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Exxon Knew about Climate Change Almost 40 Years Ago

A new investigation shows the oil company understood the science before it became a public issue and spent millions to promote misinformation

By Shannon Hall | October 26, 2015 | Véalo en español

Exxon was aware of climate change, as early as 1977, 11 years before it became a public issue, according to a recent investigation from InsideClimate News. This knowledge did not prevent the company (now ExxonMobil and the world's largest oil and gas company) from spending decades refusing to publicly acknowledge climate change and even promoting climate misinformation—an approach many have likened to the lies spread by the tobacco industry regarding the health risks of smoking.

Both industries were conscious that their products wouldn't stay profitable once the world understood the risks, so much so that they used the same consultants to develop strategies on how to communicate with the public.

Experts, however, aren't terribly surprised. "It's never been remotely plausible that they did not understand the science," says Naomi Oreskes, a history of science professor at Harvard University. But as it turns out, Exxon didn't just understand the science, the company actively engaged with it.

In the 1970s and 1980s it employed top scientists to look into the issue and launched its own ambitious research program that empirically sampled carbon dioxide and built rigorous climate models. Exxon even spent more than $1 million on a tanker project that would tackle how much CO2 is absorbed by the oceans. It was one of the biggest scientific questions of the time, meaning that Exxon was truly conducting unprecedented research.

In their eight-month-long investigation, reporters at InsideClimate News interviewed former Exxon employees, scientists and federal officials and analyzed hundreds of pages of internal documents. They found that the company's knowledge of climate change dates back to July 1977, when its senior scientist James Black delivered a sobering message on the topic. "In the first place, there is general scientific agreement that the most likely manner in which mankind is influencing the global climate is through carbon dioxide release from the burning of fossil fuels," Black told Exxon's management committee. A year later he warned Exxon that doubling CO2 gases in the atmosphere would increase average global temperatures by two or three degrees—a number that is consistent with the scientific consensus today. He continued to warn that "present thinking holds that man has a time window of five to 10 years before the need for hard decisions regarding changes in energy strategies might become critical." In other words, Exxon needed to act.

But ExxonMobil disagrees that any of its early statements were so stark, let alone conclusive at all. "We didn't reach those conclusions, nor did we try to bury it like they suggest," ExxonMobil spokesperson Allan Jeffers tells *Scientific American*. ***"The thing that shocks me the most is that we've been saying this for years, that we have been involved in climate research. These guys go down and pull some documents that we made available publicly in the archives and portray them as some kind of bombshell whistle-blower exposé because of the loaded language and the selective use of materials."***

One thing is certain: in June 1988, when NASA scientist James Hansen told a congressional hearing that the planet was already warming, Exxon remained publicly convinced that the science was still controversial. Furthermore, experts agree that Exxon became a leader in campaigns of confusion.

By 1989 the company had helped create the Global Climate Coalition (disbanded in 2002) to question the scientific basis for concern about climate change. It also helped to prevent the U.S. from signing the international treaty on climate known as the Kyoto Protocol in 1998 to control greenhouse gases. Exxon's tactic not only worked on the U.S. but also stopped other countries, such as China and India, from signing the treaty. At that point, "a lot of things unraveled," Oreskes says.

But experts are still piecing together Exxon's misconception puzzle. Last summer the Union of Concerned Scientists released a complementary investigation to the one by InsideClimate News, known as the Climate Deception Dossiers (pdf). "We included a memo of a coalition of fossil-fuel companies where they pledge basically to launch a big communications effort to sow doubt," says union president Kenneth Kimmel. "There's even a quote in it that says something like 'Victory will be achieved when the average person is uncertain about climate science.' So it's pretty stark."

Since then, Exxon has spent more than $30 million on think tanks that promote climate denial, according to Greenpeace. Although experts will never be able to quantify the damage Exxon's misinformation has caused, "one thing for certain is we've lost a lot of ground," Kimmell says. Half of the greenhouse gas emissions in our atmosphere were released after 1988. "I have to think if the fossil-fuel companies had been upfront about this and had been part of the solution instead of the problem, we would have made a lot of progress [today] instead of doubling our greenhouse gas emissions."

Experts agree that the damage is huge, which is why they are likening Exxon's deception to the lies spread by the tobacco industry. "I think there are a lot of parallels," Kimmell says. Both sowed doubt about the science for their own means, and both worked with the same consultants to help develop a communications strategy. He notes, however, that the two diverge in the type of harm done.

Tobacco companies threatened human health, but the oil companies threatened the planet's health. "It's a harm that is global in its reach," Kimmel says.

To prove this, Bob Ward—who on behalf of the U.K.'s Royal Academy sent a letter to Exxon in 2006 claiming its science was "inaccurate and misleading"—thinks a thorough investigation is necessary. "Because frankly the episode with tobacco was probably the most disgraceful episode one could ever imagine," Ward says. Kimmell agrees.

These reasons "really highlight the responsibility that these companies have to come clean, acknowledge this, and work with everyone else to cut out emissions and pay for some of the cost we're going to bear as soon as possible," Kimmell says.

It doesn't appear, however, that Kimmell will get his retribution. Jeffers claims the investigation's finds are "just patently untrue, misleading, and we reject them completely"—words that match Ward's claims against them nearly a decade ago.

http://www.eurekalert.org/pub_releases/2015-10/ason-arm101915.php

Acid reflux medications may increase kidney disease risk

Class of drugs used to treat acid reflux and other acid-related gastrointestinal conditions, may increase the risk for developing chronic kidney disease (CKD).

San Diego, CA - Certain medications commonly used to treat heartburn and acid reflux may have damaging effects on the kidneys, according to two studies that will be presented at ASN Kidney Week 2015 November 3¬-8 at the San Diego Convention Center in San Diego, CA. The drugs, proton pump inhibitors (PPIs), are among the top 10 class of prescribed medications in the United States.

The prevalence of chronic kidney disease (CKD) is on the rise, with more than 20 million Americans burdened by the disease. Diabetes and hypertension are common risk factors for CKD; however, certain medications can also play a role. Two new studies show that increased use of proton pump inhibitors (PPIs), medications that treat reflux and stomach ulcers, may be contributing to the CKD epidemic.

In one study, Benjamin Lazarus, MBBS (Johns Hopkins University) and his colleagues followed 10,482 adults with normal kidney function from 1996 to 2011. They found that PPI users were between 20% and 50% more likely to develop CKD than non-PPI users, even after accounting for baseline differences between users and non-users. This discovery was replicated in a second study, in which over 240,000 patients were followed from 1997 to 2014. "In both studies, people who used a different class of medications to suppress stomach acid, known as H2-blockers, did not have a higher risk of developing kidney disease," said Dr. Lazarus. "If we know the potential adverse effects of PPI medications we can design better interventions to reduce overuse."

In another study, Pradeep Arora, MD (SUNY, Buffalo) and his team found that among 24,149 patients who developed CKD between 2001 and 2008 (out of a total of 71,516 patients), 25.7% were treated with PPIs. Among the total group of patients, those who took PPIs were less likely to have vascular disease, cancer, diabetes, hypertension, and chronic obstructive pulmonary disease, but PPI use was linked with a 10% increased risk of CKD and a 76% increased risk of dying prematurely.

"As a large number of patients are being treated with PPIs, health care providers need to be better educated about the potential side effects of these drugs, such as CKD," said Dr. Arora. "PPIs are often prescribed outside of their approved uses, and it has been estimated that up to two-thirds of all people on PPIs do not have a verified indication for the drug."

Studies: 1) "Proton Pump Inhibitor Use is Associated with Incident Chronic Kidney Disease" (Abstract SA-OR005) 2) "Proton Pump Inhibitors Are Associated with Increased Risk of Development of Chronic Kidney Disease" (Abstract TH-PO574).

Disclosures: 1) Josef Coresh receives research funding from NKF and NIH, and is a scientific advisor to KDIGO. 2) James W. Lohr has ownership interest in and receives honoraria from Alexion, and receives research funding from Amgen.

http://www.eurekalert.org/pub_releases/2015-10/uocm-dfd102215.php

Drug for digestive problem can extend survival for many advanced cancer patients

Patients with advanced cancers taking methylnaltrexone lived longer and had fewer reports of tumor progression than cancer patients not taking the drug

Patients with advanced cancers who took a drug designed to relieve constipation caused by pain killers lived longer and had fewer reports of tumor progression than cancer patients who did not receive the drug, according to results presented Oct. 27 at the 2015 meeting of the American Society of Anesthesiologists in San Diego. This is the first study in humans to associate opioid blockade with improved survival.

The finding suggests that the drug -- methylnaltrexone, approved for use by the United States Food and Drug Administration in 2008 to treat opioid-induced constipation -- could play a role in cancer therapy.

"Early on, we began to suspect that methylnaltrexone might inhibit cancer growth" said Jonathan Moss, MD, PhD, lead author of the study and professor of anesthesia and critical care at the University of Chicago. "After more than a decade in the lab trying to assess how methylnaltrexone affects cancer, we have

the first evidence that it can decrease tumor growth and extend survival in patients who respond to the drug."

