical Genomics at Sanford-Burnham Medical Research Institute in La Jolla, California. This work was funded in part from National Institutes of Health / National Cancer Institute grant R01CA136665; Florida Department of Health Bankhead-Coley Cancer Research Program (FL09B202, FL3BF01, JAC); Mr. and Mrs. Ompal Chauhan Research Fund; Scheidel Foundation; Fraternal Order of Eagles Florida State Auxiliary; a grant for rare cancers from Dr. Ellis and Dona Brunton; Mayo Sanford-Burnham Medical Research Institute Collaborative Drug Discovery Program; a gift from Alfred D. and Audrey M. Petersen; the Francis and Miranda Childress Foundation Fund for Cancer Research; John A. and Bette B. Klacsmann Fund for Cancer Research at Mayo Clinic in Florida; and the Betty G. Castigliano Fund in Cancer Research Honoring S. Gordon Castigliano, M.D. cancer research at Mayo Clinic in Jacksonville, Florida.

http://www.eurekalert.org/pub_releases/2015-02/uoc-mib021615.php

Molecular inhibitor breaks cycle that leads to Alzheimer's

A molecule that can block the progress of Alzheimer's disease at a crucial stage in its development has been identified by researchers in a new study, raising the prospect that more such molecules may now be found.

The report shows that a molecular chaperone, a type of molecule that occurs naturally in humans, can play the role of an "inhibitor" part-way through the molecular process that is thought to cause Alzheimer's, breaking the cycle of events that scientists believe leads to the disease.

Specifically, the molecule sticks to threads made up of malfunctioning proteins, called amyloid fibrils, which are the hallmark of the disease. By doing so, it stops these threads from coming into contact with other proteins, thereby helping to avoid the formation of highly toxic clusters that enable the condition to proliferate in the brain.

This step - where fibrils made up of malfunctioning proteins assist in the formation of toxic clusters - is considered to be one of the most critical stages in the development of Alzheimer's in sufferers. By finding a molecule that prevents it from occurring, scientists have moved closer to identifying a substance that could eventually be used to treat the disease. The discovery was made possible by an overall strategy that could now be applied to find other molecules with similar capabilities, extending the range of options for future drug development.

The research was carried out by an international team comprising academics from the Department of Chemistry at the University of Cambridge, the Karolinska Institute in Stockholm, Lund University, the Swedish University of Agricultural Sciences, and Tallinn University. Their findings are reported in the journal Nature Structural & Molecular Biology.

Dr Samuel Cohen, a Research Fellow at St John's College, Cambridge, and a lead author of the report, said: "A great deal of work in this field has gone into understanding which microscopic processes are important in the development of Alzheimer's disease; now we are now starting to reap the rewards of this hard work. Our study shows, for the first time, one of these critical processes being specifically inhibited, and reveals that by doing so we can prevent the toxic effects of protein aggregation that are associated with this terrible condition."

Alzheimer's disease is one of a number of conditions caused by naturally occurring proteins molecules folding into the wrong shape and then sticking together - or nucleating - with other proteins to create thin filamentous structures called amyloid fibrils. Proteins perform important functions in the body by folding into a particular shape, but sometimes they can misfold, potentially kick-starting this deadly process.

Recent research, much of it by the academics behind the latest study, had however suggested a second critical step in the disease's development. After amyloid fibrils first form from misfolded proteins, they help other proteins which come into contact with them to misfold and form small clusters, called oligomers. These oligomers are highly toxic to nerve cells and are now thought to be responsible for the devastating effects of Alzheimer's disease.

This second stage, known as secondary nucleation, sets off a chain reaction which creates many more toxic oligomers, and ultimately amyloid fibrils, generating the toxic effects that eventually manifest themselves as Alzheimer's. Without the secondary nucleation process, single molecules would have to misfold and form toxic clusters unaided, which is a much slower and far less devastating process.

By studying the molecular processes by which each of these steps takes effect, the research team assembled a wealth of data that enabled them to model not only what happens during the progression of Alzheimer's disease, but also what might happen if one stage in the process was somehow switched off.

"We had reached a stage where we knew what the data should look like if we inhibited any given step in the process, including secondary nucleation," Cohen said. "Working closely with our collaborators in Sweden - who had developed groundbreaking experimental methods to monitor the process - we were able to identify a molecule that produced exactly the results that we were hoping to see in experiments."

The results indicated that the molecule, Brichos, effectively inhibits secondary nucleation. Typically, Brichos functions as a "molecular chaperone" in humans; a term given to "housekeeping" molecules that help proteins to avoid misfolding and aggregation. Lab tests, however, revealed that when this molecular chaperone encounters an amyloid fibril, it binds itself to catalytic sites on its surface. This essentially forms a coating that prevents the fibrils from assisting other proteins in misfolding and nucleating into toxic oligomers.

The research team then carried out further tests in which living mouse brain tissue was exposed to amyloid-beta, the specific protein that forms the amyloid fibrils in Alzheimer's disease. Allowing the amyloid-beta to misfold and form amyloid increased toxicity in the tissue significantly but, in the presence of the molecular chaperone, amyloid fibrils still formed but the toxicity did not develop in the brain tissue, confirming that the molecule that the team had identified had suppressed the chain reaction from secondary nucleation that feeds the catastrophic production of oligomers leading to Alzheimer's disease.

By modelling what might happen if secondary nucleation is switched off and then finding a molecule that performs that function, the research team suggest that they have discovered a strategy that may lead to the discovery of many similar molecules that could have a similar effect.

"It may not actually be too difficult to find other molecules that do this, it's just that it hasn't been clear what to look for until recently," Cohen said. "It's striking that nature - through molecular chaperones - has evolved a similar approach to our own by focusing on very specifically inhibiting the key steps leading to Alzheimer's. A good tactic now is to search for other molecules that have this same highly targeted effect and to see if these can be used as the starting point for developing a future therapy."

The other members of the Cambridge team were Dr Tuomas Knowles (tpjk2@cam.ac.uk), Dr Paolo Arosio, Professor Michele Vendruscolo and Professor Chris Dobson. All are members of the Centre for Misfolding Diseases, which is based in the University's Department of Chemistry.

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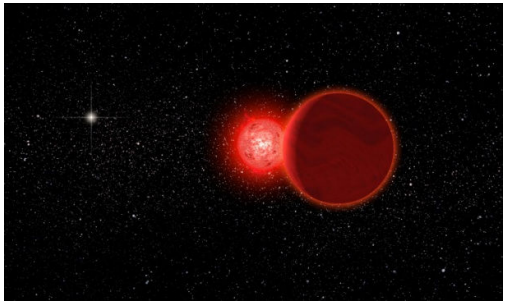
A close call of 0.8 light years

Astronomers identify the closest known flyby of a star to our solar system: A dim star that passed through the Oort Cloud 70,000 years ago

A group of astronomers from the US, Europe, Chile and South Africa have determined that 70,000 years ago a recently discovered dim star is likely to have passed through the solar system's distant cloud of comets, the Oort Cloud. No other star is known to have ever approached our solar system this close - five times closer than the current closest star, Proxima Centauri.

In a paper published in Astrophysical Journal Letters, lead author Eric Mamajek from the University of Rochester and his collaborators analyzed the velocity and trajectory of a low-mass star system nicknamed "Scholz's star."

The star's trajectory suggests that 70,000 years ago it passed roughly 52,000 astronomical units away (or about 0.8 light years, which equals 8 trillion kilometers, or 5 trillion miles). This is astronomically close; our closest neighbor star Proxima Centauri is 4.2 light years distant. In fact, the astronomers explain in the paper that they are 98% certain that it went through what is known as the "outer Oort Cloud" - a region at the edge of the solar system filled with trillions of comets a mile or more across that are thought to give rise to long-term comets orbiting the Sun after their orbits are perturbed.



This is an artist's conception of Scholz's star and its brown dwarf companion (foreground) during its flyby of the solar system 70,000 years ago. The Sun (left, background) would have appeared as a brilliant star. The pair is now about 20 light years away. **Michael Osadciw/University of Rochester**

The star originally caught Mamajek's attention during a discussion with co-author Valentin D. Ivanov, from the European Southern Observatory. Scholz's star had an unusual mix of characteristics: despite being fairly close ("only" 20 light years away), it showed very slow tangential motion, that is, motion across the sky. The radial velocity measurements taken by Ivanov and collaborators, however, showed the star moving almost directly away from the solar system at considerable speed.

"Most stars this nearby show much larger tangential motion," says Mamajek, associate professor of physics and astronomy at the University of Rochester. "The small tangential motion and proximity initially indicated that the star was most likely either moving towards a future close encounter with the solar system, or it had 'recently' come close to the solar system and was moving away. Sure enough, the radial velocity measurements were consistent with it running away from the Sun's vicinity - and we realized it must have had a close flyby in the past."

To work out its trajectory the astronomers needed both pieces of data, the tangential velocity and the radial velocity. Ivanov and collaborators had characterized the recently discovered star through measuring its spectrum and radial velocity via Doppler shift. These measurements were carried out using spectrographs on large telescopes in both South Africa and Chile: the Southern African Large Telescope (SALT) and the Magellan telescope at Las Campanas Observatory, respectively.

Once the researchers pieced together all the information they figured out that Scholz's star was moving away from our solar system and traced it back in time to its position 70,000 years ago, when their models indicated it came closest to our Sun.

Until now, the top candidate for the closest known flyby of a star to the solar system was the so-called "rogue star" HIP 85605, which was predicted to come close to our solar system in 240,000 to 470,000 years from now. However, Mamajek and his collaborators have also demonstrated that the original distance to HIP 85605 was likely underestimated by a factor of ten. At its more likely distance - about 200 light years - HIP 85605's newly calculated trajectory would not bring it within the Oort Cloud.

Mamajek worked with former University of Rochester undergraduate Scott Barenfeld (now a graduate student at Caltech) to simulate 10,000 orbits for the star, taking into account the star's position, distance, and velocity, the Milky Way galaxy's gravitational field, and the statistical uncertainties in all of these measurements. Of those 10,000 simulations, 98% of the simulations showed the star passing through the outer Oort cloud, but fortunately only one of the simulations brought the star within the inner Oort cloud, which could trigger so-called "comet showers."

While the close flyby of Scholz's star likely had little impact on the Oort Cloud, Mamajek points out that "other dynamically important Oort Cloud perturbers may be lurking among nearby stars." The recently launched European Space Agency Gaia satellite is expected to map out the distances and measure the velocities of a billion stars. With the Gaia data, astronomers will be able to tell which other stars may have had a close encounter with us in the past or will in the distant future.

Currently, Scholz's star is a small, dim red dwarf in the constellation of Monoceros, about 20 light years away. However, at the closest point in its flyby of the solar system, Scholz's star would have been a 10th magnitude star - about 50 times fainter than can normally be seen with the naked eye at night. It is magnetically active, however, which can cause stars to "flare" and briefly become thousands of times brighter. So it is possible that Scholz's star may have been visible to the naked eye by our ancestors 70,000 years ago for minutes or hours at a time during rare flaring events. The star is part of a binary star system: a low-mass red dwarf star (with mass about 8% that of the Sun) and a "brown dwarf" companion (with mass about 6% that of the Sun). Brown dwarfs are considered "failed stars;" their masses are too low to fuse hydrogen in their cores like a "star," but they are still much more massive than gas giant planets like Jupiter.

The formal designation of the star is "WISE J072003.20-084651.2," however it has been nicknamed "Scholz's star" to honor its discoverer - astronomer Ralf-Dieter Scholz of the Leibniz-Institut für Astrophysik Potsdam (AIP) in Germany - who first reported the discovery of the dim nearby star in late 2013. The "WISE" part of the designation refers to NASA's Wide-field Infrared Survey Explorer (WISE) mission, which mapped the entire sky in infrared light in 2010 and 2011, and the "J-number" part of the designation refers to the star's celestial coordinates.

http://www.eurekalert.org/pub_releases/2015-02/uob-wcw021315.php

Who cares? Why evolution suggests parenting responsibility is seldom equally shared

Why is caring for young shared unequally between the sexes in so many animal species?

Research from the University of Bristol, UK suggests that small initial differences which predispose one sex to care more are exaggerated once the ability to care evolves. As a result, one sex evolves attributes - such as mammary glands in female mammals or increased brain size in some fish - that enhance the ability to care, and so this sex does most or all of the care. Patterns of parenting in nature range from care by one parent only (seen in many mammals), to male/female biased care, to care by both parents (seen in many birds).

Parental care involves one of the fundamental conflicts of interest between the sexes. Care by either partner is beneficial to both partners as it increases the health and survival prospects of the common young; providing care is costly only to the caring individual. As a result, each partner does best in a situation where most of the care is provided by the other partner--an outcome that is clearly impossible.

Differences in care can be explained by differences in the costs and benefits of caring with two factors currently considered to be the key drivers: certainty of parentage (which decreases the benefit of care for the less certain sex - usually the male) and sexual selection (which increases the cost of care for the sex that can mate again faster).

Professor John McNamara, of the University of Bristol's School of Mathematics, and Dr Max Wolf of the Leibniz-Institute of Freshwater Ecology and Inland Fisheries, used a modelling approach to show that even in the complete absence of these factors, substantial differences in care are to be expected.

They found that sex differences in both the ability to care and levels of care are prone to spontaneously evolve as a result of the sexual conflict of interest over parental care and the co-evolutionary interaction between levels of care and ability to care.

Professor McNamara said: "While the coevolution of care and the ability to care thus predicts strong sex differences in care to emerge, it does not predict which sex is more likely to care. However, once other factors that give rise to even the slightest differences in the cost and benefits of care between the sexes, such as differences in certainty of parentage, are taken into account, a clear directionality emerges. The sex with the lower cost or higher benefit of care evolves to both be more able to care and to provide much higher levels of care than the other sex."

The findings, published today in Proceedings of the Royal Society B, thus suggest that the coevolution of levels of care and the ability to care may be a key factor underlying the evolution of sex differences in caring for young.

'Sexual conflict over parental care promotes the evolution of sex differences in care and the ability to care 'by John M. McNamara and Max Wolf in Proceedings of the Royal Society B

http://bit.ly/1FwxeNE

The Inventor Who Has Developed a Sweet-Smelling "Fart Pill"

One eccentric French man wants to take the guilt out of gas with a tablet designed to make farts smell like flowers, ginger or chocolate

By Laura Clark

From the man who brought the world toilet paper printed with news articles for combined bathroom utility and entertainment comes Pilule Pet, a “fart pill” seriously intended to rid us all of the offensive smell of human gas.