The study, a retrospective survival analysis, included 229 patients who participated in two randomized, controlled clinical trials focused on relief of constipation for patients receiving palliative care for various types of late-stage cancer and other terminal diseases. None of the patients enrolled responded to conventional laxatives.

In these two trials, 117 cancer patients received methylnaltrexone (marketed as Relistor®) for opioid-induced constipation, while 112 were given a placebo. Fifty-seven percent of the patients who received methylnaltrexone experienced relief from constipation; 43 percent did not.

Those who received and responded to methylnaltrexone lived, on average, twice as long (118 days versus 58 days) as those who did not respond or were given the placebo. Patients who responded to methylnaltrexone also had significantly fewer reports of tumor progression (7.6 percent) compared to those who did not respond (22 percent) or who took the placebo (25.4 percent), based on physician reports of adverse events.

The researchers also analyzed the effects of methylnaltrexone on another 135 patients from the same trials who had advanced illnesses other than cancer, such as congestive heart failure, advanced chronic obstructive pulmonary disease or neurologic diseases. Methylnaltrexone relieved constipation for more than half of the patients, but brought no additional survival, even for those who responded to the drug's digestive effects.

"This makes it far less likely that improved bowel function is the only explanation for our finding of improved survival in cancer patients," said study co-author Filip Janku, MD, PhD, assistant professor of investigational cancer therapeutics at the University of Texas MD Anderson Cancer Center in Houston.

"We are not precisely sure why methylnaltrexone was associated with fewer reports of tumor progression and longer survival in our patients," Janku said. "Proving what causes this response is very difficult. But it could be that methylnaltrexone influences several side effects of opioids unrelated to pain relief. The findings are consistent with what we saw in the lab."

Methylnaltrexone was invented in 1979 by the late University of Chicago pharmacologist Leon Goldberg. Struck by the suffering of a friend with cancer who complained more about his morphine-induced constipation than his cancer-related pain, Goldberg tested derivatives of naltrexone, an established morphine-blocking drug.

He developed a version of naltrexone that could not cross the protective barrier that surrounds and protects the brain. So it blocked morphine's effects on the bowels, where it caused painful constipation, but it did not interfere with morphine's beneficial effect on pain, centered in the brain. Nearly three decades later it won FDA approval. Since then more than 800,000 patients have received the drug.

Meanwhile, suspicion emerged that opioids such as morphine could encourage cancer growth. In 2002, Moss and colleagues began to notice that some cancer patients in early studies of methylnaltrexone lived longer than expected.

"These were patients with advanced cancer and a life expectancy of one to two months yet several lived for another five or six months," Moss said. "It made us wonder: could there possibly be a direct effect on the tumors?"

Moss and colleague Patrick Singleton, PhD, assistant professor of medicine at the University of Chicago, subsequently found that cells from various human cancers have far more opioid receptors than non-cancerous cells. In the laboratory they showed how morphine can increase proliferation, migration and invasion of tumor cells.

"We also found that methylnaltrexone reduced tumor growth and spread in several cancer models," Singleton said. "Some of our findings with methylnaltrexone occurred without opioids, suggesting that the opioid receptor and its pathway may be a therapeutic target for cancer treatment."

"Animal models, however, do not always translate to humans," he added. "It is exciting to see new human clinical data that is consistent with what we saw in the laboratory."

"Whether our findings in advanced cancers can be extended to the treatment of earlier cancers, or whether the medication can help physician anesthesiologists improve care during cancer surgery (where opioids are often given) will need to be tested directly," Moss said.

"This study raises novel questions about the role of the opiate receptor in cancer progression," said Ralph Weichselbaum, MD, chairman of radiation oncology and co-director of the Ludwig Center for Metastasis Research at the University of Chicago. "Could the opiate receptor become a therapeutic target? What are the significant side effects of opiates in cancer care? This is an important, hypothesis-generating result."

Additional authors include Andrew Barrett, PhD, and Lorin K. Johnson, PhD, of Salix, and Daniel D. Karp, MD, of MD Anderson Cancer Center.

Moss is a developer of methylnaltrexone and receives royalties through the University of Chicago. He also is a paid consultant for Salix Pharmaceuticals, which markets MNTX. Salix did not contribute to funding for this study. The company was recently acquired by Valeant Pharmaceuticals International, Inc.

http://www.eurekalert.org/pub_releases/2015-10/au-bmo102715.php

Bodily maps of touch and social relationships are tightly linked

A study conducted by Aalto University and the University of Oxford shows that the bodily maps of touch are consistent across a wide range of European cultures.

The recent results obtained by a Finnish-English research group show that the human body has a precisely defined touch maps that are tightly linked to social touch that is allowed in different kinds of human relationships.

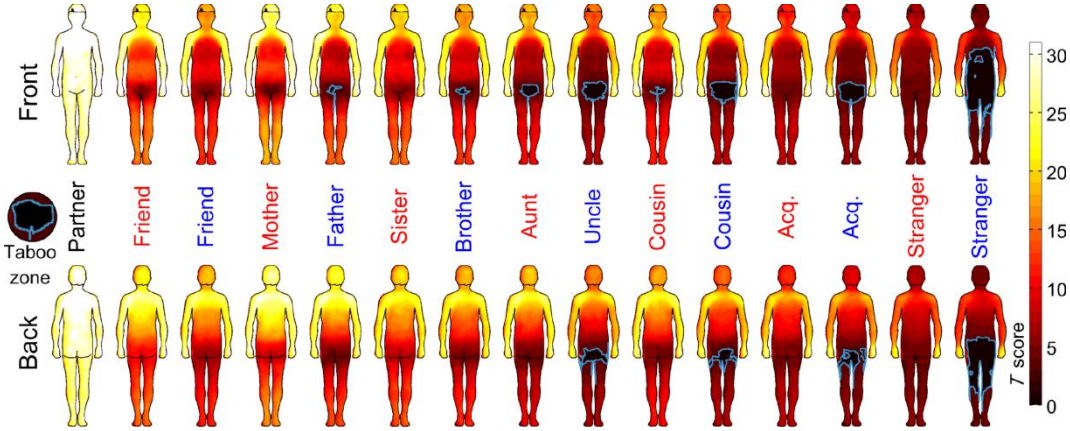
The closer the person in social relationship, the larger the body area this person is allowed to touch. The bodily maps of touch were similar in all five cultures studied.

Social touching thus seems to be a biologically determined and evolutionarily developed way to form social relationships.

The results were recently published in Proceedings of the National Academy of Sciences of the United States of America.

'Our findings indicate that touching is an important means of maintaining social relationships.

The bodily maps of touch were closely associated with the pleasure caused by touching. The greater the pleasure caused by touching a specific area of the body, the more selectively we allow others to touch it,' says researcher Juulia Suvilehto from Aalto University.



Bodily maps of touch are closely linked to social relationships. The brighter the colour of the body area, the more likely the person concerned is allowed to touch it. Any touching of the 'taboo zones' marked with black colour and blue borders is entirely forbidden. **Aalto University**

'The results emphasise the importance of non-verbal communication in social relationships. Social relationships are important for well-being throughout peoples' life, and their lack poses a significant psychological and somatic health risk.

Our results help to understand the mechanisms related to maintaining social relationships and the associated disorders,' says Professor Lauri Nummenmaa.

The study was conducted in the form of an online questionnaire in which more than 1300 people from Finland, England, Italy, France and Russia participated. The study commenced with the mapping of the participants' social network.

The participants were then asked to colour the areas of human body shown on a computer where different members of the social network could touch them.

The research was funded by the European Research Council (ERC), the Academy of Finland and the Emil Aaltonen Foundation.

The results were published on 26 October 2015 by the US National Academy of Sciences in its Proceedings of The National Academy of Sciences of The United States of America (PNAS).

Link to the article: http://www.pnas.org/content/early/2015/10/21/1519231112.abstract

http://www.bbc.com/news/health-34616695

Five old remedies that are still healing us today

Many gems unearthed from the past have true testable medical benefits

One of the recent winners of the Nobel Prize for medicine discovered a breakthrough drug after poring over 2,000 ancient herbal recipes.

Dr Tu Youyou's discovery, the anti-malarial artemisinin, derived from wormwood, is credited with saving millions of lives.

From opium in poppies, to quinine derived from the cinchona tree, to digoxin from foxgloves, there are many gems unearthed from the past that have true testable medical benefits. In fact, there is now a whole branch of science dedicated to the study of traditional medicine, ethnopharmacology.

But it is not as simple as isolating the active ingredient from a plant.

Apart from the fact lots of these plants in their raw form are poisonous, making useful drugs for a population requires planning and sufficient raw material.

"We have to develop drug strategies, and considerations of treating large numbers of people have to be taken into account," Michael Heinrich, professor of pharmacognosy (medicinal plant research) at UCL, says.