Over at The Verge, Amar Toor recently produced a funny and informative exploration of the man behind the invention, Christian Poincheval, who Toor describes as “some sort of hippie Da Vinci; a compulsive inventor-artist-musician living in the rural hills of northwest France.”

Poincheval lives with his wife in a cottage in Gèsvres, a tiny French town, with his guitar, sculptures and a variety of goods that his meandering interests have led him to invent. Perhaps his most interesting creation is the fart pill, for which he has already fulfilled over 2,000 orders. According to Toor, the idea for the invention came to Poincheval in 2004 after a huge and hearty meal that “resulted in a chorus of particularly pungent flatulence”.

Already an avid practitioner of homeopathic remedies, he began researching ingredients and spent three months testing different formulas with the help of a French laboratory. They finally arrived on the perfect combination of vegetable carbon, fennel, and other natural ingredients, and set about bringing their rose and violet pills to market.

"I wanted to undress the shame you feel when you fart at the table," Poincheval explained to me, "the fear you feel that the fart may travel farther. I wanted to remove this complex, if you will."

He started with pills to turn your toots into rose-, violet- and chocolate-scented delights and, more recently, released a ginger-scented pill for Valentine’s Day. It

is intended, according to the tagline, to help "your sweetheart feel your love!"
And let's not forget those deadly bombs dropped by our canine friends: Poincheval has a powder for dogs, too.
So, is the proof in the pooting? Does the pill actually work? Depends on who you talk to. Some say that the invention has certainly changed the smell of their expulsions for the better. But a gastroenterologist interviewed by Toor says that, while the pill is likely capable of somewhat altering the smell of farts, differing diets and complex intestinal bacteria make the possibility of totally perfumed gas "scientifically 'questionable.'"
But according to Poincheval, creating an effective mask for offensive odors was really only part of his goal for the pills: "At their core, they provoke discussions, debate, and try to liberate the fart, which is something totally natural," he told Toor. He also said he is planning a newly scented fart pill "for summer" and may also develop a similar approach to attempt to rid the world of stinky-smelling poop, to which we can only say: God speed.

http://bbc.in/1LdvF5Y

Limpet teeth set new strength record

Engineers in the UK have found that limpets' teeth consist of the strongest biological material ever tested.

By Jonathan Webb Science reporter, BBC News

Limpets use a tongue bristling with tiny teeth to scrape food off rocks and into their mouths, often swallowing particles of rock in the process. The teeth are made of a mineral-protein composite, which the researchers tested in tiny fragments in the laboratory. They found it was stronger than spider silk, as well as all but the very strongest of man-made materials.

The limpet has a tongue or 'radula' covered in tiny teeth that scrape away at the rock surface

The findings, published in the Royal Society's journal Interface, suggest that the secret to the material's strength is the thinness of its tightly packed mineral fibres - a discovery that could help improve the man-made composites used to build aircraft, cars and boats, as well as dental fillings.
"Biology is a great source of inspiration as an engineer," said the study's lead author Prof Asa Barber, of the University of Portsmouth. "These teeth are made up of very small fibres, put together in a particular way - and we should be thinking about making our own structures following the same design principles."

'Better than Kevlar'

Those fibres, consisting of an iron-based mineral called goethite, are laced through a protein base in much the same way as carbon fibres can be used to strengthen plastic.
The teeth themselves are less than a millimetre long, but Prof Barber and his colleagues ground 10 of them into a minuscule dog-bone shape in order to precisely measure the composite's tensile strength: the amount of force it can withstand before breaking. The middle part of these samples was more than 100 times thinner than a human hair.
With either end glued to specialised levers inside a device called an atomic force microscope, the engineers applied a pulling force to each of these milled tooth samples until they snapped. The strength they calculated for the tooth material was, on average, about five gigapascals (GPa) - some five times greater than most spider silk.
This sets a new record for biology, Prof Barber said, even when his team considered the most unusual spiders. "People are always trying to find the next strongest thing, but spider silk has been the winner for quite a few years now," he told the BBC. "So we were quite happy that the limpet teeth exceeded that. "One of my colleagues on the paper, from Italy, found some exotic spider silk that was about 4.5GPa, and we measured about 5GPa."
This measurement is about the same as the pressure needed to turn carbon into diamond beneath the Earth's crust. Alternatively, as Prof Barber explained, it can be compared to a single string of spaghetti holding up 3,000 half-kilogram bags of sugar.

'Bulldozers of the shore'

In terms of man-made materials, the limpet tooth is stronger than Kevlar fibres and almost as good as the best high-performance carbon fibre materials.
The key, Prof Barber said, is that its strength-giving mineral fibres are very thin - the ideal width, in fact, for avoiding holes or flaws that would weaken the structure. This is something that engineers could learn from.
"Generally as you make something bigger, the thing that you've got has more flaws in it. And those flaws reduce the strength of the structure. "With carbon fibre processing, they work very hard to take the flaws out of the fibres. But you could say, well, if I just make my fibres below a certain width, then maybe they wouldn't have to work so hard to get rid of the flaws."
Prof Anne Neville, of the University of Leeds, was impressed by the findings, particularly the way the tooth strength appears to be maximised by a specific fibre

size. "Strengths lower than theoretical values come about due to defects - and this material is apparently free from defects," said Prof Neville, who holds a Royal Academy of Engineering chair in emerging technologies. "Measuring these tensile properties is difficult and has been made possible through a careful set of experiments using some of today's most advanced microscopy techniques."
Biologists who study limpets are intrigued but unsurprised by the mollusc's new place in the record books.
"Limpets are the bulldozers of the seashore," said Prof Steven Hawkins, of the University of Southampton. "The reason limpet teeth are so hard is that when they're feeding, they actually excavate rock. In fact, if you look at their faecal pellets they actually look like little concrete blocks - because by the time it's gone through their gut it's hardened."

http://nyti.ms/1FwCjFR

Medicine Given Even Before Smokers Are Ready to Quit Is Found to Help Them

Researchers have found that anti-smoking pills were effective in helping people quit smoking, even if they didn't want to stop right away

By Sabrina Tavernise Feb. 17, 2015

WASHINGTON - Doctors typically wait until smokers are ready to quit before prescribing pills to help them do it. But a new study has found that even for those who are not ready to stop smoking immediately, medicine taken over time can substantially improve their chances of eventually quitting.
Clinical practice guidelines have long advised doctors to have their patients set a precise quit date before prescribing medicine such as Chantix, the pills used to treat nicotine addiction that were examined in the study. The idea was that such medicine should not be prescribed for someone who is not serious about quitting. In some cases, insurance plans would not pay for the pills if no quit date had been set.
But in a study published in JAMA on Tuesday, researchers found that even for patients who wanted to stop smoking eventually, the pills were effective, opening the way to a much larger population of patients whom doctors could potentially treat.
David Abrams, executive director of the Schroeder Institute for Tobacco Research and Policy Studies, said studies of nicotine replacement therapy, such as patches and gum, had long shown that attempts to quit gradually over time are a good way to change lifetime habits. The current study appears to show the same for pills, he said.
“Sometimes serious addiction needs to be coaxed down the stairs one at a time, not thrown off the top floor,” said Dr. Abrams, who was not involved in the study.
The study was funded by Pfizer, the drug company that makes Chantix, a treatment that costs about $250 a month. Federal regulators require companies to conduct studies proving the effectiveness of such therapies, and monitor them closely. The practice is common for smoking cessation therapies, said Robert West, director of tobacco studies at University College London, who was among the study’s authors. If such studies were funded by the government, which sustains a lot of academic research, taxpayers would bear the burden for what the company would eventually profit from, he said.
Still, some researchers not involved in the study said the topic required more work.
“The approach taken here is a very reasonable one that appears to have been successful,” said Gary A. Giovino, a professor of health behavior at the State University of New York at Buffalo. “But the findings from one study do not make a fact. We need more studies, funded by someone other than the company that makes the product.”
Smoking is the largest cause of preventable death in the United States, killing more than 480,000 Americans a year. The smoking rate has declined substantially since the 1960s, but the pace of decline has slowed in recent years and health experts are trying to figure out how to get more smokers to quit.
About 1,500 patients at 61 clinics in the United States and abroad participated in the study. None were willing to quit immediately, but all said they wanted to smoke less and to quit for good within three months. They were randomly assigned to two groups. One got Chantix, the brand name of the drug varenicline, which is taken twice a day by mouth as a pill; the other group got a placebo.
Almost a third of the patients who got the drug quit within six months of starting the pills, compared with 6 percent who took the placebo. The study did not follow patients long term, so it was unclear whether those who quit smoking had permanently rid themselves of the habit.
The study cited a survey of smokers that found about a third of the 42 million smokers in the United States wanted to quit in the next one to six months, and concluded that the more gradual treatment could be effective for as many as 14 million American smokers.
It is unclear what the finding will mean for the clinical guidelines, which were set most recently in 2008 by a panel of experts convened by the Public Health Service, which is part of the Department of Health and Human Services.
The study’s authors said the findings had the potential to change practice.
“It’s a paradigm shift because instead of only giving the medication to patients who have set a quit date, you are potentially giving it to every smoker,” said Dr. Jon O. Ebbert, one of the authors, who is a professor of medicine at the Mayo

Clinic College of Medicine in Minnesota. “It opens the door to a much larger population of smokers that we can treat.”

Most surprising, he said, was the fact that the rates of quitting for smokers in this study who received the treatment and did not want to quit right away were about the same as those in previous studies of patients who wanted to quit abruptly.

http://nyti.ms/1Er8qTI

Doctors Strive to Do Less Harm by Inattentive Care

Reducing patient suffering caused by medical care itself has become a medical goal

By GINA KOLATA FEB. 17, 2015

Suffering. The very word made doctors uncomfortable. Medical journals avoided it, instructing authors to say that patients “ ‘have’ a disease or complications or side effects rather than ‘suffer’ or ‘suffer from’ them,” said Dr. Thomas H. Lee, the chief medical officer of Press Ganey, a company that surveys hospital patients.

But now, reducing patient suffering - the kind caused not by disease but by medical care itself - has become a medical goal. The effort is driven partly by competition and partly by a realization that suffering, whether from long waits, inadequate explanations or feeling lost in the shuffle, is a real and pressing issue.

It is as important, says Dr. Kenneth Sands, the chief quality officer at Harvard’s Beth Israel Deaconess Medical Center in Boston, as injuries, like medication errors or falls, or infections acquired in a hospital.

Dr. Sands and his colleagues decided to start by asking their own patients what made them suffer. They found several categories. Communications - for example, a doctor blurting out, “Oh, it looks like you have cancer.” Or losing a valuable, like a wedding ring. Or loss of privacy - a doctor discussing a patient’s medical condition where an adjacent patient could hear.

“These are harms,” Dr. Sands said. “They elicit suffering. They can be long lasting, and they currently are largely unquantified, uncounted, unrecorded.”

One way to quantify these harms is to observe and note them, which is part of what Beth Israel Deaconess is doing. Another is to supplement efforts with patient surveys. Patient surveys, of course, have been around for decades. And since 2007, Medicare has required short surveys after discharge.

But patient surveys were usually not used by hospitals to measure suffering. Now they are. And even when a survey question does not directly ask about suffering, sharp-eyed administrators are seeing a suffering component.

That is how Dr. Michael Bennick, the medical director for patient experience at Yale-New Haven Hospital, solved a problem. He noticed a question on a Medicare survey asking, Is it quiet in your room at night?

Maybe, Dr. Bennick thought, what is really being asked is: Can you get a good night’s sleep without interruption? Is it really necessary to wake patients again and again to take blood pressure and pulse rates, to draw blood, to give medications? He issued instructions for his unit. No more routinely awakening patients for vital signs. And plan the timing of medications; outside intensive care units, three-quarters of drugs can be given before patients go to sleep and again in the morning.

Then there were the blood tests. “Doctors love blood tests,” Dr. Bennick said, and want results first thing in the morning when they make rounds. That meant waking patients in the wee hours. “I told the resident doctors in training: ‘If you are waking patients at 4 in the morning for a blood test, there obviously is a clinical need. So I want to be woken, too, so I can find out what it is.’ ” No one, he said, ever called him. Those middle-of-the-night blood draws vanished.

Without anything else being done about noise in the halls, the medical unit’s score on that question rose from the 16th percentile to the 47th nationally in the Medicare survey. Now the entire hospital follows that plan.

“And it did not cost a penny,” Dr. Bennick said. “The only cost was thinking not from our perspective but from a patient’s perspective.”

Dr. Lee says he joined Press Ganey - he had been network president for Partners HealthCare System, a Harvard-affiliated hospital system - because one of its goals was to reduce suffering. At first, he said, he was a bit uncomfortable with the concept. “I wondered whether it was a tad sensational, a bit too emotional,” he wrote in The New England Journal of Medicine. Then he realized reducing suffering was one of the most important challenges in health care.

Press Ganey administers detailed surveys to discharged patients, asking things like how well the medical staff responded to them and their emotional needs, and how well the doctors and nurses informed and educated them. The company also encourages hospitals to let doctors know the results.

Surveys can be misleading, though, cautions Dr. Scott Ramsey, a health care economist and cancer researcher at the Fred Hutchinson Cancer Research Center in Seattle. Patients, worried about saying something bad about a hospital they depend on, may not reveal what they really experienced. Or they may look back and, not wanting to live a life of regrets, excuse a doctor who seemed not to listen.

On the other hand, Dr. Ramsey said, the suffering issues are real, and if survey answers can get doctors and hospitals to change their ways, “that is great.”

Although half the nation’s hospitals use Press Ganey surveys, it is not clear what many do with the data. But at some places, like the University of Utah, the survey and other efforts prompted significant change. One Utah doctor said he was stunned when his patients rated him in the first percentile nationally, about as low

as a score can go. “I was thinking: That’s just crazy. Something wasn’t entered right,” said the doctor, James Ashworth. Then he decided to take the criticisms to heart. The next quarter, he was rated in the upper 90s. The big difference was slowing down and listening to patients, answering their questions.

Utah began its program a few years ago by showing its 1,200 doctors, nurses and other workers their scores. Next, said Dr. Vivian S. Lee, the hospital system’s chief executive, they showed them how colleagues did. Then they posted individuals’ scores and patient comments online.

There was an immediate and noticeable change. When the university began, it was in about the 30th percentile nationally on the Press Ganey survey. Now, half its providers are in the 90th percentile and 26 percent are in the 99th percentile.

“It’s unbelievable,” Dr. Lee, the chief executive, said. “We were not like that before, I can tell you.” “People wanted to improve,” she added.

The comments, she said, are more revealing than the scores. Not all are complimentary. “There are still cases where people say: ‘I loved Dr. So-and-so. Too bad I had to wait so long to see him,’ ” she said.

At Stanford Health Care, said Amir Rubin, the president and chief executive, “we are reducing suffering.” To do it, the medical system changed its focus.

“We train each and every staff member,” Mr. Rubin said. “We talk to staff, we talk to patients, we hear from patients directly.”

Supervisors coach doctors and nurses, giving feedback every month. The initiative changed hiring, he said. Administrators tell job candidates: “These are our care standards. Do you think you can always do it for every person every time?” They carefully observe new hires to see if they can provide care that minimizes suffering. “Every patient visit is a high-stakes interaction,” Dr. Thomas Lee says he has learned. “It is a big deal for the patient and it is a big deal for you.” “And all you have to do is be the kind of physician your patient is hoping you will be.”

http://www.eurekalert.org/pub_releases/2015-02/usmc-ctc021715.php

Cancer treatments could evolve from research showing that acetate supplements speed up cancer growth

Giving mice a compound produced by host bacteria in the gut sped the growth and metastasis of tumors

DALLAS - UT Southwestern Medical Center researchers seeking novel ways to combat cancer found that giving acetate, a major compound produced in the gut by host bacteria, to mice sped up the growth and metastasis of tumors.

Bacteria living inside the gut can have beneficial, but potentially also harmful effects on human health. Further studies are needed to determine whether restricting acetate production by gut bacteria will affect growth of tumors.

"With insights generated from our current studies, we may be able to design therapies that treat cancer patients by modulating acetate production in the body," said Dr. Joseph Garcia, Associate Professor of Internal Medicine at UT Southwestern and staff physician-scientist at the VA North Texas Health Care System.

The work is published in the February issue of the journal PLOS ONE.

Cancer, the second leading cause of death in the US, is estimated to account for nearly 1 out of every 4 deaths in 2014. It can have a significant impact on length and quality of life, which carries a tremendous economic burden. Cancer can develop in any part of the body and some are notoriously difficult to treat, although recent discoveries from basic science laboratories hold great promise for more effective treatments and potential cures.

In cancer cells, low oxygen and low glucose conditions turn on signaling pathways that allow otherwise healthy cells to survive these stresses. UT Southwestern researchers previously discovered a critical pathway that controls the response of cells and organs to low oxygen conditions, a state known as hypoxia. In this study, the researchers show that the production of acetate is also stimulated by low glucose conditions, another condition frequently found in solid tumors.

Acetate, in turn, activates a molecular pathway that ultimately results in the production of several proteins that stimulate the growth and spread of tumors.

"Our study shows that acetate functions in this context as a growth signal for cancer cells, one that links changes in metabolism within cancer cells that occur during tumor growth with activation of a selective stress-signaling pathway. This same signaling pathway is normally protective in healthy individuals. In fact, stimulating this pathway in anemic mice without cancer has a profound effect on restoring red blood cell levels to near-normal or normal levels, and is otherwise very safe" said Dr. Garcia, a member of the Harold C. Simmons Comprehensive Cancer Center.

"The challenge facing us now is to define which patients may benefit from having this pathway stimulated and which patients will benefit from having this pathway inhibited. Preclinical studies of this nature are essential for informing the pharmaceutical and federal health oversight agencies about potential benefits as well as potential harms that may result from use of compounds that affect this key signaling pathway," said Dr. Garcia.

Other researchers involved in the work include Dr. Robert D. Gerard, Associate Professor of Molecular Biology; Min Xu, Research Scientist; Jason Nagati, Research Assistant; researchers Alok Das and Richard Hogg; and Dr. Rui Chen, former Assistant Professor of Internal Medicine.

The research was supported by funds provided by the Department of Veterans Affairs and the National Institutes of Health.

http://www.eurekalert.org/pub_releases/2015-02/sri-sfs021715.php

Scripps Florida scientists announce anti-HIV agent so powerful it can work in a vaccine

Novel drug candidate is so potent and universally effective, it might work as part of an unconventional vaccine

JUPITER, FL - In a remarkable new advance against the virus that causes AIDS, scientists from the Jupiter, Florida campus of The Scripps Research Institute (TSRI) have announced the creation of a novel drug candidate that is so potent and universally effective, it might work as part of an unconventional vaccine.

The research, which involved scientists from more than a dozen research institutions, was published February 18 online ahead of print by the prestigious journal Nature.

The study shows that the new drug candidate blocks every strain of HIV-1, HIV-2 and SIV (simian immunodeficiency virus) that has been isolated from humans or rhesus macaques, including the hardest-to-stop variants. It also protects against much-higher doses of virus than occur in most human transmission and does so for at least eight months after injection.

"Our compound is the broadest and most potent entry inhibitor described so far," said Michael Farzan, a TSRI professor who led the effort. "Unlike antibodies, which fail to neutralize a large fraction of HIV-1 strains, our protein has been effective against all strains tested, raising the possibility it could offer an effective HIV vaccine alternative."

Blocking a Second Site

When HIV infects a cell, it targets the CD4 lymphocyte, an integral part of the body's immune system. HIV fuses with the cell and inserts its own genetic material--in this case, single-stranded RNA--and transforms the host cell into a HIV manufacturing site. The new study builds on previous discoveries by the Farzan laboratory, which show that a co-receptor called CCR5 contains unusual modifications in its critical HIV-binding region, and that proteins based on this region can be used to prevent infection.

With this knowledge, Farzan and his team developed the new drug candidate so that it binds to two sites on the surface of the virus simultaneously, preventing entry of HIV into the host cell.

"When antibodies try to mimic the receptor, they touch a lot of other parts of the viral envelope that HIV can change with ease," said TSRI Research Associate Matthew Gardner, the first author of the study with Lisa M. Kattenhorn of Harvard Medical School. "We've developed a direct mimic of the receptors without providing many avenues that the virus can use to escape, so we catch every virus thus far."

The team also leveraged preexisting technology in designing a delivery vehicle--an engineered adeno-associated virus, a small, relatively innocuous virus that causes no disease. Once injected into muscle tissue, like HIV itself, the vehicle turns those cells into "factories" that could produce enough of the new protective protein to last for years, perhaps decades, Farzan said.

Data from the new study showed the drug candidate binds to the envelope of HIV-1 more potently than the best broadly neutralizing antibodies against the virus. Also, when macaque models were inoculated with the drug candidate, they were protected from multiple challenges by SIV.

"This is the culmination of more than a decade's worth of work on the biochemistry of how HIV enters cells," Farzan said. "When we did our original work on CCR5, people thought it was interesting, but no one saw the therapeutic potential. That potential is starting to be realized."

In addition to Farzan, Gardner and Kattenhorn, authors of the study, "AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges," include Hema R. Kondur, Tatyana Dorfman, Charles C. Bailey, Christoph H. Fellinger, Vinita R. Josh, Brian D. Quinlan, Pascal Poignard and Dennis R. Burton of TSRI; Jessica J. Chiang, Michael D. Alpert, Annie Y. Yao and Ronald C. Desrosiers of Harvard Medical School; Kevin G. Haworth and Paula M. Cannon of the University of Southern California; Julie M. Decker and Beatrice H. Hahn of the University of Pennsylvania; Sebastian P. Fuchs and Jose M. Martinez-Navio of the University of Miami Miller School of Medicine; Hugo Mouquet and Michel C. Nussenzweig of The Rockefeller University; Jason Gorman, Baoshan Zhang and Peter D. Kwong of the National Institutes of Health; Michael Piatak Jr. and Jeffrey D. Lifson of the Frederick National Laboratory for Cancer Research; Guangping Gao of the University of Massachusetts Medical School; David T. Evans of the University of Wisconsin; and Michael S. Seaman of Beth Israel Deaconess Medical Center.

The work was supported by the National Institutes of Health (grants R01 AI091476, R01 AI080324, P01 AI100263, RR000168 and R01AI058715).

http://www.eurekalert.org/pub_releases/2015-02/nu-abf021815.php

A bodyguard for your ears

Scientists discover novel pain sensors in inner ear that warn of dangerously loud noise

CHICAGO - Our hearing has a secret bodyguard, a newly discovered connection from the cochlea to the brain that warns of intense incoming noise that causes tissue damage and hearing loss, according to new research by Northwestern Medicine scientists.

Scientists believe they have discovered the ear's own novel pain system that protects it from very loud or damaging noise. It may be the reason you jam your

fingers in your ears when a fire engine or ambulance wails close by. The nerves that normally alert you to pain -- like touching a hot burner on a stove -- are not present in your inner ear. So, it needs its own private alert system.

The discovery may provide insight into the cause and treatment for such painful hearing conditions as hyperacusis, an oversensitivity and earache in response to everyday sounds, common in soldiers exposed to explosives in the military, and tinnitus, a persistent and uncomfortable ringing in the ears.

The pathway, which scientists named auditory nociception (pain), is different from the one that transfers information about sound to the brain and enables you to hear a bird singing or a friend gossiping. This pathway is populated by a single set of neurons activated only by noxious or dangerous levels of noise. Scientists aren't sure if the neurons are triggered by the death of hair cells (which detect normal level sound as part of hearing) or simply dangerous sound levels.

"It's very important for your system to have protection from damaging sound," said study senior author Jaime García-Añoveros, associate professor of anesthesiology at Northwestern University Feinberg School of Medicine. "When sensory hair cells in the ear die, they are not repopulated. That's why hearing loss is irreversible. You need to be able to detect dangerous sound the way your nerve cells alert you to the danger of putting your hand on a hot iron."

García-Añoveros also is an investigator at Northwestern's Knowles Hearing Center and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The study will be highlighted Feb. 20 in Nature Reviews Neuroscience and was recently published in Current Biology. The research was conducted with mice, and García-Añoveros believes the pathway has an equivalent in humans. Next, he wants to research the human pathway.

Hearing loss is the most common degenerative condition in humans, because we are exposed to noise throughout our lives and are living longer, García-Añoveros said. The discovery offers an entirely new way of looking at the painful and intractable hearing conditions hyperacusis and tinnitus.

"We do not know how to treat these debilitating conditions, and understanding what neuronal pathway might be involved is essential, " García-Añoveros said. "If we find they are actually pain syndromes rather than hearing syndromes, perhaps they could be treated effectively with analgesic pain medication that acts on the brain." "We think the pain these patients feel may be from a dysfunction in this inner ear pain system and similar to neuropathic pain," García-Añoveros said.

The pain system could trigger a protective autonomic reflex such as stiffening the inner ear muscles to reduce the level of sound entering the ear, García-Añoveros said. Or, it might cause a sensation of pain that causes you to plug your fingers in your ears when you're exposed to a jackhammer on a street corner.

Next, Northwestern scientists want to learn what parts of the brain are involved in this sensation. They want to use brain imaging to see if pain areas are activated in the brain when ears are exposed to loud noises.

Other Northwestern authors on the study include Emma N. Flores, Anne Duggan, Thomas Madathany, Ann K. Hogan, Freddie G. Márquez and Gagan Kumar.

The study was funded by grants R21DC006089 and F31DC012013 from the National Institute of Deafness and Other Communication Disorders and R01NS044363 from the National Institute of Neurological Disorders and Stroke, all of the National Institutes of Health, and N00014-14-1-0709 from the Office of Naval Research.

http://www.eurekalert.org/pub_releases/2015-02/aaon-cpv021115.php

Chicken pox virus may be linked to serious condition in the elderly

New study links virus causing chicken pox and shingles to giant cell arteritis.

MINNEAPOLIS - A new study links the virus that causes chicken pox and shingles to a condition that inflames blood vessels on the temples and scalp in the elderly, called giant cell arteritis. The study is published in the February 18, 2015, online issue of Neurology®, the medical journal of the American Academy of Neurology. The condition can cause sudden blindness or stroke and can be life-threatening.

The varicella zoster virus, of the herpes virus family, can cause chicken pox and may reactivate later in life in the form of shingles, a very painful rash.

"Our analysis, which is the largest to-date, provides compelling evidence that the virus also reactivates in people over 60 in another way, triggering giant cell arteritis," said study author Don Gilden, MD, Professor of Neurology at the University of Colorado School of Medicine in Denver and a Fellow of the American Academy of Neurology.

Giant cell arteritis causes swelling and tenderness of the arteries on the scalp and temples of people over the age of 50. Gilden noted that it is the most common type of inflammation of blood vessels in the elderly, affecting an estimated 29 out of 100,000 people. Symptoms include a new severe headache, scalp tenderness, jaw discomfort, blurred vision, fever, weight loss and tiredness. Importantly, the cause of this condition has been uncertain, prompting the present study.

For the study, researchers searched for evidence of the virus in 13 temporal artery biopsies of people who died and had no previous symptoms of giant cell arteritis and in 84 temporal artery biopsies of people with giant cell arteritis. All of the biopsies were from people over the age of 50. The virus was found in 74 percent of the biopsies with giant cell arteritis and in only 8 percent of the normal skin biopsies.

"If the association can be replicated in other studies, clinical trials should focus on treating people with giant cell arteritis with a combination of the current steroid

drugs used for the condition, plus anti-viral treatment for the virus," said Gilden, CBE, MD, PhD, DSc, the Burton Chair of Neurology at Glasgow University in Scotland, in a corresponding editorial.

The study was supported by the National Institutes of Health.

http://www.eurekalert.org/pub_releases/2015-02/lsoa-nii021815.php

New insights into origins of the world's languages

Study by Berkeley linguists gives evidence that 'Indo-European' languages first emerged ca. 6500 years ago

Linguists have long agreed that languages from English to Greek to Hindi, known as 'Indo-European languages', are the modern descendants of a language family which first emerged from a common ancestor spoken thousands of years ago. Now, a new study gives us more information on when and where it was most likely used. Using data from over 150 languages, linguists at the University of California, Berkeley provide evidence that this ancestor language originated 5,500 - 6,500 years ago, on the Pontic-Caspian steppe stretching from Moldova and Ukraine to Russia and western Kazakhstan.