Milkweed

The white sap from this common weed, also known as petty spurge, was described by Nicolas Culpeper's Complete Herbalist (1826) as "a good treatment for warts". Don't try this at home, however, as it's also an irritant. Milkweed made its way from its native Europe to Australia, where biochemist Dr Jim Aylward had it in his garden. "My mum grew it for 20 years and swore by it," he says.

"She always told me to put it on my skin to help sunspots."

In 1997, Dr Aylward isolated its active ingredient, ingenol mebutate, which he discovered was toxic to rapidly replicating human tissue.

And recent clinical trials of Picato, a gel derived from milkweed sap, suggest it is effective at stopping lesions turning into skin cancer.

Petty spurge (Euphorbia peplus)

Leeches

Leeches were one of the more civilised methods of bloodletting, a popular cure for disease.

For the Ancient Greek physician Hippocrates, any imbalance in the four bodily "humours" (blood, black bile, yellow bile, and phlegm) would cause disease.

RIA NOVOSTI/SCIENCE PHOTO LIBRARY

And the best way to correct this was to drain the excess - often blood.

Fast-forward to 1830s Europe, and bloodletting was big business.

Use of leeches to treat almost all ailments had reached its peak, with France importing about 40 million every year.

With the rise of "rational" science, and no evidence to back it up, bloodletting died out. But recent advances in surgery mean leeches are back on the wards.

Hospitals such as UCLH in London use these bloodthirsty worms to drain excess blood after microsurgery, which helps to promote natural healing.

They can be used in postoperative care of skin grafts, or after lost fingers and ears have been reattached.

They produce a protein that stops blood clotting - and this gives tiny veins time to knit themselves back together.

Wales is now the centre for leech therapy and home to a farm supplying tens of thousands of medicinal leeches to hospitals around the world.

Willow

Both the Ancient Egyptians and Hipocrates recommended using the bark of a willow tree for pain relief. Its effectiveness was eventually proven in a study by the Royal Society in 1763. But it was not until 1915 that drugs giant Bayer started selling it over the counter as aspirin. It is now the subject of between 700 and 1,000 clinical studies each year. And recent advances have shown it is far more than just a painkiller. From reducing the risk of strokes to indications it could help prevent cancer, aspirin is the traditional remedy that keeps on giving.

Snowdrops

Science Photo Library

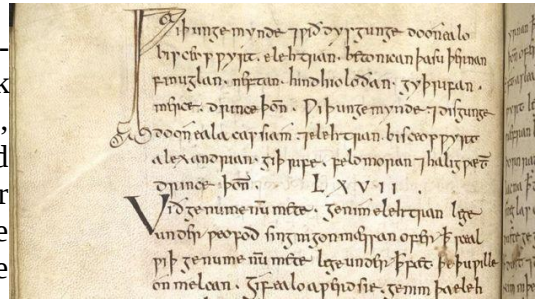
Galantamine, derived from snowdrops and now used to treat Alzheimer's disease, was first investigated by the Soviet Union, - but folk law tells of Bulgarians rubbing the flowers on their forehead to cure headaches.

Prof Heinrich says: "They were almost certainly used in traditional medicine before the Soviet's started investigating in the 50s.

"Why would you go into your garden and investigate your snowdrops?

"There must have been a reason for them to look at snowdrops in the first place"

'Cow's Stomach Juice'



A recipe for "eye salve" from 1,000-year-old Anglo-Saxon medical textbook Bald's Leechbook states onion, garlic, wine and cow's bile should be crushed together and left in a bronze vessel for nine days and nights. Now, tests have shown the eye salve kills MRSA in the lab faster than the best antibiotic.

***Bald's Leechbook* The British Library Board, Royal 12.D.XVII, f.53v**

"Anglo-Saxon remedies don't have the best reputation, but the idea that Anglo-Saxon medicine is superstition has clouded our judgment," says Dr Christina Lee, associate professor in Viking studies at Nottingham University, who translated the recipe. "We need to get rid of the whiff of homeopathy and give old remedies the credit they deserve."

http://www.bbc.com/news/health-34650370

Dementia drug 'keeps patients out of nursing homes'

A common Alzheimer's drug that is often withdrawn by the NHS in later stages of the disease can halve the chances of patients needing to be moved into nursing homes, a study suggests.

Donepezil is used to slow the decline of people with mild to moderate dementia. But it tends not to be given to patients in the late stage of the disease, because of a lack of evidence that it helps. However the study of 295 people led by University College London experts, has produced evidence that challenges that. The participants were split into groups with some being given donepezil, some another dementia drug memantine and others a dummy pill, the journal Lancet Neurology reported. Of those given donepezil, sold under the brand name Aricept, 20% were living in a nursing home within a year, compared to 37% of those not given it.

The study is part of a follow-up analysis of data first collected three years ago, which showed some improvement when the drug was given to people with moderate to late-stage dementia.

Benefits

Researchers said more investigation was needed to fully unpick the reasons for a nursing home admission. But they said their study provided evidence that needed to be considered when it comes to prescribing practices. Some 60,000 people in the UK take the drug which helps to maintain brain function and the ability to cope with everyday activities such as eating and dressing.

About 70% of older people in care homes and nursing homes have dementia - with the average cost of that care ranging between £30,732 and £34,424. Although such care is means-tested, a large chunk of the cost is borne by the individual. In comparison, a year's supply of donepezil can cost as little as £21.59, according to the Alzheimer's Society.

Lead researcher Prof Robert Howard said: "Our previous work showed that, even when patients had progressed to the moderate or severe stages of their dementia, continuing with donepezil treatment provided modest benefits in cognitive function and in how well people could perform their daily activities.

"Our new results show that these benefits translate into a delay in becoming dependent on residential care, an event that many people dread."

Dr Doug Brown, director of research and development at the Alzheimer's Society, which co-funded the trial together with the Medical Research Council (MRC), said: "These robust findings are of real significance to people with dementia who want to continue living at home for as long as possible. We urge clinicians to consider the implications of this research and adjust their prescribing patterns accordingly."

http://www.eurekalert.org/pub_releases/2015-10/uoia-bhp102815.php

Bacterial hole puncher could be new broad-spectrum antibiotic

A team of researchers developed a new broad-spectrum antibiotic that kills bacteria by punching holes in their membranes.

CHAMPAIGN, Ill.-- Bacteria have many methods of adapting to resist antibiotics, but a new class of spiral polypeptides developed at the University of Illinois targets one thing no bacterium can live without: an outer membrane.

The polypeptides, which are short protein chains, act as bacterial hole-punchers, perforating the bacterial membrane until the cell falls apart. The antimicrobial agents are dressed for their mission in a positively charged shell that lets them travel in body fluids, protected from interacting with other proteins, and also attracts them to bacterial membranes.

Led by U. of I. materials science and engineering professor Jianjun Cheng, the researchers published their findings in the Proceedings of the National Academy of Sciences.

"When you have an infection, it can be very difficult for a doctor to know which bacteria is infecting you," said postdoctoral researcher Menghua Xiong, a co-first author of the paper. "Many antimicrobial agents can only cure one class of bacteria. A doctor may try one class, and if that doesn't work, try another class. We need more broad-spectrum antimicrobial agents."

The new antimicrobial polypeptides are specially designed to fold into a rigid spiral resulting in a rodlike structure, ideal for punching holes in the bacterial membrane.

"We use a very set mechanism to puncture the bacterial membrane," Cheng said, "so the polypeptides don't really care whether the bacteria are gram positive or gram negative. They just kill the bacteria independent of their other surface properties."

Such structures have been investigated for various medical applications, but because they do not like water, they do not travel well in bodily fluids. In addition, other molecules in the cell could interact with the polypeptide to disrupt the spiral structure, making it ineffective in puncturing the membrane.

The Illinois researchers and their collaborators addressed these challenges by attaching positively charged ions to the backbone of the spiral, creating a protective shell around the polypeptide so that it is both water soluble and shielded from cross-reactions. The shielded spiral structures are inured to changes in temperature or pH, so they have a stability and predictability that similar agents lack, Cheng said. Furthermore, the positive shell has the advantage of targeting bacterial membranes while decreasing interaction with human cells.

"At the molecular level, there are big differences between bacterial and human cells in the membranes," Xiong said. "The cell membrane lipids in bacteria have a lot of negative charges, and this polypeptide is positive, so it interacts with the negatively charged bacterial membrane. But with human cells, the interaction is weaker."

Many drugs are very targeted, interacting with a particular protein or interfering with a particular pathway in the bacterial cell. Bacteria can develop resistance to the antibiotic by circumventing the specific target. Since the spiral structures simply poke holes in the physical structure of the membrane, it would be much harder for bacteria to form resistance, Xiong said. In addition, the new antimicrobial agents could be coupled with other, targeted drugs to enhance their effectiveness.

"The polypeptides punch holes in the membrane, which makes it very easy for other drugs to go through and bypass some of the drug-resistant mechanisms," Cheng said. "Together, they work even better than a single agent. "

Because the proteins have a preset design, Cheng predicts that scaling up production would not present significant challenges. The precursor elements are already manufactured at large scales and available commercially.