"Ancestry-constrained phylogenetic analysis supports the Indo-European steppe hypothesis", by Will Chang, Chundra Cathcart, David Hall and Andrew Garrett, will appear in the March issue of the academic journal Language. A pre-print version of the article is freely available from the Linguistic Society of America, the publishers of Language:

http://www.linguisticsociety.org/files/news/ChangEtAlPreprint.pdf

This article provides new support for the "steppe hypothesis" or "Kurgan hypothesis", which proposes that Indo-European languages first spread with cultural developments in animal husbandry around 4500 - 3500 BCE. (An alternate theory proposes that they diffused much earlier, around 7500 - 6000 BCE, in Anatolia in modern-day Turkey.)

Chang et al. examined over 200 sets of words from living and dead Indo-European languages; after determining how quickly these words changed over time through statistical modeling, they concluded that the rate of change indicated that the languages which first used these words began to diverge approximately 6,500 years ago, in accordance with the steppe hypothesis.

This is one of the first quantitatively-based academic papers in support of the steppe hypothesis, and the first to use a model with "ancestry constraints" which more directly incorporate previously discovered relationships between languages. In future research, methods from this study could be used to study the origins of other language families, such as Afro-Asiatic and Sino-Tibetan.

Members of the media who are interested in discussing the article and its findings may contact Brice Russ, LSA Director of Communications (bruss@lsadc.org), and Andrew Garrett, Professor of Linguistics at the University of California, Berkeley (garrett@berkeley.edu).

http://bit.ly/17YuL14

Scientists identify mineral that destroys organic compounds, with implications for Mars Curiosity mission

Scientists have discovered that the mineral jarosite breaks down organic compounds when it is flash-heated, with implications for Mars research.

Scientists have discovered that the mineral jarosite breaks down organic compounds when it is flash-heated, with implications for Mars research.

Jarosite is an iron sulphate and it is one of several minerals that NASA's Curiosity Mission is searching for, as its presence could indicate ancient habitable environments, which may have once hosted life on the red planet.

In a new study published today in the journal Astrobiology, researchers from Imperial College London and the Natural History Museum replicated a technique that one of the Curiosity Rover's on-board instruments is using to analyse soil samples, in its quest to find organic compounds. They tested a combination of jarosite and organic compounds. They discovered that the instrument's technique - which uses intense bursts of heat called flash-heating - broke down jarosite into sulphur dioxide and oxygen, with the oxygen then destroying the organic compounds, leaving no trace of it behind.

The concern is that if jarosite is present in soil samples that Curiosity analyses, researchers may not be able to detect it because both the jarosite and any organic compounds could be destroyed by the flash-heating process.

In 2014, Professor Mark Sephton, co-author of today's study, investigated the mineral perchlorate. This mineral also causes problems for flash-heating experiments as it breaks down to give off oxygen and chlorine gas, which in turn react with any organic compounds, breaking them down into carbon dioxide and water. Professor Sephton showed that though perchlorate was problematic, scientists could potentially use the carbon dioxide resulting from the experiment to detect the presence of organic compounds in the sample being analysed.

Professor Sephton, from the Department of Earth Science and Engineering at Imperial College London, said: "The destructive properties of some iron sulphates and perchlorate to organic matter may explain why current and previous missions have so far offered no conclusive evidence of organic matter preserved on Mars' surface. This is despite the fact that scientists have known from previous studies that organic compounds have been delivered to Mars via comets, meteorites and interplanetary dust throughout its history."

To make Curiosity's search for signs of life more effective, the team are now exploring how Curiosity might be able to compensate for the impact of these

minerals on the search for organic compounds. Their work could have important implications for both the Curiosity mission and also the upcoming European-led ExoMars 2018 Rover mission, which will be drilling for subsurface samples of the red planet and using the same flash-heating method to look for evidence of past or present alien life.

James Lewis, co-author of the study from the Department of Earth Science and Engineering at Imperial College London, added: "Our study is helping us to see that if jarosite is detected then it is clear that flash-heating experiments looking for organic compounds may not be completely successful. However, the problem is that jarosite is evidence of systems that might have supported life, so it is not a mineral that scientists can completely avoid in their analysis of soils on Mars. We hope our study will help scientists with interpreting Mars data and assist them to sift through the huge amount of excellent data that Curiosity is currently generating to find signs that Mars was once able to sustain life."

On Earth, iron sulphate minerals like jarosite form in the harsh acidic waters flowing out of sulphur rich rocks. Despite the adverse conditions, these waters are a habitat for bacteria that use these dissolved sulphate ions. This makes these minerals of great interest to scientists studying Mars, as their presence on the red planet provide evidence that acidic liquid water was present at the same time the minerals formed, which could have provided an environment favourable for harbouring ancient microbial Martian life.

On board Curiosity, the Sample Analysis at Mars (SAM) instrument analyses soil samples for evidence of organic compounds by progressively heating samples up to around 1000 C, which releases gases. These gases can then be analysed by techniques called gas chromatography and mass spectrometry, which can identify molecules in the gas and see if any organic compounds are present. It is these SAM instrument experiments that the researchers behind today's study replicated with jarosite and organic compounds.

The researchers stress that not all sulphates break down to react with organic compounds. For example, those containing calcium and magnesium would not break down until extremely high temperatures were reached during the analysis, and therefore would not affect any organic compounds present.

The team suggest that if jarosite is found in samples on Mars, then it may be possible for Curiosity's SAM instrument to distinguish a spike in carbon dioxide level, which, as Professor Sephton has shown previously with perchlorate, would act as an indicator that organic material is present and being broken down by the heating process.

The next step will see the researchers using synthetic jarosite in their experiments, which will enable a cleaner decomposition process to occur when the mineral is flash-heated. This will allow for more precise quantitative measurements to be taken when the oxygen is being released. Ultimately, they hope this will enable more precise calculations to be carried out on Mars mineral samples to find ways in which Curiosity can identify the presence of these mineral to mitigate their impact on organic matter.

The jarosite samples used in the experiments in the study were collected from Brownsea Island in Dorset, with the permission and assistance from the National Trust.

http://www.eurekalert.org/pub_releases/2015-02/miot-eoa021715.php

Epigenomics of Alzheimer's disease progression

Nature and nurture seem to affect very different processes in the context of Alzheimer's disease

Cambridge, MA - Our susceptibility to disease depends both on the genes that we inherit from our parents and on our lifetime experiences. These two components -- nature and nurture -- seem to affect very different processes in the context of Alzheimer's disease, according to a new study published today in the journal Nature.

The study was carried out by an interdisciplinary team at MIT and the Broad Institute, and was co-led by Li-Huei Tsai, the Picower Professor at MIT and director of the Picower Institute for Learning and Memory, and Manolis Kellis, a professor in MIT's Computer Science and Artificial Intelligence Laboratory (CSAIL).

The researchers analyzed changes that occur in genes and in regions that regulate genes as Alzheimer's disease progresses, using a mouse model of Alzheimer's disease that Tsai's lab originally developed several years ago. The mice were engineered so that the gene for a protein called p25 can be overstimulated in the brain, which prompts the mice to develop symptoms very similar to Alzheimer's disease in humans.

"These programmable mice allowed us to study, for the first time, the changes occurring during early stages of the disease, before symptoms even begin to appear," Tsai says. "We could then compare them to changes in later stages of the disease, when neurodegeneration and cognitive impairment are evident."

Opposing changes

The researchers profiled multiple chemical modifications, known as epigenetic marks, in the hippocampus of mice expressing too much p25 and compared them with control mice. These epigenetic marks reveal the activity of diverse genomic regions -- in particular, the regulatory control regions that control the expression of nearby genes. The researchers also directly profiled the levels of all genes.

"We found two opposing signatures associated with disease progression that are consistent with the pathophysiology of Alzheimer's disease," says Elizabeta

Gjoneska, joint first author of the paper and a postdoc at the Picower Institute. "Neuronal plasticity processes that are involved in learning and memory were dampened, and immune and inflammatory pathways were activated."

The active regions specifically matched regions active in a type of immune cells known as microglia, which are responsible for clearing away infected or damaged cells. They also secrete chemicals that produce inflammation.

"Our data suggest that microglia are heavily activated during Alzheimer's disease progression, although it is unknown exactly how they contribute to the disease," Tsai says. "These cells are important for normal brain function and share their key cell-surface markers, CD14, with macrophages that infiltrate the brain from elsewhere in the body during disease progression."

Conserved epigenomic signatures

The researchers then compared the results in mice with what is known about Alzheimer's disease in humans. They found that differences in gene levels in the Alzheimer's-like mouse brain matched differences previously seen in the brains of Alzheimer's patients, which prompted them to ask if the epigenetic signatures might also be conserved.

The researchers found that this was the case -- specifically, the same regulatory regions that were active or repressed in mice showed the same patterns in humans. They also found that the regions with increased activity in the mouse model of Alzheimer's disease had immune functions in humans, and the regions that showed decreased activity had neural functions in humans.

"Our results show that functional conservation between human and mouse is not restricted to protein-coding genes," says Andreas Pfenning, joint first author of the study and a postdoc at MIT. "This opens up the use of epigenomics methods in model organisms to study an inaccessible organ like the brain, and how it changes in response to activity or disease."

Genetic variants cluster in immune pathways

Previous studies of the genomes of Alzheimer's patients had identified common genetic variants associated with the disease, but scientists did not know how these DNA variants could contribute to the disease, since the majority of them are found outside of protein-coding regions.

"Our conserved epigenomic maps allowed us to now place these noncoding genetic variants in the context of disease-relevant regulatory regions and interpret their contribution to the disease predisposition," Kellis says. "As inherited common genetic variants always precede disease onset, they are always indicative of causal roles, and thus can shed additional light on the epigenomic alterations."

The researchers found that genetic variants associated with Alzheimer's disease were only associated with immune processes, and not with neural processes, indicating that genetic predisposition to Alzheimer's disease primarily affects the circuitry of immune processes, rather than neuronal processes.

"Our results suggest that repression of neural pathways does not represent genetic predisposition, even though it is a hallmark of Alzheimer's," Tsai says. "Instead, it may occur as a consequence of environmental factors and aging, and result from interactions with the altered immune pathways."

The researchers identified a small number of master regulators that target many of the regulatory regions that overlap Alzheimer's-associated genetic variants in humans. Among these, PU.1 targets a large number of altered regulatory regions, and the genetic region encoding PU.1 is associated with Alzheimer's disease, suggesting PU.1 as a potential therapeutic target.

"The new focus on immune-cell types, and the specific regulators uncovered, provide new therapeutic avenues," Kellis says. "Moreover, the conservation of epigenomic signatures between mouse and human provides a platform upon which we can test such therapeutics and their effect on cognition, pathology, and the epigenomic signatures of Alzheimer's."

Other authors are CSAIL postdoc Gerald Quon, Picower postdoc Hansruedi Mathys, and former CSAIL research scientist Anshul Kundaje.

The research was a component of the National Institutes of Health's Roadmap Epigenomics Program and was also funded by the Belfer Neurodegeneration Consortium and the Swiss National Science Foundation. The paper was published along with another, whose senior author was Kellis, reporting on the integrative analysis of 111 reference epigenomes. It joins a total of 24 related papers published this week in the Nature and other Nature journals.

http://bit.ly/1AKbPzz

Map of Second Genetic Code, the "Epigenome," Is Unveiled

Scientists for the first time have mapped out the molecular "switches" that can turn on or silence individual genes in the DNA in more than 100 types of human cells, an accomplishment that reveals the complexity of genetic information and the challenges of interpreting it.

By Sharon Begley

NEW YORK (Reuters) - Scientists for the first time have mapped out the molecular "switches" that can turn on or silence individual genes in the DNA in more than 100 types of human cells, an accomplishment that reveals the complexity of genetic information and the challenges of interpreting it.

Researchers unveiled the map of the "epigenome" in the journal Nature on Wednesday, alongside nearly two dozen related papers. The mapping effort is being carried out under a 10-year, $240 million U.S. government research program, the Roadmap Epigenomics Program, which was launched in 2008.

The human genome is the blueprint for building an individual person. The epigenome can be thought of as the cross-outs and underlinings of that blueprint:

if someone's genome contains DNA associated with cancer but that DNA is "crossed out" by molecules in the epigenome, for instance, the DNA is unlikely to lead to cancer.

As sequencing individuals' genomes to infer the risk of disease becomes more common, it will become all the more important to figure out how the epigenome is influencing that risk as well as other aspects of health. Sequencing genomes is the centerpiece of the "precision medicine" initiative that U.S. President Barack Obama announced this month.

"The only way you can deliver on the promise of precision medicine is by including the epigenome," said Manolis Kellis of the Massachusetts Institute of Technology, who led the mapping that involved scientists in labs from Croatia to Canada and the United States.

Drug makers including Merck & Co Inc., the Genentech unit of Roche Holding and GlaxoSmithKline Plc are conducting epigenetics research related to cancer, said Joseph Costello of the University of California, San Francisco, director of one of four main labs that contributed data to the epigenome map.

Epigenetic differences are one reason identical twins, who have identical DNA, do not always develop the same genetic diseases, including cancer.

But incorporating the epigenome in precision medicine is daunting.

"A lifetime of environmental factors and lifestyle factors" influence the epigenome, including smoking, exercising, diet, exposure to toxic chemicals and even parental nurturing, Kellis said in an interview. Not only will scientists have to decipher how the epigenome affects genes, they will also have to determine how the lives people lead affect their epigenome.

BOOK OF LIFE

The human genome is the sequence of all the DNA on chromosomes. The DNA is identical in every cell, from neurons to hearts to skin. It falls to the epigenome to differentiate the cells: as a result of epigenetic marks, heart muscle cells do not make brain chemicals, for instance, and neurons do not make muscle fibers.

The epigenome map published on Wednesday shows how each of 127 tissue and cell types differs from every other at the level of DNA. Because scientists involved in the Roadmap project have been depositing their findings in a public database as they went along, other researchers have been analyzing the information before the map was formally published.

One of the resulting studies show, for instance, that brain cells from people who died with Alzheimer's disease had epigenetic changes in DNA involved in immune response. Alzheimer's has never been seen as an immune-system disorder, so the discovery opens up another possible avenue to understand and treat it.

Other researchers found that because the epigenetic signature of different kinds of cells is unique, they could predict with nearly 90 percent accuracy where metastatic cancer originated, something that is unknown in 2 percent to 5 percent of patients.

As a result, epigenetic information might offer a life-saving clue for oncologists trying to determine treatment, said co-senior author Shamil Sunyaev, a research geneticist at Brigham and Women's Hospital in Boston.

There is much more to come. Instead of the epigenome map being the end, said Kellis, "I very much see (it) as beginning a decade of epigenomics."

SOURCE: http://bit.ly/1DCLVws

http://bit.ly/1AKbPzz

Mutation order reveals what cancer will do next

IT IS well known that cancers can develop from mutations in DNA – but now we've seen for the first time that a person's fate may depend on the order in which they occur.

18 February 2015 by Andy Coghlan

In every cancer, there are hundreds of mutations, but some have more of an effect on the disease than others. It has now been shown that a cancer's path changes depending on which of these "driver mutations" comes first. This affects how the cancer develops, and which treatments are likely to work best.

This finding comes from an analysis of blood samples from 246 people with blood disorders called myeloproliferative neoplasms, which develop into leukaemia in about 5 to 10 per cent of cases. Researchers had access to samples from both early and later stages of the disease, enabling them to see the order in which key mutations appeared in affected blood cells.

"It's the first time we've been able to show that the order impacts both the clinical and biological features of the disease," says David Kent of the Cambridge Institute for Medical Research in the UK, and a lead author of the study (The New England Journal of Medicine, doi.org/z9f). "Before, we didn't know that order mattered."

Kent and his colleagues focused on mutations in two genes already known to be critical for development of this type of pre-leukaemia. A mutated JAK2 gene sends production of red blood cells and platelets into overdrive. TET2 normally helps kill abnormal stem cells, but when it mutates, unhealthy cells slowly build up in the bone marrow.

A tenth of the initial 246 blood samples had both mutations. Of these, the team identified 12 samples in which TET2 had unequivocally mutated first, and another 12 in which the JAK2 mutation came first.

By taking further samples from these people and tracking their symptoms, they were able to show that the disease took a different trajectory depending on which mutation came first.

They found that disease was noticeable 10 years earlier in people with JAK2-first mutations, because they were overproducing blood cells at high levels from the outset. In cell culture, these mutants were easier to kill with targeted JAK2 inhibitor drugs than cells from those with TET2-first mutations, but Kent's team has yet to test that this is also true inside the human body.

By contrast, the disease was more hidden in those who developed TET2 mutations first and was more likely to develop into full-blown leukaemia, but people in this group were less likely to suffer or die from blood clots than those who developed JAK2 mutations first. "It's not a case of one being milder than the other, but that they drive disease in different directions," says Kent.

"This is a landmark study," says Charles Swanton of Cancer Research UK's London Research Institute. "It's the first to conclusively demonstrate that the order in which two driver events occur influences the subsequent evolution of the tumour, the underlying biological behaviour, type of disorder and clinical presentation of the disease," he says.

If the effects of mutation order were established for all common cancers, it could have a dramatic impact on treatment, says Kent. Doing this is likely to be easiest for cancers for which regular early biopsies are taken, such as breast and prostate cancer.

"We hope that our study will stimulate the search in other cancers for whether or not the order of mutation acquisition matters," he says.

http://nyti.ms/1vJuZOy

Paper Test Quickly Detects Ebola, Dengue, And Yellow Fever

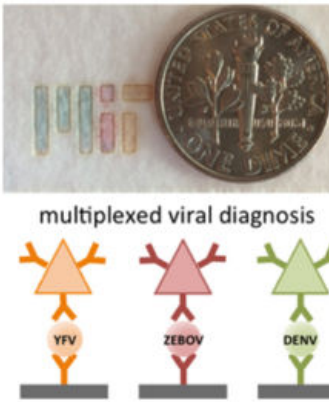
Silver nanoparticles on paper reveal three diseases with the speed and simplicity of a home pregnancy test

February 18, 2015 |By Vicki Davison and ChemistryWorld

Researchers in the US have developed a silver nanoparticle-based paper test to simultaneously detect dengue, yellow fever and Ebola. This could provide a cheap and reliable diagnosis for all three diseases, that's as quick as a home pregnancy test. The Ebola epidemic in West Africa underscores an urgent need for rapid diagnostics; quick identification and patient isolation can benefit the sick and the healthy. However, dengue, yellow fever and Ebola all initially manifest as a fever and headache, so are easily mixed up.

Now, this huge problem has a tiny solution – an 8×3cm lateral flow test. Lee Gehrke and his team at the Massachusetts Institute of Technology and Harvard Medical School adapted the traditional single marker lateral flow test to diagnose several diseases at once. It costs $2, takes 10 minutes, and there is no need power supply, trained specialist or expensive equipment.

The test is made from strips of paper containing antibodies attached to triangular silver nanoparticles of varying size according to the disease they recognize and bind to. Silver nanoparticles appear as different colours according to their size, so when a patient's serum sample migrates through the device, distinctive colored lines appear on the paper to indicate positive results for Ebola, dengue or yellow fever. This pattern of lines can be analysed by eye but the team are also working on a mobile phone application to aid diagnosis.



The sensor exploits the size-dependent optical properties of silver nanopar detect yellow fever, Ebola and deng

'An app could be very useful for diseases that are mosquito-spread,' says G 'It adds a date and geographical stamp to the test results so the spread of dis can be followed in real-time.'Warren Chan, an expert in nanomaterials-base diagnostics at the University of Toronto in Canada, sees the research as an exciting step forward: 'They have solved the immense problem of detecting multiple disease targets at the same time. The next step will be to clinically validate the technology.' Gehrke's team are now testing the device in both and clinical studies, and plan to adapt it to diagnose a wider range of viruse

http://www.eurekalert.org/pub_releases/2015-02/nyu-ddm021815.ph

Does dark matter cause mass extinctions and geologic uphea

Earth's path around and through our Galaxy's disc may have a direct significant effect on phenomena occurring on Earth

Research by New York University Biology Professor Michael Rampino co that Earth's infrequent but predictable path around and through our Galaxy's may have a direct and significant effect on geological and biological pheno occurring on Earth. In a new paper in Monthly Notices of the Royal Astron Society, he concludes that movement through dark matter may perturb the of comets and lead to additional heating in the Earth's core, both of which c be connected with mass extinction events.

The Galactic disc is the region of the Milky Way Galaxy where our solar sy resides. It is crowded with stars and clouds of gas and dust, and also a

concentration of elusive dark matter--small subatomic particles that can be detected only by their gravitational effects.

Previous studies have shown that Earth rotates around the disc-shaped Galaxy once every 250 million years. But the Earth's path around the Galaxy is wavy, with the Sun and planets weaving through the crowded disc approximately every 30 million years. Analyzing the pattern of the Earth's passes through the Galactic disc, Rampino notes that these disc passages seem to correlate with times of comet impacts and mass extinctions of life. The famous comet strike 66 million ago that led to the extinction of the dinosaurs is just one example.

What causes this correlation between Earth's passes through the Galactic disc, and the impacts and extinctions that seem to follow?

While traveling through the disc, the dark matter concentrated there disturbs the pathways of comets typically orbiting far from the Earth in the outer Solar System, Rampino observes. This means that comets that would normally travel at great distances from the Earth instead take unusual paths, causing some of them to collide with the planet.

But even more remarkably, with each dip through the disc, the dark matter can apparently accumulate within the Earth's core. Eventually, the dark matter particles annihilate each other, producing considerable heat. The heat created by the annihilation of dark matter in Earth's core could trigger events such as volcanic eruptions, mountain building, magnetic field reversals, and changes in sea level, which also show peaks every 30 million years. Rampino therefore suggests that astrophysical phenomena derived from the Earth's winding path through the Galactic disc, and the consequent accumulation of dark matter in the planet's interior, can result in dramatic changes in Earth's geological and biological activity.

His model of dark matter interactions with the Earth as it cycles through the Galaxy could have a broad impact on our understanding of the geological and biological development of Earth, as well as other planets within the Galaxy.

"We are fortunate enough to live on a planet that is ideal for the development of complex life," Rampino says. "But the history of the Earth is punctuated by large scale extinction events, some of which we struggle to explain. It may be that dark matter - the nature of which is still unclear but which makes up around a quarter of the universe - holds the answer. As well as being important on the largest scales, dark matter may have a direct influence on life on Earth."

In the future, he suggests, geologists might incorporate these astrophysical findings in order to better understand events that are now thought to result purely from causes inherent to the Earth. This model, Rampino adds, likewise provides new knowledge of the possible distribution and behaviour of dark matter within the Galaxy.

http://www.eurekalert.org/pub_releases/2015-02/iocr-crl021815.php

Cancer risk linked to DNA 'wormholes'

Single-letter genetic variations within parts of the genome once dismissed as 'junk DNA' can increase cancer risk through wormhole-like effects on far-off genes, new research shows.

Researchers found that DNA sequences within 'gene deserts' - so called because they are completely devoid of genes - can regulate gene activity elsewhere by forming DNA loops across relatively large distances.

The study, led by scientists at The Institute of Cancer Research, London, helps solve a mystery about how genetic variations in parts of the genome that don't appear to be doing very much can increase cancer risk.

Researchers developed a new technique to study the looping interactions and discovered that single-letter DNA variations linked to the development of bowel cancer were found in regions of the genome involved in DNA looping.

Their study, published today (Thursday) in Nature Communications, is the first to look comprehensively at these DNA interactions specifically in bowel cancer cells, and has implications for the study of other complex genetic diseases.

It was funded by the EU, Cancer Research UK, Leukaemia & Lymphoma Research, and The Institute of Cancer Research (ICR).

The researchers developed a technique called Capture Hi-C to investigate long-range physical interactions between stretches of DNA - allowing them to look at how specific areas of chromosomes interact physically in more detail than ever before. Previous techniques used to investigate long-range DNA interactions were not sensitive enough to produce definitive results.

The researchers assessed 14 regions of DNA that contain single-letter variations previously linked to bowel cancer risk. They detected significant long-range interactions for all 14 regions, confirming their role in gene regulation.

These interactions are important because they can control how genes behave, and alterations in gene behaviour can lead to cancer - in fact most genetic variations that have been linked to cancer risk are not in genes themselves, but in the areas of the genome that regulate them.

Study leader Professor Richard Houlston, Professor of Molecular and Population Genetics at The Institute of Cancer Research, London, said:

"Our new technique shows that genetic variations are able to increase cancer risk through long-range looping interactions with cancer-causing genes elsewhere in the genome. It is sometimes described as analogous to a wormhole, where

distortions in space and time could in theory bring together distant parts of the universe.

"Understanding how long-range genetic regulation works is crucial to understanding how cancer develops - and could be important in finding new ways to treat the disease in the future."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"A lot of the genetic variants already linked to cancer occur in gene deserts - often very long and quite mysterious DNA sequences that don't actually contain 'genes', but which are involved in causing cancer in ways we do not yet fully understand.

"DNA looping is notoriously difficult to study but this research has taken an important step to understanding what genetic variations in DNA deserts might do to drive the development of bowel cancer."

http://www.eurekalert.org/pub_releases/2015-02/yu-sct021615.php

Sunlight continues to damage skin in the dark

Much of the damage that ultraviolet radiation (UV) does to skin occurs hours after sun exposure

New Haven, Conn. -- Much of the damage that ultraviolet radiation (UV) does to skin occurs hours after sun exposure, a team of Yale-led researchers concluded in a study that was published online Feb. 19 by the journal Science.

Exposure to UV light from the sun or from tanning beds can damage the DNA in melanocytes, the cells that make the melanin that gives skin its color. This damage is a major cause of skin cancer, the most common form of cancer in the United States. In the past, experts believed that melanin protected the skin by blocking harmful UV light. But there was also evidence from studies suggesting that melanin was associated with skin cell damage.

In the current study, Douglas E. Brash, clinical professor of therapeutic radiology and dermatology at Yale School of Medical, and his co-authors first exposed mouse and human melanocyte cells to radiation from a UV lamp. The radiation caused a type of DNA damage known as a cyclobutane dimer (CPD), in which two DNA "letters" attach and bend the DNA, preventing the information it contains from being read correctly. To the researchers' surprise, the melanocytes not only generated CPDs immediately but continued to do so hours after UV exposure ended. Cells without melanin generated CPDs only during the UV exposure.

This finding showed that melanin had both carcinogenic and protective effects. "If you look inside adult skin, melanin does protect against CPDs. It does act as a shield," said Brash, also a member of Yale Cancer Center. "But it is doing both good and bad things."

The researchers next tested the extent of damage that occurred after sun exposure by preventing normal DNA repair in mouse samples. They found that half of the CPDs in melanocytes were "dark CPDs" -- CPDs created in the dark.

In searching for an explanation of these results, Sanjay Premi, associate research scientist in the Brash laboratory, discovered that the UV light activated two enzymes that combined to "excite" an electron in melanin. The energy generated from this process -- known as chemiexcitation -- was transferred to DNA in the dark, creating the same DNA damage that sunlight caused in daytime. Chemiexcitation has previously been seen only in lower plants and animals.

While noting that news of the carcinogenic effect of melanin is disconcerting, the researchers also pointed to a ray of hope: The slowness of chemiexcitation may allow time for new preventive tools, such as an "evening-after" sunscreen designed to block the energy transfer.

Other study authors include Yale's Silvia Wallisch, Camila M. Mano, Adam B. Weiner, Antonella Bacchiocchi, and Ruth Halaban; Kazumasa Wakamatsu of Fujita Health University School of Health Sciences in Japan; Etelvino J. H. Bechara of Universidade de São Paulo in Brazil; and Thierry Douki Commissariat à l'Energie Atomique in France.

The study was supported in part by Department of Defense CDMRP grants CA093473P1 and CA093473 (D.E.B. and R.H.), and NIH grant 2 P50 CA121974 (R.H. and D.E.B.).

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http://www.eurekalert.org/pub_releases/2015-02/ki-nbm021715.php

New brain mapping reveals unknown cell types

Single cell sequencing produces detailed map of cortical cell types shows 47 different kinds of cell

Using a process known as single cell sequencing, scientists at Karolinska Institutet have produced a detailed map of cortical cell types and the genes active within them. The study, which is published in the journal 'Science', marks the first time this method of analysis has been used on such a large scale on such complex tissue. The team studied over three thousand cells, one at a time, and even managed to identify a number of hitherto unknown types.

"If you compare the brain to a fruit salad, you could say that previous methods were like running the fruit through a blender and seeing what colour juice you got from different parts of the brain," says Sten Linnarsson, senior researcher at the Department of Medical Biochemistry and Biophysics. "But in recent years we've developed much more sensitive methods of analysis that allow us to see which genes are active in individual cells. This is like taking pieces of the fruit salad, examining them one by one and then sorting them into piles to see how many different kinds of fruit it contains, what they're made up of and how they interrelate."