Next, the researchers will continue to improve the antimicrobial polypeptides, further decreasing interaction with human cells, and working to more specifically target pathogenic bacteria.

http://www.eurekalert.org/pub_releases/2015-10/uomh-dht102615.php

Do hospitals tell patients about charity care options? Study finds room for improvement

As Affordable Care Act requirements take full effect next year, patients with no insurance or big bills should ask about available help, U-M team says

ANN ARBOR, Mich. -- If you don't have health insurance, or your insurance coverage still leaves you with big bills, hospitals are supposed to let you know if you qualify for free or reduced-price care, and to charge you fairly even if you don't. That is, if they want to keep their tax-free nonprofit status under the Affordable Care Act's new Section 501(r) rules.

But a new study from the University of Michigan Institute for Healthcare Policy and Innovation finds many nonprofit hospitals have room to improve.

Writing in the October 29 issue of the New England Journal of Medicine, the researchers report results from their review of Internal Revenue Service forms submitted by more than 1,800 nonprofit hospitals nationally. They looked at records for 2012, the first year hospitals had to comply with the ACA's requirements and the most recent year for which data were available.

A mixed bag of findings

IHPI post-doctoral fellow Sayeh Nikpay, Ph.D., MPH and IHPI director John Z. Ayanian, M.D., MPP, call hospitals' performance "far from perfect". Their key findings:

Nearly all of the hospitals reported having a written charity care and emergency care policies, to guide them on deciding which patients could get free or reduced-price care. Though the ACA doesn't tell hospitals which patients to offer discounts to, or how generous to be, it does say they must have such policies and make them known.

Only 29 percent of the hospitals reported they had begun charging uninsured and under-insured patients the same rate that they charged private insurers and the Medicare systems. Such rates are often far lower than the "chargemaster" rates hospitals set as the starting point for negotiating with insurers about how much they will actually accept.

Only 42 percent of the hospitals reported they were notifying patients about their potential eligibility for charity care before attempting to collect unpaid medical bills. The ACA requires such notifications to give patients a chance to explore their options, and apply to get some or all of their costs written off.

One in five hospitals had not yet stopped using extraordinary debt-collection steps when patients failed to pay their medical bills. Such steps, such as reporting patients to credit agencies in ways that can damage their credit scores, placing liens on their property or garnishing their wages, are now banned.

Hospitals in states that have not expanded Medicaid reported having less generous charity care policies, and were less likely to have a policy about notifying patients of charity care options before they left the hospital. In general, patients have to be poorer to get free or discounted care in these states than in states that have expanded Medicaid.

Only 11 percent of hospitals reported having conducted a community health needs assessment in the past three years as of 2012. Such assessments, to identify pressing health issues in the population they serve, don't necessarily affect charity care.

Playing by the rules?

Nonprofit hospitals are exempt from paying most taxes, which was valued at $24.6 billion in 2011. In return, they must justify their nonprofit status to the IRS each year by showing how much care they write off for those who cannot pay.

When Congress wrote the ACA, they sought to use the tax tools available to them to reduce hospitals' use of aggressive methods to pursue payment, and perhaps to prevent individual bankruptcies or credit score damage caused by medical bills.

Though hospitals had to report for tax year 2012, the federal government did not issue final language about exactly how to comply and penalties for non-compliance until 2014. Nikpay and Ayanian will continue to study the issue as new IRS data become available. They are already working on 2013 data.

"Hospitals are generally complying with the part of the rules that require they establish charity care policies and publicize them, but this may not impact the

amount of charity care they provide," says Nikpay, who is also a visiting scholar at the University of California, Berkeley. "So far, it appears many aren't complying with the part of the rules that could increase their charity care."

Ayanian, a professor at the U-M Medical School with joint appointments in public policy and public health, says physicians and patients should familiarize themselves with policies at their hospitals.

"Financial protection for patients is an under-recognized component of the ACA, and it's important that hospitals are required to have policies, that they disclose these policies, and that they enable people apply for help in a timely way," he says. "This will be most important for patients living in states that have not expanded Medicaid to cover people with lower incomes. Hospitals in those states will likely experience additional demand for charity care because they now need to publicize their charity care policies and comply with other IRS provisions."

With these added requirements, hospitals may start to pull back on how generous they make their charity care policies - and section 501(r) of the ACA does not set standards for that, Nikpay notes.

As more Americans enroll in insurance plans that have high deductibles, they may find they need to ask for financial relief after a hospital stay. Even a single person earning $40,000 a year, or a family of four with an income around $80,000, might qualify for discounted care from hospitals.

Reference: New England Journal of Medicine, DOI: 10.1056/NEJMp1508605

http://www.eurekalert.org/pub_releases/2015-10/cndi-tf102615.php

The first 'molecular labels' that predict the organs where metastases will form, discovered

Evidence that exosomes trigger the necessary molecular response to receive the tumour cells and then to proliferate

Understanding why a tumour metastasises in specific organs and do not in others is one of the top goals of oncology, and also one of the oldest. 126 years ago, the British physician, Stephen Paget, formulated his 'seed and soil theory', which advocates that metastasis requires the dispersal of tumour cells, 'seeds', as well as a welcoming environment, 'fertile soil', in the recipient organ.

However, since then "the progress made in deciphering the mechanisms that guide metastasis to specific organs has been insufficient," write the authors in the report published in 'Nature'.

In recent years, Héctor Peinado, Head of the Microenvironment and Metastasis Group at the Spanish National Cancer Research Centre (CNIO), David Lyden from Weill Cornell Medical College, and Jaqueline Bromberg from the Memorial Sloan Kettering Cancer Center, have developed a theory that supports Paget's 'seed and soil' theory.

Ayuko Hoshino and Bruno Costa-Silva, co-first authors in this publication, together with Peinado and Lyden, have collected evidence that tumours release millions of vesicles carrying representative samples of their proteins and genetic content.

These are called exosomes and, like 'messenger vessels' or 'scouts', they are in charge of ensuring that the recipient organs are prepared to host the tumour cells. Specifically, the exosomes trigger the necessary molecular response -- inflammation, vascularization, etc. -- in the recipient organ to welcome the tumour cells, so that when they arrive they can proliferate.

"So far, this is the first study defining the role of tumour-secreted exosomes in organ-specific metastasis," explains Peinado. The current work corroborates its existence, since it confirms that exosomes play a crucial role in the formation of metastasis in precise organs.

But the researchers wanted to go even further. They knew that of the millions of exosomes originating from the tumour, only a few will nest and, moreover, they will not do so in any random organ, but in some more than others. Why? Could it be possible that the exosomes, the tumour 'scouts', have molecular labels that in some way direct them to specific organs?

'Zip Codes' In The Exosomes

To investigate this hypothesis, the authors selected 20 tumour cell lines from around ten different tumours, in which it is known that some metastasise to specific target organs; the lungs, liver, brain or bones. They analysed the proteins in their exosomes, nearly a thousand proteins, searching for those that could fulfil the role of a zip code.

They focused on a family of proteins called integrins, because these are present on the membrane of the exosomes where, theoretically, the destination 'label' should be found. This proved to be a sound strategy.

From among a thousand proteins, they found that there were indeed specific combinations of integrins associated with metastasis to the lungs, and with metastasis to the liver.

As Peinado points out, "we have determined that there is a combination of integrins in tumour exosomes that predisposes the formation of metastatic niches in different organs, specifically in the lungs and the liver."

"Our results suggest that there is a sort of 'zip code' on the surface of the exosomes that makes them go to specific organs and accumulate where the metastasis is going to occur," continues the CNIO researcher.

If a tumour is 'tricked', by changing the destination code, it will colonise the organ that is specified. This has been tested with tumour cells that normally would go to the bones and, following the intervention of the researchers, went to the lungs.

These data support that the 'soil' is as important as the 'seed' in the metastatic process.

Additional proof of the importance of integrins in metastatic nesting is that, as the study shows, when specific integrins are blocked in tumours that metastasize to specific organs -- for example breast cancer to lungs and pancreas cancer to the liver -- metastasis is reduced in these organs.

Laying The Groundwork

The researchers have also discovered the molecular signals that intercede in the reaction of the recipient tissue when the exosomes arrive. Specifically, these signals involve an increase in genes of the S100 family, which is known for provoking inflammatory signals; inflammation is a process associated with cancer.

These results represent the identification of potential new pharmacological targets, says Peinado: "We have defined a new type of mechanism for metastasis to specific organs that involves integrins and S100 proteins, which could be used as new anti-metastatic targets."

The study was performed using human and mouse tumour cell lines, pre-clinical mouse models, as well as plasma from cancer patients.

The latter served for the preliminary study of the predictive power of the integrins identified, that is, whether analysis of the exosome integrins alone will make it possible to know in which organs there could be metastasis.

"Our work suggests that a high level of certain integrins in the plasma of patients with breast cancer and pancreas cancer seems to predict the organ where the metastasis will occur," says Peinado. "But these data will have to be validated on larger cohort studies and predictive tests must be developed."