The knowledge that all living organisms are built up of cells is almost 200 years old. Since the discovery was made by a group of 19th century German scientists, we have also learnt that the nature of a particular body tissue is determined by its constituent cells, which are, in turn, determined by which genes are active in their DNA. However, little is still known about how this happens in detail, especially as regards the brain, the body's most complex organ.

In the present study, the scientists used large-scale single-cell analysis to answer some of these questions. By studying over three thousand cells from the cerebral cortex in mice, one at a time and in detail, and comparing which of the 20,000 genes were active in each one, they were able to sort the cells into virtual piles. They identified 47 different kinds of cell, including a large proportion of specialised neurons, some blood vessel cells and glial cells, which take care of waste products, protect against infection and supply nerve cells with nutrients. With the help of this detailed map, the scientists were able to identify hitherto unknown cell types, including a nerve cell in the most superficial cortical layer, and six different types of oligodendrocyte, which are cells that form the electrically insulating myelin sheath around the nerve cells. The new knowledge the project has generated can shed more light on diseases that affect the myelin, such as multiple sclerosis (MS).

"We could also confirm previous findings, such as that the pyramidal cells of the cerebral cortex are functionally organised in layers," says Jens Hjerling-Leffler, who co-led the study with Dr Linnarsson. "But above all, we have created a much more detailed map of the cells of the brain that describes each cell type in detail and shows which genes are active in it. This gives science a new tool for studying these cell types in disease models and helps us to understand better how brain cell respond to disease and injury."

There are estimated to be 100 million cells in a mouse brain, and 65 billion in a human brain. Nerve cells are approximately 20 micrometres in diameter, glial cells about 10 micrometres. A micrometre is equivalent to a thousandth of a millimetre.

The study was carried out by Sten Linnarsson's and Jens Hjerling-Leffler's research groups at the department of medical biochemistry and biophysics, in particular by Amit Zeisel and Ana Muños Manchado. It also involved researchers from Karolinska Institutet's Department of Oncology-Pathology, and Uppsala University.

The study was financed with grants from several bodies, including the European Research Council, the Swedish Research Council, the Swedish Cancer Society, the EU's Seventh Framework Programme, the Swedish Society of Medicine, the Swedish Brain Fund, Karolinska Institutet's strategic programme for neuroscience (StratNeuro), the Human Frontier Science Program, the Åke Wiberg Foundation and the Clas Groschinsky Memorial Fund.

Publication: 'Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq', Amit Zeisel, Ana B. Muñoz Manchado, Simone Codeluppi, Peter Lönnerberg, Gioele La Manno, Anna Juréus, Sueli Marques, Hermany Munguba, Liqun He, Christer Betsholtz, Charlotte Rolny, Gonçalo Castelo-Branco, Jens Hjerling-Leffler, and Sten Linnarsson, Science online 19 February 2015.

http://www.eurekalert.org/pub_releases/2015-02/uoms-rst021915.php

Research shows that innovative transfusion approach has the potential to save lives

University of Maryland School of Medicine takes part in groundbreaking transfusion study

Baltimore, Md. - The University of Maryland School of Medicine is part of a nationwide, multi-site study that may help save hundreds of lives among trauma patients with major bleeding. The study, which was published earlier this month in JAMA, compared two different methods of blood transfusion, and found that one approach gave patients a significantly better chance of survival within the first 24 hours.

"This study is an important milestone in trauma care," said Thomas M. Scalea, M.D., who is the Francis X. Kelly Distinguished Professor of Trauma Surgery as well as Physician-in-Chief of the R Adams Cowley Shock Trauma Center at the University of Maryland Medical Center. Dr. Scalea oversaw the school's participation in the study. Scalea was part of the committee that designed and oversaw the study. The Center enrolled approximately 40 patients. "These results will allow doctors to provide better, more effective care for trauma patients, whose lives often hang in the balance."

The study compared two transfusion techniques: One gave patients equal ratios of plasma, platelets, and red blood cells; the other gave patients a ratio that had equal numbers of plasma and platelets, but twice as many red blood cells. The study was led by John B. Holcomb, MD, of the University of Texas Health Science Center in Houston. The research, which began in 2012, included 680 severely injured patients who received treatment at one of 12 Level I trauma centers around the country, including the Shock Trauma Center in Baltimore. The patients were randomly assigned to receive one of the two transfusion mixtures during their treatment.

The study found that subjects in the equal-ratio group were more likely to stop bleeding, and had a better chance of surviving, in the first 24 hours, compared to patients in the other group. The two groups had the same overall level of survival at 30 days.

Death from loss of blood within the first 24 hours is a common cause of mortality for such patients. This cause of death significantly decreased in the equal-ratio

group: 9.2 percent, compared with 14.6 percent in unequal-ratio group. In addition, bleeding stopped in 86 percent of patients in the equal-ratio group, compared with 78 percent in the unequal-ratio group.

Loss of blood plays a key role in 20 percent to 40 percent of trauma deaths that occur after the patient is at the hospital. It may be possible to avoid some of these deaths with equal-ratio transfusion. The new approach was first developed by trauma surgeons in the U.S. military treating soldiers injured in the Afghanistan and Iraq Wars. This technique is now used by most military and civilian hospitals in the U.S. Observational studies had offered evidence that the protocol was more effective than the older approach, but the two techniques had not been studied in a large prospective trial.

Some researchers have expressed concern that the equal-measure blood would cause increased inflammation, and might lead to problems such as organ failure, infection and blood clots. However, the study found no evidence that equal-ratio patients had any more inflammation-related problems. Overall, the study looked at 23 complications that can occur with transfusion and found that the risks of the two approaches were not significantly different.

In the article, Holcomb and the other authors recommend that healthcare providers should consider using the equal-ratio blood when giving transfusions to trauma patients.

"This impressive collaboration has the potential to yield immediate benefit for trauma patients," said Dean E. Albert Reece, MD, PhD, MBA, who is also the vice president for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean of the School of Medicine. "Dr. Scalea has spent his career trying to improve the care of these patients, and this is just the latest example of his hard work in this essential area."

http://www.medscape.com/viewarticle/839677?src=rss

Coughing Child, Weary Parents: Is Placebo the Right Call?

Placebo Effect in the Treatment of Acute Cough in Infants and Toddlers: A Randomized Clinical Trial

William T. Basco, Jr., MD, MS *JAMA Pediatr.* 2014;168:1107-1113

Study Summary

Parents and providers face a dilemma in wanting to help children with cough but also recognizing that over-the-counter medications have limited clinically proven benefit and real safety concerns when administered to young children. Because recent studies[1,2] have demonstrated the potential benefit of honey, Paul and colleagues sought to test agave nectar, a similar substance, to determine whether it could also be effective in controlling cough symptoms. They used a pasteurized agave nectar preparation in a randomized, placebo-controlled trial to assess whether it improved nocturnal cough and sleep.

The children were enrolled in 2013 and 2014 from two outpatient clinics. Children were 2-47 months old with a cough history of less than 1 week. Children with chronic respiratory diseases or severe respiratory diseases (such as pneumonia) were excluded. Children were randomly assigned to one of three groups. The treatment group received pasteurized agave nectar with grape flavoring, the placebo group received grape-flavored water with artificial coloration, and a third group received no treatment. Children were asked to avoid other medications and caffeine for the one night of the study. Children were enrolled on the basis of parental answers to a seven-item survey that assessed nocturnal respiratory symptoms. Only children with "moderate" or greater symptom severity were enrolled in the trial.

On the morning after a single bedtime dose of the child's assigned preparation administered by the parents, the parents completed the same seven-item survey to assess nocturnal symptoms, including cough, congestion, and rhinitis, from the previous night. The instrument also assessed the sleep of the child and the parent. Parents were asked to complete the follow-up survey within 30 minutes of awakening the morning after administering the study preparation.

Study Findings

The mean age of children was 22.9 months. The sample was 50% girls, and 86.6% were white, non-Hispanic. The active preparation group had 39 children; there were 40 children in each of the other groups. There were no differences among the groups at baseline on either demographic factors or severity of illness. Of interest, each group experienced improvement in symptoms scores on the second day. For all seven question items, plus a combination score, the differences in improvement between the agave nectar group and the no treatment group were statistically significant, and for many of the measures there was also a significant difference between the placebo group (grape-flavored water) and the no treatment group. However, for all measures, the agave group and placebo group experienced no significant differences in symptom improvement (both improved equally).

In secondary outcomes, it was evident that the parents did not sleep well and checked on their child approximately four times per night. Neither duration of illness nor the use of other therapies prior to enrollment had any effect on the outcomes. Parents in both the nectar group and the placebo group were generally able to guess which preparation their child had received. The investigators concluded that there is a significant placebo effect when treating the nocturnal cough symptoms of young children and that watchful waiting with no treatment may not be the best approach.

Viewpoint

This study is very interesting in that it had both a placebo and a "no treatment" group. The significant response experienced by the placebo group is the primary basis for the researchers' conclusions. In an accompanying editorial, Taylor and Opel[3] commented that placebo effects can be powerful and in this case may actually be beneficial. The parents reported overnight sleep quality, but the recall nature of the survey means that the clinician cannot be sure whether improved sleep actually occurred. However, an approach that uses a placebo hopefully, at a minimum, meets the "do no harm" precept to which clinicians aspire while providing some meaningful benefit to the parents, as in this case.

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A New Theory on How Neanderthal DNA Spread in Asia

Further evidence that our genomes contain secrets about our evolution that we might have missed by looking at fossils alone

Carl Zimmer

I n 2010, scientists made a startling discovery about our past: About 50,000 years ago, Neanderthals interbred with the ancestors of living Europeans and Asians. Now two teams of researchers have come to another intriguing conclusion: Neanderthals interbred with the ancestors of Asians at a second point in history, giving them an extra infusion of Neanderthal DNA.

The findings are further evidence that our genomes contain secrets about our evolution that we might have missed by looking at fossils alone. “We’re learning new, big-picture things from the genetic data, rather than just filling in details,” said Kirk E. Lohmueller, a geneticist at the University of California, Los Angeles, and co-author of one of the new studies.

The oldest fossils of Neanderthals date back about 200,000 years, while the most recent are an estimated 40,000 years old. Researchers have found Neanderthal bones at sites across Europe and western Asia, from Spain to Siberia.

Some of those bones still retain fragments of Neanderthal DNA. Scientists have pieced those DNA fragments together, reconstructing the entire Neanderthal genome. It turns out that Neanderthals had a number of distinct genetic mutations that living humans lack. Based on these differences, scientists estimate that the Neanderthals’ ancestors diverged from ours 600,000 years ago.

Our own ancestors remained in Africa until about 60,000 years ago, then expanded across the rest of the Old World. Along the way, they encountered Neanderthals. And our DNA reveals that those encounters led to children.

Today, people who are not of African descent have stretches of genetic material almost identical to Neanderthal DNA, comprising about 2 percent of their entire genomes. These DNA fragments are the evidence that Neanderthals interbred with the early migrants out of Africa, likely in western Asia.

Researchers also have found a peculiar pattern in non-Africans: People in China, Japan and other East Asian countries have about 20 percent more Neanderthal DNA than do Europeans.

Last year, Sriram Sankararaman, a postdoctoral researcher at Harvard Medical School, and his colleagues proposed that natural selection was responsible for the difference. Most Neanderthal genes probably had modestly bad effects on the health of our ancestors, Dr. Sankararaman and other researchers have found. People who inherited a Neanderthal version of any given gene would have had fewer children on average than people with the human version.

As a result, Neanderthal DNA became progressively rarer in living humans. Dr. Sankararaman and his colleagues proposed that it disappeared faster in Europeans than in Asians. The early Asian population was small, the researchers suggested, and natural selection eliminates harmful genes more slowly in small groups than in large populations. Today, smaller ethnic groups, like Ashkenazi Jews and the Amish, can have unusually high rates of certain genetic disorders.

Joshua M. Akey, a geneticist at the University of Washington, and the graduate student Benjamin Vernot recently set out to test this hypothesis. They took advantage of the fact that only some parts of our genome have a strong influence on health. Other parts — so-called neutral regions — are less important.

A mutation in a neutral region won’t affect our odds of having children and therefore won't be eliminated by natural selection. If Dr. Sankararaman’s hypothesis were correct, you would expect Europeans to have lost more harmful Neanderthal DNA than neutral DNA. In fact, the scientists did not find this difference in the DNA of living Europeans.

Dr. Akey and Mr. Vernot then tested out other possible explanations for the comparative abundance of Neanderthal DNA in Asians. The theory that made the most sense was that Asians inherited additional Neanderthal DNA at a later time. In this scenario, the ancestors of Asians and Europeans split, the early Asians migrated east, and there they had a second encounter with Neanderthals. Dr. Akey

and Mr. Vernot reported their findings in the American Journal of Human Genetics.

Dr. Lohmueller and the graduate student Bernard Y. Kim approached the same genetic question, but from a different direction. They constructed a computer model of Europeans and Asians, simulating their reproduction and evolution over time. They added some Neanderthal DNA to the ancestral population and then watched as Europeans and Asian populations diverged genetically.

The scientists ran the model many times over, trying out a range of likely conditions. But no matter which variation they tried, they couldn't find one explaining why Asians today have extra Neanderthal DNA.

But when they ran a model that included a second interbreeding, another "pulse" of Neanderthal genes into the Asian population, the researchers had better luck. "We find that the two-pulse model can fit the data really well," Dr. Lohmueller said. He and Mr. Kim published their results in a separate paper in the American Journal of Human Genetics.

Dr. Akey is pleased that the two studies reached the same conclusion. "Together, they tell the same story, just from different perspectives," he said.

Dr. Sankararaman agreed that the new research cast doubt on his proposal that natural selection stripped Neanderthal DNA from Europeans more quickly than from Asians. "The analysis from both papers gives strong support to the two-pulse model in Asians," he said.

But the two-pulse hypothesis also poses a puzzle of its own.

If Neanderthals became extinct 40,000 years ago, they may have disappeared before Europeans and Asian populations genetically diverged. How could there have been Neanderthals left to interbreed with Asians a second time?

It is conceivable that the extinction of the Neanderthals happened later in Asia. If that is true, there might yet be more recent Neanderthal fossils waiting to be discovered there.