These results generate a list of immediate tasks for researchers, from expanding the studies with patients in order to improve the predictive power of the integrins -- with specific analytical technologies that are yet to be developed -- to identifying other 'zip codes' that determine metastasis to the brain or bones.

No less important is the search for new drugs: "In the future, we envisage the development of molecules to block combinations of integrins specifically in tumour tissues," states Peinado.

This work is the result of an international, multidisciplinary and multi-institutional collaboration, which involves obtaining multiple cellular and pre-clinical models, as well as human samples. The search for these models has been carried out over the last three years with the participation of many teams, as reflected in the large number of authors in the article.

Reference article:

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Scientists identify main component of brain repair after stroke

NIH-funded research pinpoints protein that sprouts into action, activating stroke repair

Looking at brain tissue from mice, monkeys and humans, scientists have found that a molecule known as growth and differentiation factor 10 (GDF10) is a key player in repair mechanisms following stroke. The findings suggest that GDF10 may be a potential therapy for recovery after stroke. The study, published in Nature Neuroscience, was supported by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

"These findings help to elucidate the mechanisms of repair following stroke. Identifying this key protein further advances our knowledge of how the brain heals itself from the devastating effects of stroke, and may help to develop new therapeutic strategies to promote recovery," said Francesca Bosetti, Ph.D., stroke program director at NINDS.

Stroke can occur when a brain blood vessel becomes blocked, preventing nearby tissue from getting essential nutrients. When brain tissue is deprived of oxygen and nutrients, it begins to die. Once this occurs, repair mechanisms, such as axonal sprouting, are activated as the brain attempts to overcome the damage. During axonal sprouting, healthy neurons send out new projections ("sprouts") that re-establish some of the connections lost or damaged during the stroke and form new ones, resulting in partial recovery. Before this study, it was unknown what triggered axonal sprouting.

Previous studies suggested that GDF10 was involved in the early stages of axonal sprouting, but its exact role in the process was unclear. S. Thomas Carmichael, M.D., Ph.D., and his colleagues at the David Geffen School of Medicine at the University of California Los Angeles took a closer look at GDF10 to identify how it may contribute to axonal sprouting.

Examining animal models of stroke as well as human autopsy tissue, Dr. Carmichael's team found that GDF10 was activated very early after stroke. Then, using rodent and human neurons in a dish, the researchers tested the effect of GDF10 on the length of axons, the neuronal projections that carry messages between brain cells. They discovered that GDF10 stimulated axonal growth and increased the length of the axons.

"We found that GDF10 caused many different neurons in a dish to grow, including human neurons that were derived from stem cells," said Dr. Carmichael.

His group also found that GDF10 may be important for functional recovery after stroke. They treated mouse models of stroke with GDF10 and had the animals perform various motor tasks to test recovery. The results suggested that increasing

levels of GDF10 were associated with significantly faster recovery after stroke. When the researchers blocked GDF10, the animals did not perform as well on the motor tasks, suggesting the repair mechanisms were impaired--and that the natural levels of GDF10 in the brain represent a signal for recovery.

"We were surprised by how consistently GDF10 caused new connections to form across all of the levels of analysis. We looked at rodent cortical neurons and human neurons in dish as well as in live animals. It's a demanding gauntlet to run, but the effects of GDF10 held up in all of the levels that we tested," said Dr. Carmichael.

It has been widely believed that mechanisms of brain repair are similar to those that occur during development. Dr. Carmichael's team conducted comprehensive analyses to compare the effects of GDF10 on genes related to stroke repair with genes involved in development and learning and memory, processes that result in connections forming between neurons.

Surprisingly, there was little similarity. The findings revealed that GDF10 affected entirely different genes following stroke than those involved in development or learning and memory.

"We found that regeneration is a unique program in the brain that occurs after injury. It is not simply Development 2.0, using the same mechanisms that take place when the nervous system is forming," said Dr. Carmichael.

More research is necessary to determine whether GDF10 can be a potential treatment for stroke recovery.

This work was supported by grants from the NINDS (NS085019, NS086431) and the American Heart Association (09SDG2310180).

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Should Doctors Be Tested for Competence at Age 65?

The Case for Testing Older Physicians

Leigh Page

Should older physicians be forced to stop practicing once they begin to slow down? Some experts in competency testing are calling for doctors to be evaluated as early as age 65, arguing that that's when physical and mental disabilities start to become apparent.

A few hospitals have already started evaluating physicians in their 70s for competency. When results show significant impairment, these physicians are required to get remediation, submit to limitations of their privileges, or retire completely, depending on the severity of the impairment.

Some experts argue that the cutoff age for these exams should be 65 years, which would have a huge impact on America's doctors. Owing to the baby boom, 240,000 doctors are now in that age group—a fourfold increase since 1975, according to the American Medical Association (AMA).

In June 2015, delegates to the AMA decided to bring together stakeholders to create guidelines for such testing. But other physician groups are still on the fence, and the issue divides the medical community.

Proponents of age-based testing say it's no longer permissible to simply allow aging physicians to determine when they should retire, because many of them stay on after impairment sets in. But critics assert that younger physicians are just as likely to be impaired, and targeting older physicians is unnecessarily humiliating.

Senior Doctors Are Divided

Doctors in their 70s are taking leading roles on both sides of the debate.

Claire Wolfe, MD, a 71-year-old physiatrist in Dublin, Ohio, was a key player in the AMA's decision to draft preliminary guidelines. She's a member of the governing council of the AMA Senior Physicians Section, which spearheaded the AMA's decision to take up the issue.

Last year, the section introduced a resolution to the AMA House of Delegates calling for mandatory testing of older physicians. After spirited debate, the House referred the matter for study. The resulting study,[1] presented at this year's annual meeting, proposed what the AMA should do, and the House approved it in May with reportedly little debate.

Dr Wolfe says there are several reasons why age-based testing is needed. "Unfortunately, older physicians don't always know when to quit practicing," she says, and "it's very difficult to get physicians to identify impaired colleagues" and convince them to quit.

She says older physicians who aren't impaired should be allowed to practice no matter how old they are. Even when impairments are identified, every effort should be made to help physicians alter their practice without ending their careers, she says. But if they have serious impairments, such as dementia, they'll need to resign.

Dr Wolfe fully expects that many physicians will resist age-based testing. "This isn't going to be an easy sell to the medical community," she says.

Insurgents against the policy are already at the barricades—for example, Frank E. Stockdale, MD, also a septuagenarian. The 79-year-old breast cancer physician leads a group of 13 older physicians who have forced Stanford Medical Center to rewrite its age-based testing policy and have rallied Stanford faculty to come out against it.

"Older physicians aren't the problem," says Dr Stockdale. "Mid-career physicians are responsible for a disproportionately higher number of bad outcomes."

Although he's slowing down physically, Dr Stockdale says he has learned to adjust. "My memory isn't as good as it used to be and I don't play basketball anymore, but that doesn't mean I'm not competent to practice medicine," he says. "You learn to compensate." Older physicians tend to see fewer patients; focus on patients with less acuity; and spend more time with them, which patients like, he says.

Dr Wolfe has a markedly similar view about her own ability to continue practicing. Although she now works just 2 days a week, she doesn't think she's lost her mental acuity. "If I started to lose it, my colleagues would tell me." But she thinks many other end-of-career physicians are less willing to quit when impairment strikes. "Doctors say they'll know when they need to quit, but in many cases they won't do it," she says.

A Call for Preliminary Guidelines

The AMA Senior Physicians Section is just a couple of years old, and age-based testing was a topic for the section to make its mark, Dr Wolfe says. "We thought this issue was where we could be of value to the AMA." For the past few AMA meetings, the section has been inviting experts on physician performance and quality to speak on the aging doctor. She says the sessions drew so many attendees that there were no chairs left.

She's somewhat disappointed with the AMA report, however. The 21-page document "presented a lot of powerful reasons why testing is needed, but the recommendations didn't come out forcefully for testing," Dr Wolfe says. "A lot of people felt they were a little tepid."

Rather than fully embrace this approach, the report states that "formal guidelines on the timing and content of testing of competence may be appropriate," and called for the creation of "preliminary guidelines."

Dr Stockdale has a very different view of the AMA report. Having read many of the same studies cited in the report while on a Stanford committee probing the issue, he thinks it accepted favorable findings on age-based testing "with an uncritical eye." A lot of the studies, he maintains, "depend on samples that are too small, or make conclusions based on very slight differences in performance that have no clinical importance."

The Stanford professor says his own informal review of the data shows that older doctors aren't responsible for more mistakes than those of other age groups. For example, when he looked at "never" events—serious events that could have been prevented—"the percentage involving older physicians was not disproportionate for this age group," he says.

Some Hospitals Have Created Policies

A small but growing number of hospitals have age-based testing policies, according to Jonathan Burroughs, MD, a healthcare consultant in New Hampshire. Altogether, he says, about 50 hospitals he advises have some kind of policy to screen older providers. He cites age-based testing programs at Driscoll Children's Hospital in Corpus Christi, Texas; Jewish Hospital and Sts. Mary and Elizabeth Hospital in Louisville, Kentucky; and Portsmouth (New Hampshire) Regional Hospital.