Or perhaps Asians interbred with some other group of humans that had interbred with Neanderthals and carried much of their DNA. Later, that group disappeared. "That's a paradox the field needs to address," Dr. Lohmueller said.

http://nyti.ms/1w7ZgMD

Deadly CRE Germs Linked to Hard-to-Clean Medical Scopes

Officials at the U.C.L.A. Medical Center reported this week that a superbug had infected seven people, killing two of them

By SABRINA TAVERNISE FEB. 19, 2015

WASHINGTON - Federal officials warned health care providers across the country on Thursday that difficult-to-clean medical scopes inserted down the throat might be infecting patients with deadly drug-resistant bacteria. The alert from the Food and Drug Administration came a day after California hospital officials reported that seven patients had fallen ill and two had died from what they said were improperly sterilized scopes at Ronald Reagan U.C.L.A. Medical Center.

The likely cause was a superbug that may have been transmitted during procedures using the devices, the hospital said. The family of germs, known as CRE, which stands for carbapenem-resistant Enterobacteriaceae, are deadly because they are resistant even to last-resort antibiotics.

The CRE germs usually strike people receiving medical care in hospitals or nursing homes, including patients on breathing machines or dependent on catheters. Healthy people are rarely, if ever, affected. But the bugs attack broadly, and the infections they cause are not limited to people with severely compromised immune systems, said Dr. Thomas R. Frieden, director of the federal Centers for Disease Control and Prevention.

"This is exactly what we are worried about," Dr. Frieden said of the California infections in an interview. "CRE is becoming increasingly common in hospitals around the U.S. If we aren't careful, it may well get out into the community and make common infections, like urinary infections, and cuts potentially deadly."

The devices implicated in the California cases are inserted down the throat and through the stomach to the top of the small intestine, an area called the duodenum. Called duodenoscopes, they were used to diagnose and treat diseases of the liver, bile ducts and pancreas.

About 500,000 such procedures are performed annually in the United States, according to the F.D.A. The devices themselves pose little risk to patients, but their design, which includes microscopic crevices nearly impossible to reach with a brush, makes them difficult to disinfect.

"Residual body fluids and organic debris may remain in these crevices after cleaning and disinfection," the agency warned. "If these fluids contain microbial contamination, subsequent patients may be exposed to serious infections."

The U.C.L.A. Health System, of which the Ronald Reagan hospital is a part, has identified and notified at least 179 patients who may have been exposed during procedures performed from October to January, it said in a statement. Patients are being offered free home testing kits that can be analyzed at U.C.L.A.

Of the seven scopes in use in the hospital system during the time in question, two were suspected of transmitting the germs. The hospital informed all 179 patients who were examined with any of the seven instruments "out of an abundance of caution."

The scopes had been sterilized to the manufacturer's standards, according to the statement. Two were immediately removed from use after health workers discovered the contamination in an internal hospital investigation in late January,

and the health system is now decontaminating the devices in a way "that goes above and beyond the manufacturer and national standards," the statement said. The U.C.L.A. hospital system said the Olympus Medical Systems Group manufactured the scopes.

CRE germs often begin as a normal part of the human gut bacteria, but they can develop a certain enzyme and become resistant. The C.D.C. has estimated that they account for about 9,300 infections and 610 deaths a year.

Aggressive methods to contain the bugs include isolating patients who have the infection; dedicating specific rooms, equipment and staff to patients with highly drug-resistant infections; and requiring more aggressive, systematic hand-washing by hospital staff, Dr. Frieden said. He said that Israel and the state of Florida had succeeded in bringing down CRE infection rates.

The F.D.A. said it was closely monitoring the connection between sterilized scopes and the transmission of dangerous antibiotic-resistant bacteria. It received 75 reports from January 2013 to December 2014 of bacterial infections across the country believed to be linked to the scopes. A majority of the 135 patients who were affected in those reports had infections that were resistant to antibiotics, including CRE, the agency said. The F.D.A. can order manufacturers to stop distributing and even recall devices they make. It did not comment on the California case, but said through a spokeswoman that it was "concerned by the risk to public health that could be created by removing the devices from the market, as there are no alternative devices."

http://www.eurekalert.org/pub_releases/2015-02/hlmc-nha021915.php

New HPV approved after international phase 2/3 trial involving Moffitt Cancer Center

Vaccine protects boys and girls against nine HPV types known to cause cancer and other diseases

TAMPA, Fla. - Approximately 12,000 women are diagnosed with cervical cancer each year in the United States and another 4,000 die annually from the disease. However, most cervical cancers are preventable through immunization against the human papillomavirus (HPV). A pivotal international phase 2/3 clinical trial involving Moffitt Cancer Center faculty demonstrated that vaccination with Gardasil 9 protects against nine HPV types, seven of which cause most cases of cervical, vulvar, and vaginal disease. The trial data indicate that if populations are vaccinated with Gardasil 9 approximately 90 percent of all cervical cancers worldwide can be prevented.

HPV is the most common sexually transmitted virus. The virus is typically cleared by a person's own immune system within two years, resulting in no lasting health concerns. However, in some cases, HPV can lead to significant health problems, including genital warts and cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers. There are no clinically approved tests to distinguish those who will clear the virus from those who are at high risk of developing cancer.

A large, randomized, international phase 2/3 trial was initiated to compare the safety and efficacy of Gardasil 9 with Gardasil in more than 14,200 women, ages 16 to 26. Gardasil 9 was 97 percent effective at preventing high-grade cervical, vulvar and vaginal disease caused by HPV 31, 33, 45, 52 and 58, and was equally effective at preventing disease induced by HPV 6, 11, 16 and 18. Each case of high-grade disease that occurred in patients vaccinated with Gardasil 9 occurred in those who were already infected with HPV before they completed the study. This underlines "the importance of early vaccination prior to HPV exposure," said Giuliano. "More importantly, the vaccine was found to be safe with no significant vaccine-associated health concerns."

The vaccine trial results were published today in the New England Journal of Medicine, and the trial was funded by Merck & Co., Inc.

Until late 2014, there were two vaccines available to protect against as many as four HPV types - 6, 11, 16 and 18. The vaccines protect against 70 percent of HPVs that cause cervical cancer and also significantly reduce the risks of other types of cancer and genital warts. However, researchers have been trying to narrow the gap and completely eliminate any risk of HPV-induced disease. In December 2014, the Food and Drug Administration approved Gardasil 9, a vaccine that protects against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). According to Anna R. Giuliano, Ph.D., director of the Center for Infection Research in Cancer (CIRC) at Moffitt, Gardasil 9 "offers the potential to increase overall cervical cancer prevention from 70 to 90 percent, nearly eliminating this cancer from our communities."

http://www.eurekalert.org/pub_releases/2015-02/dgms-pdn022015.php

Powerful dengue neutralizing antibody found

A new Duke-NUS-led study has identified a super-potent antibody which requires a minute amount to neutralize the dengue virus.

The study, published online on 20 February 2015, in the journal Nature Communications, showed how a newly identified antibody 5J7, is highly effective in killing dengue virus whereby only 10-9 g of antibody is needed to stop the infection of dengue serotype 3 virus (DENV-3).

This new finding gives hope for the development of effective dengue treatments. Over the last 50 years, the incidence of dengue virus has increased by 30 times worldwide. The virus causes fever, rashes and joint pain and in severe cases,

bleeding and shock. It is estimated to be endemic in 100 countries and is a huge burden on healthcare systems.

However, till now, there is no licensed dengue vaccine or therapeutic agent due to the presence of four circulating virus serotypes (DENV1-4) complicating their development.

Senior author Associate Professor Shee Mei Lok from Duke-NUS Graduate Medical School Singapore (Duke-NUS) focuses her research on understanding the pathology and structure of the dengue virus to develop effective therapeutics.

Her lab has already discovered antibodies that are effective against DENV-1. Her strategy to develop a safe therapeutic is to combine four antibodies that each bind and potently inhibit infection of each of the dengue virus serotypes.

In this recent study, researchers isolated 5J7 from 200 different candidate antibody molecules by studying blood samples from a dengue infected patient.

By examining the virus-antibody complex structure at very high magnification, they showed that each arm of the antibody is surprisingly effective in grabbing three surface proteins on the surface of the virus at the same time.

In addition, the sites on the virus where the antibody was bound were critical for the virus to invade cells.

"This kind of binding with the virus has never been observed and it explains why the antibody itself is so highly potent." said A/Prof Lok, who is from the Emerging Infectious Diseases Programme at Duke-NUS. "The movement of virus surface proteins is highly essential for invading cells - you can think of antibody 5J7 locking the virus surface proteins, thus strapping the virus."

While antibody 5J7 has been found to be effective against DENV-3, the remaining two serotypes of dengue virus (DENV-2 and DENV-4) have to be considered. When a patient is infected by one serotype - this stimulates the production of a variety of antibodies that kills that serotype and that patient will have life-time immunity towards that particular serotype.

However, in this process, the patient will also produce antibodies that will bind the other three if they are infected by them.

This may enhance their secondary infection and cause the development of a more severe form of the disease.

"We need to test the efficacy in mouse models first and then move to clinical trials," said A/Prof Lok about the next step after this promising finding.

"We are optimistic that we will make a treatment breakthrough within these few years but antibodies against all the other serotypes have to be identified first."

This study is a collaboration between first author Research Fellow Guntur Fibriansah and researchers from Duke-NUS, the University of North Carolina and Vanderbilt University.

http://www.medscape.com/viewarticle/839924

Is the Diabetes Epidemic Leveling Off?

Diabetes incidence may be leveling off, but not in all populations. Dr Nichols describes trends reported in two new studies.

Gregory A. Nichols, PhD

Trends in Diabetes Incidence: The Framingham Heart Study

Abraham TM, Pencina KM, Pencina MJ, Fox CS *Diabetes Care.* 2014 Dec 31.

This report from the Framingham Heart Study updates previous work that showed rising diabetes incidence from the 1970s to the 1980s and into the 1990s in the Offspring Cohort. The update includes data from the Generation 3 Cohort, which allows for analysis of incidence in the 2000s.

To harmonize the data across decades, the authors limited the analysis to participants between age 40 and 55 years who were free of diabetes at their "baseline" examinations. Incident diabetes was defined as fasting plasma glucose ≥126 mg/dL or use of glucose-lowering medication at the follow-up examination that occurred approximately 8 years later.

The overall annualized rates of diabetes per 1000 individuals were 3.0 in the 1970s, 4.1 in the 1980s, 6.0 in the 1990s, and 5.5 in the 2000s. Using the 1970s as the reference, the age-adjusted relative risks for diabetes were 1.37 in the 1980s, 1.99 in the 1990s, and 1.81 in the 2000s.

Compared with the 1990s, the age-adjusted relative risk for diabetes incidence in the 2000s was 0.85. Thus, while incidence grew among the Offspring participants from the 1970s to 1990s, the addition of the Generation 3 cohort suggested that incidence did not continue to increase in the 2000s.

Trends in Diabetes Incidence Among 7 Million Insured Adults, 2006-2011: The SUPREME-DM Project

Nichols GA, Schroeder EB, Karter AJ, et al *Am J Epidemiol.* 2015;181:32-39

Picking up where Framingham left off, this study evaluated annual diabetes incidence rates between 2006 and 2011 in an observational cohort analysis conducted within the SUrveillance, PREvention and ManagEment of Diabetes Mellitus (SUPREME-DM) DataLink, a consortium of 11 integrated healthcare delivery systems with electronic health records from 10 states across the United States.

From nearly 7 million adults age 20 years or older, the study estimated annual diabetes incidence per 1000 adults overall, and for age, sex, race/ethnicity, and body mass index subgroups.

The authors found 289,050 incident cases of diabetes over the 6 years of the analysis. Age- and sex-adjusted population incidence was relatively stable between 2006 and 2010, ranging from 10.3/1000 adults to 11.3. In 2011, adjusted

incidence was significantly higher (11.5) than in the 2 years with the lowest incidence. A similar pattern was observed in most prespecified subgroups, but only the differences for non-white persons were statistically significant.

In 2006, 56% of incident cases used the glycated hemoglobin (A1c) test as one of the pair of events identifying diabetes. By 2011, that percentage was 74%, suggesting that increases in A1c testing may have contributed to rising diabetes incidence among non-whites. Abstract

What Does It All Mean?

There is no doubt that more people are living with diabetes today than ever before. Crude prevalence of diabetes continues to rise to the extent that the lifetime risk of developing diabetes is about 40%.[1,2]

The growth in prevalence is fueled by the obesity epidemic, an aging population, and substantial reductions in mortality over time, primarily related to improvement in survival from cardiovascular disease.[3] These trends in prevalence are occurring worldwide and impart an enormous financial burden.[4,5]

Nevertheless, the two studies described here suggest that the rate at which new cases occur may have stabilized.

These findings are consistent with current National Health Interview Survey (NHIS) data[6] indicating that the annual percentage change in diabetes incidence may have declined from 2008-2012 compared with 1990-2008.

Reports from New York, the United Kingdom, and Denmark also suggest a leveling off of diabetes incidence in recent years.[7-9] This apparent trend seems counterintuitive. Rates of obesity continue to rise,[10] and if diabetes is indeed a consequence of obesity, why would diabetes incidence be flattening or even declining?

The Framingham and SUPREME-DM studies provide some clues. Both reports discuss a "saturation effect" whereby those most susceptible to developing diabetes may have done so in earlier years, leaving the pool of people without diabetes at relatively lower risk. This could as easily occur on a national or international scale as in these studies.

In any case, as noted in the aforementioned NHIS study and also reported in SUPREME-DM, diabetes incidence in Hispanic and non-Hispanic blacks continues to rise.

Thus, even if overall incidence rates appear flat, there are rapidly growing subgroups (eg, Hispanics) that are at greater than average risk of developing diabetes. SUPREME-DM asserts that at least some of the increase in incidence among non-whites could be attributed to the shift in diagnostic practices from use of fasting glucose to A1c tests, because of inherent racial and ethnic differences in A1c levels at similar glucose tolerance levels.[11]

This highlights the importance of research on disparities, such as the half dozen studies featured in the February edition of *Diabetes Care*, summarized by Cefalu and Golden.[12]

The main takeaway message is that even if overall diabetes incidence appears to be leveling off, the diabetes epidemic is far from over.

As stated, more people than ever before are living with diabetes today, and those people will be joined by many more in the coming years, albeit at a stabilized or even declining rate of incidence.

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http://www.bbc.com/news/magazine-31552562

The blind breast cancer detectors

Women being screened for breast cancer in Germany may find themselves in the hands of a blind examiner.

By Abby d'Arcy BBC News, Duisburg

The idea has been around for a few years, and unpublished research suggests that it really works - that blind people can in fact detect tumours earlier than their sighted counterparts. Could blindness help detect breast cancer?