In many cases, hospitals that initiated policies "had an issue with an older doctor who was incapacitated but had not yet gotten into trouble," Dr Burroughs says. "This was a ticking time bomb."

He added that some hospitals considered age-related policies but then backed off, after pushback from doctors on staff. "They (hospitals) know this is the right thing to do, but they're worried about upsetting their doctors," Dr Burroughs says. "Ultimately, most hospitals are going to put patient safety ahead of physician autonomy."

A formal policy on age-based testing is necessary, he says, because hospitals that choose to sanction on older physician will need to have an airtight case that he or she is too impaired to practice, and then provide solutions that treat the doctor fairly without violating the law.

What's an Appropriate Cutoff Age?

Dr Burroughs, a 65-year-old former emergency physician, thinks that hospitals should start testing doctors at his current age, because that's when age-based disabilities start to become pronounced in some physicians. But in his consultant role, he recommends age 70 years, and then seeks to reduce the age limit after the policy becomes more acceptable to physicians on staff.

"It has to do with 'change management,'" he says. "A lot of doctors on staff are in their 60s and are more likely to accept the policy if it's limited to older physicians."

Even at age 70, though, many physicians would be affected if every hospital had such policies. According to the Federation of State Medical Boards,[2] 64,000 physicians in their 70s had an active license in 2010.

What's more, the number of older physicians has been rising as the baby boom generation reaches retirement. According to the AMA,[3] the proportion of physicians aged 65 years or older rose from 9.4% in 1985 to 15.1% in 2011.

How would older physicians be tested? Under D Burroughs' approach, they would get a face-to-face "fitness to work" evaluation by a vocational specialist—someone who is trained to assess commercial airline pilots and other professionals. The evaluation takes about an hour and covers cognitive, metabolic, psychological,

and physical domains. Doctors who have any possible deficits in any of these areas would be directed to a more intensive exam.

Dr Burroughs says the initial evaluation costs about $300-$500, which he thinks the hospital should pay for. Doctors identified as impaired in some way would confidentially work out a mutually agreed-upon resolution with hospital authorities on what work they could continue to perform. For example, an older doctor might agree not to take overnight call, deal with lengthy surgeries, or work long shifts.

Experts often mention the option of simply stopping doctors from practicing when they reach a specific age. For example, US commercial pilots are required to retire at age 65 years, and 15 years ago, some hospitals in Britain's National Health Service required surgeons to retire at age 65, but that policy has reportedly been rescinded.

Mandatory retirement would be easier to administer than testing programs, but experts have roundly rejected this option, noting that many physicians are quite capable of practicing into their 80s (such as famed cardiac surgeon Dr Michael E. DeBakey) and that forcing all older doctors to retire would hasten a looming physician shortage. Almost one third of physicians were 60 years of age or older in 2012, according to the Association of American Medical Colleges.[4]

The Push to Standardize Policies

AMA officials are just beginning to plan how they'll carry out the House's recent action, according to Richard E. Hawkins, MD, vice president of medical education programs at the AMA. The first step is to convene a meeting of stakeholders in such areas as continuing education, licensure, and certification, as well as representatives of medical societies, he wrote in an email to Medscape. Dr Hawkins added, "We expect the first meeting to be held in the next 6 months."

Although no state or specialty society has endorsed age-based testing, some of them are studying the matter. In emails to Medscape, a spokesman for the American College of Surgeons (ACS) said that an ACS task force is focusing on the matter, and a spokeswoman for the California Medical Association (CMA) said that it is studying the issue.

The CMA is already tangentially involved in the issue. Along with the California Hospital Association, it sponsors a coalition called California Public Protection and Physician Health, which issued a guideline,[5] on how hospitals and group practices should conduct age-based assessments while still observing older physicians' legal rights.

The guideline, released in April, states that assessments should include a physical examination, peer assessments, and a test of cognitive functions, which may be followed by further testing if any concerns are raised. Physicians identified with possible impairments would then meet confidentially with medical staff representatives to discuss reducing their scope of practice, or even dropping their privileges.

The guideline, which elicited input from healthcare lawyers, stated that as long as these physicians make voluntary changes in privileges, they wouldn't be reported to their licensing board.

Speaking of which, why not have specialty or licensing boards conduct age-based testing? Although seemingly logical, proponents of age-based testing tend to oppose this approach. "I think doctors would be very apprehensive about getting the licensure boards involved," Dr Wolfe says. "The concern would be that the process might not be confidential." Moreover, the boards haven't expressed any interest in taking on this issue.

Stanford's Policy Under Fire

The struggle over Stanford Medical Center's age-based testing policy shows how difficult it can be to implement such policies.

The medical center initiated an age-based testing program in 2012 for doctors on staff who were approaching age 75 years. Around 17 physicians, including Dr Stockdale, were scheduled to have a physical exam, cognitive test, and peer review. But Dr Stockdale says he and several others refused to take the cognitive test, questioning its validity. "The administration was put in a tight spot," he recalls. "If they had followed the policy, they would have had to remove all of us, but they didn't want to do that."

So the medical center set aside the cognitive test and appointed a committee, including Dr Stockdale, to study the test's validity. After 2 months surveying the literature, he says, the committee concluded that the cognitive test "does not rest on sound scientific grounds" and called for an end to the program.

In an email to Medscape, Ann Weinacker, MD, a Stanford quality improvement expert representing the medical center, confirmed that the cognitive test was dropped because "there are insufficient data at present to support cognitive screening of late-career physicians."

Instead, she says, Stanford is using "a more robust peer-review process," which both sides agree has been validated. Peer reviewers fill out the Clinical Excellence Core Competencies Evaluation form,[6] which is already used to evaluate residents. Dr Stockdale says low scores for residents have been linked to higher levels of disciplinary actions against them later in their careers.

In response to the committee's call to end the program, the administration put it up for a vote. In what was reportedly the largest voter turnout ever among physicians on staff at the medical center, the policy prevailed, by a margin of 53% to 47%.[7]

Dr Stockdale maintains that many physicians voted "yes" to please department chairs aligned with the administration. He and his allies pressed on with their campaign, however, bringing the matter to the attention of the Stanford University Faculty Senate—which represents all faculty members, not just doctors.

In May, the faculty senate heard arguments from Dr Stockdale's group opposing the policy, and from Dr Weinacker and the dean of the medical school in its defense. The faculty senate then voted 20 to 9 to reject the policy.

Dr Stockdale argues that the vote should be binding because Stanford faculty members are on staff at the medical center. But the administration contends the vote isn't binding because the medical center is independent of the university.

Has anyone failed the Stanford assessment since its adoption? In her email, Dr Weinacker replied that the testing is "not a pass/fail screen," but rather, "it is intended to evaluate for concerns that may require further evaluation." She wouldn't say whether any doctors required further evaluation, but Dr Stockdale says that to his knowledge, no one has been found to be subpar, and no limitations have been put on anyone's privileges.

How Big Is the Problem?

There's no well-informed estimate on how many impaired older physicians might still be practicing, but there are many scientific studies on various aspects of this topic. The AMA report cites 72 such studies, many of which point to issues with older physicians, although they may not necessarily be age-related. For example:

- A 2005 study[8] showed a much higher rate of disciplinary actions against doctors out of medical school for 40 years compared with those out of school 10 years.
- Another study, also from 2005,[9] indicated that performance on a range of outcomes declined as physicians' years in practice increased.
- A 2008 study[10] found "no notable relationship" between older physicians' own assessment of their cognitive skills and objective cognitive measures, indicating that the physicians may be unaware of their impairments.
- Older surgeons, although competent in routine operations, performed more poorly in complicated procedures, such as coronary artery bypass graft surgery, according to a 2006 study.[11]

But even the most convincing studies show that a significant percentage of older physicians have no serious competency problems, even when they're at an advanced age. For example, a 2010 study[12] found that one third of surgeons in their 70s still matched younger surgeons in competence on a variety of tasks.

However, Dr Stockdale disputes that loss of cognitive ability is the main reason why physicians make mistakes. "The major reason for errors," he says, "is not cognitive problems but behavioral ones," such as alcoholism, substance abuse, and failure to document, which occur more frequently in younger physicians. "The mid-career is a more risky time for physicians," he asserts. "These doctors are 15 years or more beyond training, and what they learned has started to wane."

Rather than focus on end-of-career physicians, Dr Stockdale believes hospitals should beef up evaluations of all doctors, regardless of age. He noted that the Joint Commission already requires hospitals to regularly evaluate physicians' competence[13] in six areas, including patient care, clinical knowledge, and interpersonal skills.

Is Cognitive Testing Right for Physicians?

Owing to concerns about cognitive impairment in older physicians, many age-based testing programs use cognitive tests, such as MicroCog™ and the Montreal Cognitive Assessment, as assessment tools. Such tests have been used for years by physician health programs, which evaluate doctors who may be impaired.

In many age-based testing programs, physicians start with a fairly short cognitive screening, such as the Mini-Mental State Examination. If the findings show any concerns, doctors then get the full-blown exam, which is given by a neuropsychologist and lasts about 10 hours, spread over 2 days.

But as Stanford Medical Center concluded, cognitive tests haven't been validated for use on physicians. When scoring the test, the baseline for the general population is known, but experts say physicians should have to meet a higher baseline, which hasn't yet been identified.

To establish the physician baseline, researchers would have to a conduct a very expensive round of testing in each metric, according to Peter Donovick, PhD, a neuropsychologist at Binghamton University in Binghamton, New York, who has tested physicians. "You would need to evaluate a large group of several hundred fully functioning physicians and put each of them through a thorough cognitive evaluation," he says.

Doris Gundersen, MD, a psychiatrist who is president of the Federation of State Physician Health Programs and medical director of the Colorado physician health program, agrees that "no cognitive screening tests that I'm aware of have been validated specifically for the physician population," but she thinks age-based testing programs should use cognitive testing anyway. "We don't have the luxury of waiting for the 'gold standard' screening instrument," she says.

However, some age-based testing programs in addition to Stanford's program don't use cognitive tests. The College of Physicians and Surgeons of Ontario requires active physicians who reach age 70 to be evaluated, but rather than use cognitive tests, they're assessed by their peers, who review the doctors' medical records and how they treat patients.[14]

Some physicians would rather have peer review than a cognitive test. William Wilkoff, MD, a 70-year-old pediatrician in Brunswick, Maine, who retired 2 years ago, says he would feel uncomfortable with a cognitive test. "I wouldn't want to know that I have incipient Alzheimer disease and have only a few more years of clear thinking ahead of me," he says.

This glimpse into the future is made possible with cognitive testing. In fact, Dr Gundersen and a colleague reported[15] that 80% of the physicians identified with mild cognitive impairment would develop dementia within 6 years.

How Should Surgical Skills Be Evaluated?

In addition to cognitive testing, many experts believe that surgeons and other procedure-oriented specialists should be further tested, on such things as hand/eye coordination, visual acuity, and trembling hands.

The Aging Surgeon program at Sinai Hospital in Baltimore, for example, offers tests of surgical skills, such as the Biodex Balancing System™ (Biodex Medical Systems, Inc.; Shirley, New York), and Vision Coach™ 1 and 2 (Perceptual Testing, Inc.; San Diego, California). Mark R. Katlic, MD, chief of surgery at Sinai and founder of the program, says he's received about 100 inquiries from hospital CEOs and chiefs of surgery who have aging surgeons suspected of having impairments. However, no one has enrolled in the program yet.

One reason may be the cost—$17,000 for 2 days of both physical and cognitive skills testing. Another reason is that sometimes, the need for testing goes away. "A number of these older surgeons voluntarily retired when threatened with our program," Dr Katlic says.

Stuart A. Green, MD, a retired orthopedic surgeon, has studied surgical skills tests, such as computer-based exercises that teach surgical skills to residents. He has also looked at some of the same tests that Dr Katlic offers, such as quickly pointing to dots that pop up on a screen, and believes that computerized tests of driver's skills could be adapted for surgeons. But none of these tests have been validated to assess whether surgeons should continue practicing, he says.

Dr Green became interested in age-based testing several years ago, when he served on the ethics committee of the American Academy of Orthopaedic Surgeons (AAOS). "Hospitals were trying to push out older physicians who seemed to be at risk," he recalls, and these surgeons would write the AAOS asking for help.

At first, Dr Green opposed age-based testing. But after meeting a surgeon who seemed to be cognitively impaired—and whose problem had been covered up—he proposed that the AAOS endorse such testing, but there wasn't much interest, he says. He felt vindicated when he read about the AMA vote.

"I was waiting for the moment when someone would do something about this," he says. Now 72, Dr Green has stopped practicing because of back pain and not cognitive impairment, but he still teaches residents.

Concerns About Overzealous Enforcement

Some critics of age-based testing programs are concerned that they'll drive away older physicians who would rather retire than face the possibility of being diagnosed with dementia. "In an effort to identify a few addled physicians," Dr Wilkoff says, "how many really talented older physicians would you discourage from further practice?"

Indeed, Dr Gundersen reports that when one hospital implemented an evaluation program for physicians at age 70, the handful of doctors who would be affected chose to retire rather than take the test—much the same as Dr Katlic discovered at Sinai Hospital.

"It was simply because the policy was new and unfamiliar to these older physicians, who may have anticipated discipline," Dr Gundersen says. She thinks the problem could be addressed by being sensitive to affected doctors and educating them about the process.

Dr Burroughs conceded that testing programs could get too "proscriptive." For example, he says physicians who have no significant deficits might be forced to limit their privileges, or the hospital might simply rely on the results of a cognitive screening test, rather than a vocational specialist's face-to-face evaluation.

Such concerns point to the need to create guidelines for testing programs, as the AMA plans to do. Rather than forcing someone to retire, many programs allow older physicians who have been identified with impairments to opt for remedial training on their weaknesses, such as clinical record-keeping. Or they could agree to restrict their activities, such as not taking call, dropping procedural work, and seeing fewer patients while spending more time with each one.

"In many cases, the solution is to change the way you practice, rather than to end your career," Dr Gundersen says. "Physicians will accept these programs once they see that only in some doctors will deficits be identified, and when they witness that these physicians will be treated in a confidential and respectful manner."

What About Age Discrimination?

Several federal laws, including the Age Discrimination in Employment Act, protect older physicians against adverse actions, even when they're just on staff and aren't direct employees of the hospital.

Several attorneys who have studied the matter say age-based testing programs can comply with federal laws. Edwards Wildman Palmer, a large Boston law firm,

reports[16] on its website that the program must demonstrate that it's "reasonably necessary" for public safety and that it would be impractical to test every doctor on staff individually.

However, the risk of being charged with age-based discrimination by the Equal Employment Opportunity Commission (EEOC) in these cases is real.

Consider the case of Warren Guntheroth, MD, a cardiologist at the University of Washington (UW) Medical School, as reported[17] by the *Seattle Times*.

In 2006, when Dr Guntheroth was 79, the medical center started to investigate his skills after he was accused of becoming isolated from other doctors, writing inappropriately short assessments of patients, and misreading cardiology tests.

Three outside doctors appointed to assess Dr Guntheroth concluded that only his clinical documentation was poor. As a result, UW decided to restrict his privileges. His patient records were monitored, he was limited on where he could practice, and he was required to attend sessions on cardiology topics.

Dr Guntheroth claimed he was being retaliated against for publicly criticizing the medical school on several policy issues, and he reported the medical school to the EEOC. UW insisted that it wasn't engaging in age discrimination because none of the 14 other on-staff physicians older than 70 were under review.

In 2008, the EEOC concluded that Dr Guntheroth had not "engaged in misconduct which would warrant the adverse treatment" he received, and there was "reasonable cause" to believe that he'd been discriminated against. Nevertheless, the EEOC didn't take any further action. To force UW to revoke its action against Dr Guntheroth, the EEOC would have had to sue the university, and the agency rarely brings lawsuits, the *Times* reported.

Conclusion

The AMA's ability to produce guidelines on age-based testing will depend to some extent on whether other physician groups endorse the policy, which they have balked at doing so far. Yet even if the AMA comes up with guidelines, it will be up to each hospital to adopt them, unless the Joint Commission establishes requirements.

The policies themselves will need to weigh patient safety against the ability of physicians to continue practicing. Speaking on behalf of surgeons, Dr Katlic says, "We need to balance patient safety and liability risk with respecting the dignity of surgeons and their value to society."

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http://www.bbc.com/news/uk-england-sussex-34659771

Multiple sclerosis patient walks after taking HIV drugs

A woman with multiple sclerosis (MS) says her symptoms improved so dramatically she was able to walk again after being prescribed HIV drugs.

Shana Pezaro, 36, from Hove, East Sussex, was given antiretroviral drugs after fearing she may have contracted HIV. Within days, Miss Pezaro noticed an easing of her MS symptoms. When a doctor saw her walking up stairs after years of using a wheelchair he set up a clinical trial.

Multiple sclerosis is an incurable condition that can lead to sight loss, pain, fatigue and disability. It affects around 100,000 people in the UK.

Miss Pezaro was a dancer and piano teacher before being diagnosed with MS at the age of 28. The condition affected her hands and feet and she used a wheelchair.

Multiple sclerosis

In MS the coating around the nerve fibres is damaged causing a range of symptoms
Once diagnosed there is no cure, but treatments can help manage the condition
MS affects almost three times as many women as men
Physical symptoms of MS might commonly include vision problems, balance problems and dizziness, fatigue, bladder problems and stiffness and/or spasms
MS can affect memory and thinking and also can have an impact on emotions

(Source: Multiple Sclerosis Society)

About a year ago, Miss Pezaro thought she may have been exposed to HIV and her doctor prescribed emergency antiretroviral drugs. "Three days after I took the drugs I walked up a flight of stairs," she said. "That was an unbelievable, massive change."