This surprising, yet simple idea came to a German doctor one morning while he was in the shower: would blind women actually do his job a lot better than he does? "Three minutes is all the time I have to do clinical breast examinations in my practice," says Duisburg-based gynaecologist, Dr Frank Hoffmann.

"That's not enough time to find small lumps in the breast tissue, which is crucial to catching breast cancer early."

People trained to read Braille have a highly developed sense of touch, so Hoffmann guessed that blind and visually-impaired women would be better qualified than anyone else to carry out breast examinations on his patients.

The evidence is now unequivocal, he says. In an as yet unpublished study carried out with Essen University, blind women are said to have detected nearly a third more lumps than regular gynaecologists. "Women doing self-examinations can feel tumours which are 2cm and larger," Hoffmann says.

"Doctors usually find tumours between 1cm and 2cm, whereas blind examiners find lumps between 6mm and 8mm. That makes a real difference. That's the time it takes a tumour to spread its cells into the body."

In both Germany and the UK, regular mammograms and screening programmes are only offered to women aged 50 and over - but in both countries it is the biggest killer of women between 40 and 55, and in Germany the age of the women affected is falling.

Hoffmann says he founded his organisation, Discovering Hands, in order to save lives through early detection. He devised a course to train blind women to become Medical Tactile Examiners or MTEs, and there are now 17 working in practices across Germany.

One of them, Filiz Demir, sees about seven women a day, performing examinations which can last up to 45 minutes, which would be unheard of for a gynaecologist. Just over a year ago Demir was working in a travel agency, but when she turned 35 her sight slowly deteriorated and it became harder and harder to do her job. She quit, retrained and learned Braille but found it impossible to even get invited for job interviews.

"Blindness was always my disability back then," she says. "I could never work as fast as the others. I was always behind. Now my disability has become my strength. I'm not reliant on anyone and I can help others. It's a great feeling."

Curious to know how Demir and her colleagues work, I decided to have an examination myself. Using strips of tape marked with co-ordinates in Braille, the MTE makes a grid on the breast. She slowly feels her way along this grid so that wherever she finds a lump she can tell the doctor its exact location.

Demir does an exhaustive examination, but the 30 minutes fly past. It's a calming, relaxed atmosphere, not at all uncomfortable and there's ample opportunity to ask questions.

After seven months in this practice, Demir's clearly relieved to have found mostly benign tumours. Just a few weeks back she found the first malignant one, which shook her a bit. But it's my turn to be taken aback when she removes the Braille strips and cautiously tells me she's found something. A lump on each side, in fact.

Had I been a regular patient in the practice, I would have gone into the next room for an ultrasound. Unfortunately, I have to take this information back to my gynaecologist in Berlin where I get a referral for an ultrasound and mammogram.

After a couple of weeks waiting for an appointment, the ultrasound finally shows up nothing. The radiologist tells me it doesn't make sense to do a mammogram - and unhelpfully suggests that the examiner probably just felt a bit of my ribs.

Hoffmann's advice in such a situation is to repeat the MTE check a few weeks later in the first half of the menstrual cycle. If a lump can still be detected by palpitation "a mammography makes sense", he says.

It's exactly this cycle of check-ups which can lead to false alarms, angst and harmful, unnecessary surgery, according to Prof Gerd Gigerenzer, director of the Max Planck Institute for Human Development. "I know many women who have been frightened by false alarms. Some have a biopsy done, which showed nothing, but they live their lives from one mammogram to the next."

There's little consensus over the benefits of breast screening programmes and whether regular examinations actually save lives. Gigerenzer explicitly warns against them, and does not rejoice at the idea that it's now possible to detect smaller lumps.

"The finer and more precise the diagnostic techniques are, the more clinically irrelevant cancers will be detected," he says. "This can lead to unnecessary surgery or radiation therapy. In this case, early detection only harms."

The jury, he says, is out on the Discovering Hands method until the team can provide the necessary evidence, proving whether their technique actually reduces mortality.A study on this is expected to be completed and published later this year.

Meanwhile, one of Hoffmann's patients, Heike Gothe, tells me she owes her life to one of these examiners.

Still grappling with the shock of her husband's untimely death from illness, Gothe took up the helm of the family business, a successful small company exporting internationally. But it wasn't long before she received her own diagnosis.

"I had felt a lump on my right breast and went to see the doctor," Gothe says. "They confirmed what I'd found and then detected a very small lump on the left, just 2mm in size. It didn't even show up on the ultrasound or mammogram, it was just the blind MTE who felt it."

Finding this remarkably small tumour may well have saved her life. Both tumours were diagnosed as malignant, but with chemotherapy and radiotherapy, she beat the cancer.

Gothe is a fighter but she puts her energy and positivity down to these intensive examinations by an MTE every six months. According to Gothe, that's why she can sleep at night and how she gets out to run her business. "Fear rears its ugly head every now and then," Gothe says. "And the only way I can deal with it is that I know I'm in good hands."

A handful of German insurance companies are also convinced. Six of them now cover the costs for their patients to have these clinical breast examinations.

While new MTEs take up permanent positions in clinics across Germany and in Austria, the founder of Discovering Hands, Frank Hoffmann, is in talks with Israel and Colombia. He sees opportunities even further afield.

"I'm convinced," he says, "that especially in countries that aren't technically so advanced as Germany - this model could improve the quality of medical standards very dramatically."

Gerd Gigerenzer's test

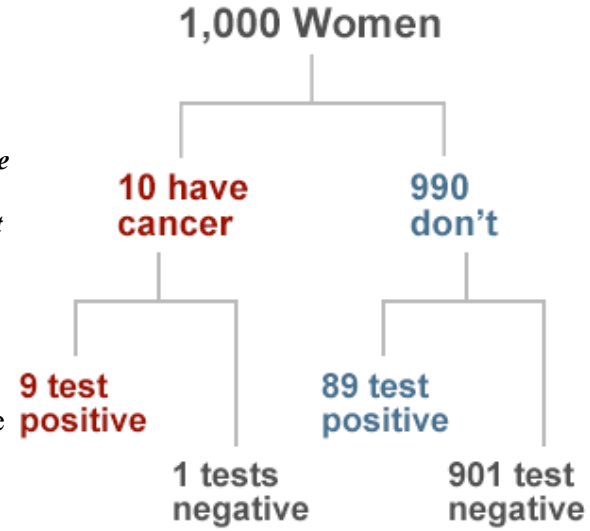
In 2006 and 2007 Gigerenzer gave a series of statistics workshops to gynaecologists, and kicked off every session with the same question:

A 50-year-old woman, no symptoms, participates in routine mammography screening. She tests positive, is alarmed, and wants to know from you whether she has breast cancer for certain or what the chances are. Apart from the screening results, you know nothing else about this woman. How many women who test positive actually have breast cancer? What is the best answer?

- ***nine in 10***
- ***eight in 10***
- ***one in 10***
- ***one in 100***

Gigerenzer then supplied the doctors with data about Western women of this age. (His figures were based on US studies from the 1990s, rounded up or down for simplicity - recent stats from Britain's National Health Service are slightly different.)

1. The probability that a woman has breast cancer is 1% ("prevalence")
2. If a woman has breast cancer, the probability that she tests positive is 90% ("sensitivity")
3. If a woman does not have breast cancer, the probability that she nevertheless tests positive is 9% ("false alarm rate")



In one session, almost half the gynaecologists said the woman's chance of having cancer was nine in 10. Only 21% said that the figure was one in 10 - which is the correct answer.

Do doctors understand test results?

http://www.eurekalert.org/pub_releases/2015-02/dc-bfp021815.php

Baby formula poses higher arsenic risk to newborns than breast milk, Dartmouth

Study shows that formula-fed infants had higher arsenic levels than breast-fed infants

HANOVER, N.H. - In the first U.S. study of urinary arsenic in babies, Dartmouth College researchers found that formula-fed infants had higher arsenic levels than breast-fed infants, and that breast milk itself contained very low arsenic concentrations. The findings appear Feb. 23 online in the journal Environmental Health Perspectives. A PDF is available on request.

The researchers measured arsenic in home tap water, urine from 72 six-week-old infants and breast milk from nine women in New Hampshire. Urinary arsenic was 7.5 times lower for breast-fed than formula-fed infants. The highest tap water arsenic concentrations far exceeded the arsenic concentrations in powdered formulas, but for the majority of the study's participants, both the powder and water contributed to exposure.

"This study's results highlight that breastfeeding can reduce arsenic exposure even at the relatively low levels of arsenic typically experienced in the United States," says lead author Professor Kathryn Cottingham. "This is an important public health benefit of breastfeeding."

Arsenic occurs naturally in bedrock and is a common global contaminant of well water. It causes cancers and other diseases, and early-life exposure has been associated with increased fetal mortality, decreased birth weight and diminished cognitive function. The Environmental Protection Agency has set a maximum contaminant level for public drinking water, but private well water is not subject to regulation and is the primary water source in many rural parts of the United States.

"We advise families with private wells to have their tap water tested for arsenic," says senior author Professor Margaret Karagas, principal investigator at Dartmouth's Children's Environmental Health and Disease Prevention Research Center. Added study co-lead author Courtney Carignan: "We predict that population-wide arsenic exposure will increase during the second part of the first year of life as the prevalence of formula-feeding increases."

http://bbc.in/1JBTLvC

Healthy dose of hope for one-use syringes

The people of the farming community of Roka in Cambodia are living through exactly the nightmare scenario that the World Health Organisation wants to stamp out with a new policy on syringes.

In wooden huts and farmhouses dotted among paddy fields, families are struggling to cope with the bombshell of a sudden and frightening mass infection of HIV.

To the astonishment and shock of this rural backwater, babies, schoolchildren and even the 82-year-old abbot of the local Buddhist temple, who is celibate, have all tested HIV-positive. And there is one common factor that links them, directly or indirectly: nearly all of them received injections from an unlicensed doctor suspected of re-using his syringes.

The virus would have been spread from one patient to another, resulting in an escalating tally of infections that now stands at 272, with further rises expected as more tests are carried out. Four of the victims - three elderly women and a baby - have since died.

Every year, millions of people around the world are infected when syringes are used on more than one person, not only spreading HIV but also Hepatitis B and C, and other diseases. The WHO's hope is to try to achieve a global switch to what are called "auto-disable" syringes that are designed with a feature which effectively breaks them once an injection has been given. But for the people of Roka, all that is too late.

Looking tired and desperate, with her four-month-old daughter Tola on her lap, Yong Sothom described to me how she became infected with HIV and then unwittingly passed on the virus through her breast milk. "I feel sad, very very sad," she said, "because it's a pity for my child - she is innocent yet she is also infected."

For her, the outbreak has become almost apocalyptic in that it has stretched across four generations of her extended family, hitting no fewer than 19 relations.

The family's matriarch, 76-year-old Chay Yao, spoke with great dignity and determination as she tried to convey the scale of the tragedy that has struck an otherwise calm existence. "It is not like a normal sadness, it's so difficult, especially for these small children. "It's no worry for me to die but I feel pity for the children about their future, about how they will make a living, how they will get food, this is what I am thinking about."

So, amid the soaring temperatures and dust of the dry season here, a sombre mood has descended over a community wholly unprepared for what has developed into a national health crisis. Most of the victims, including the abbot, Mom Heng, have now been prescribed anti retroviral drugs but, in an effort to head off panic, he's been working with a local charity to persuade people not to worry.

We travelled with him to one particularly unfortunate family where the mother and four of her five children are all infected with HIV.

The father, Sokhaa Vech, a local chief, recalled seeing the unlicensed medic visiting a neighbouring family before coming to his, and he noticed how the man handled his equipment. "The syringe was in his bag," he told me. "He pulled it out of its plastic wrapping, gave an injection, put it back in its wrapping - and then I saw him using it again on everyone else."

The medic, Yem Chrin, was by all accounts a popular figure in the area, dispensing injections at a far cheaper price than charged by the local government clinic and prepared to make home visits. We also heard that he offered his treatments on credit and was content to be paid in commodities such as rice.

One charity worker described him as "uncle easy", and the abbot and Chay Yao, the matriarch of the family with 19 victims, are among those to emphasise his attentiveness. Since the crisis started, Chrin has been in custody and now faces an array of charges including murder.

One striking feature of this outbreak is how the villagers are evidently keen on injections, preferring them to pills, often receiving dozens of jabs for ailments such as dysentery and fever. This is a cultural phenomenon - not just in Cambodia but in many developing countries - in which the technology of a highly visible procedure is sought after, and the risks are probably not considered.

This is the reality facing campaigners who have long argued that the safety of syringes is pivotal to cutting infection rates.

With us on the visit to Roka was Marc Koska, the British inventor of a type of syringe that is disabled once used.

For years, through his charity SafePoint, he has argued - with health authorities, at conferences and in the media - that the world needs to ditch the standard kind of syringe because it carries too many dangers.

When we encountered a team of medics sent in from the capital Phnom Penh to help cope with the outbreak, he had a chance to demonstrate how his system works. Marc unwrapped one of his syringes, depressed the plunger as if giving an injection and then, when he tried to pull the plunger out, showed how it snapped - making reuse impossible.

The medics, all specialists in HIV/Aids, were amazed and immediately saw the benefit. One of the team, Te Naisam, smiled at the sight and said: "I've never seen this before. I've been a nurse for more than 20 years and I've just seen today this modern syringe. "If they are available, imported into my country, it would be very good to help reduce the HIV/Aids infection."

In fact these auto-disable syringes have been in use for international immunisation programmes for the past decade and a growing number of companies produce them. But immunisations account for less than 10% of the estimated 16 billion injections given globally every year - so the real challenge is to persuade the manufacturers and national governments to agree to work towards a total switch.

Marc Koska said: "What's happening here in Roka should just never have occurred. "I've got a design and there are other designs for safety syringes that you simply cannot use more than once. And they're the same price as a normal needle and syringe. "We've just got to get on with this and then we can stop any similar outbreak around the world."

Our final stop was at the home of the man at the centre of the crisis. Yem Chrin's shop was closed up but his sister-in-law agreed to fetch a copy of his driving licence so we could see his picture. She then revealed something none of us had heard before: that she was among those infected with HIV, along with Chrin's mother-in-law and grandson, presumably treated in the same way as all the others.

The plight of the grandson seems especially poignant: an innocent in a crisis, infected in his own home, and all because of something as simple as a dirty syringe.