Prof Julian Gold from the Prince of Wales Hospital in Sydney, saw a video of Miss Pezaro climbing the stairs and a clinical trial was set up to look at the impact of single or combination antiretroviral drugs on MS patients.

An earlier study led by Dr Gold conducted with Queen Mary University, London and the University of Oxford showed an association between HIV and MS.

They reported antiretroviral treatment may suppress other viruses such as those which may cause MS.

Dr Gold said: "The next stage of the investigation is to use a very similar combination [of HIV drugs] that Shana took. I think that might be quite optimistic."

A spokeswoman for the MS Society said: "Our growing understanding tells us that viruses have a role to play in multiple sclerosis and it will be interesting to see the trial results - positive findings mean another step on the road to beating MS."

Analysis: BBC South East health correspondent, Mark Norman

Shana and Dr Gold would be very keen not to raise any false hope.

The study builds on a lot of work already done with HIV patients who simply don't get multiple sclerosis. This is really about finding a cause and increasingly people think the cause may be a virus. When scientists use words like "amazing" and "intriguing" you have to stand up and listen.

http://www.bbc.com/news/health-34649024

'Milestone' prostate cancer drug

The first drug that targets precise genetic mutations in prostate cancer has been shown to be effective in a "milestone" trial by UK scientists.

By James Gallagher Health editor, BBC News website

The study, at the Institute of Cancer Research in London, took place on 49 men with untreatable cancer. The drug, olaparib, had low overall success, but slowed tumour growth in 88% of patients with specific DNA mutations. Cancer Research UK said the trial was exciting.

The future of cancer medicine is treating cancers by their mutated DNA rather than what part of the body they are in. The breast cancer drug Herceptin is already used only in patients with specific mutations. Olaparib targets mutations that change the way DNA is repaired. The trial results, published in the New England Journal of Medicine, showed the drug worked in 14 out of 16 men with such mutations.

Levels of Prostate Specific Antigen, which is produced by tumours, was more than halved and there were also significant falls in the number of prostate cancer cells detected in the blood and in the size of secondary tumours.

Patients responded to the drug for between six months and nearly a year and a half.

One of the researchers, Dr Joaquin Mateo, told the BBC News website: "It is very promising. "Those entering the trial had an expected survival of 10 to 12 months and we have many patients on the drug for longer than a year."

Prostate cancer is the fifth most deadly type of cancer in men. However, a larger clinical trial is needed before doctors can say if the drug extends life expectancy.

Dr Mateo added: "This is the first drug that targets specific genetically defined populations and we are going to see more and more of these coming in the next few years."

The advantage of targeted drugs is they can be given only to those patients who will respond, which both saves money and spares patients unnecessary side effects.

Some of the patients in the study were born with mutated DNA repair genes while in others the mutation developed inside the tumour.

'Significant step'

Professor Johann de Bono, the head of drug development at the Institute of Cancer Research said: "Our trial marks a significant step forward in the treatment of

prostate cancer. "I hope it won't be long before we are using olaparib in the clinic to treat prostate cancer."

However, the drugs watchdog in England - the National Institute for Health and Care Excellence - has already rejected olaparib for ovarian cancer on grounds - at £4,000 a month - of cost.

Cancer Research UK's Dr Aine McCarthy added: "This trial is exciting because it could offer a new way to treat prostate cancer by targeting genetic mistakes in cancers that have spread. "The hope is that this approach could help save many more lives in the future."

http://www.eurekalert.org/pub_releases/2015-10/ps-qbc102915.php

Gut bacteria could be blamed for obesity and diabetes

An excess of bacteria in the gut can change the way the liver processes fat and could lead to the development of metabolic syndrome, according to health researchers.

Metabolic syndrome is a group of conditions including obesity, type 2 diabetes, high blood pressure, high blood sugar and excess body fat around the waist. People experiencing three or more of these conditions are considered to have metabolic syndrome and are vulnerable to liver and heart diseases. Approximately 20 to 25 percent of adult Americans have the syndrome, according to the American Heart Association.

Research supported by the National Institutes of Health has recommended that Americans add more fiber to their diets because higher fiber diets have been found to improve many aspects of health. However in a certain segment of the population, this advice could be doing more harm than good.

"It is a common misconception that plant-derived dietary fiber contains zero calories," said Matam Vijay-Kumar, assistant professor of nutritional sciences and medicine at Penn State.

While it's true that neither people nor mice can digest plant-derived fiber, their gut bacteria can readily ferment the fibers and then release them as energy-rich short-chain fatty acids, such as acetic acid.

Once they reach the liver, these compounds convert into lipids and add to fat deposits that could potentially lead to the development of metabolic syndrome, especially in people and mice lacking toll-like receptor 5 (TLR5).

TLR5 is a receptor for bacterial flagellin and is part of the innate immune system that maintains gut-bacteria homeostasis, keeping gut bacteria from over-proliferating.

Approximately 10 percent of the human population has a genetic mutation in TLR5, resulting in a complete lack of its function, according to Vijay-Kumar. These individuals have a weakened immune system that may increase the risk of developing metabolic syndrome.

"Our present study suggests that bacterial fermentation of dietary fiber and the production of short-chain fatty acids contribute to deposition of fat in the liver," said Vijay-Kumar, adding that it may be detrimental to the liver if these processes become dysregulated, especially in individuals with excess gut bacteria commonly associated with intestinal and liver disorders.

Short-chain fatty acids may be beneficial to the host's health, but could be unfavorable in certain contexts where dysregulated gut bacteria generate uncontrolled short-chain fatty acids for a prolonged period of time.

In the current study, published today (Oct. 29) in the journal Cell Metabolism, the researchers found a link between unchecked bacterial fermentation, short-chain fatty acids and increased liver lipids -- which can cause non-alcoholic fatty liver disease, leading to liver damage.

They also found that overconsumption of dietary fiber may have adverse consequences in mice with compromised TLR5 function and gut bacterial overgrowth.

"Most of the observations describing the beneficial effects of short-chain fatty acids in metabolic disorders are from short-term studies and primarily from healthy subjects and experimental animals," said Vishal Singh, postdoctoral fellow in nutritional sciences, Penn State.

"Our next goal is to analyze the long-term effects of short-chain fatty acids, specifically in experimental models of type 2 diabetes and/or metabolic syndrome. We envision that our studies would drive the field towards 'personalized' cautioned dietary intake of plant-derived fiber in immunocompromised individuals."

Vijay-Kumar is a member of the Huck Institutes of the Life Sciences and has a joint appointment in the department of medicine, College of Medicine and the department of nutritional sciences, College of Health and Human Development. Also collaborating on this research, along with V. Singh; were Beng San Yeoh, Xia Xiao, and Rachel Walker, graduate students; Manish Kumar, postdoctoral fellow; Kamil Borkowski, research assistant; and Gregory C. Shearer, associate professor, all in nutritional sciences, Penn State. In veterinary and biomedical sciences, Penn State were Limin Zhang, research associate, Jingwei Cai, graduate student and Andrew D. Patterson, associate professor and Kevin Harvatine, associate professor, animal science, Penn State.

Other researchers include Benoit Chassaing, assistant professor, Mark T. Baker, Ph.D. student and Andrew T. Gewirtz, all in the Institute for Biomedical Sciences, Georgia State University; Nagendra Singh, assistant professor, Georgia Regents University; James M. Ntambi, professor, biochemistry and nutritional sciences, University of Wisconsin - Madison; and Bina Joe, professor, physiological genomics, University of Toledo.

The National Institutes of Health supported this research.

http://www.eurekalert.org/pub_releases/2015-10/byu-scy102815.php

Study: Count your bites; count down the pounds

Pilot test subjects lose nearly four pounds over a month's time by reducing bites

Forget counting calories. The next new diet trend could be as simple as counting bites. A new study from BYU health science researchers found people who counted bites over a month's time lost roughly four pounds--just about what the CDC recommends for "healthy" weight loss.

Those in the pilot test counted the number of bites they took each day and then committed to taking 20 to 30 percent fewer bites over the next four weeks. Participants who stuck with the task saw results despite changing nothing else about their eating and exercising routine.

"This study confirms what we already knew: consuming less food makes a difference," said lead study author Josh West. "We're not advocating people starve themselves, what we're talking about is people eating less than they're currently eating."

West and BYU coauthors Ben Crookston and Cougar Hall say that as a matter of priority, people who are overweight need to be more focused on the quantitative aspects of food and less on the qualitative aspects.

Their experiment asked 61 participants to count the number of times they lifted food to their mouth and the number of gulps of liquids, other than water, each day. At the end of each day, the subjects texted or emailed their totals to researchers.

The 41 test subjects who finished the experiment produced encouraging results, Crookston said, but there is more research needed to validate this strategy for long-term success. "We felt pretty good about how much weight they lost given the relatively short span of the study," he said. "Now we need to follow up to see if they keep it off, or if they lose more weight."

Researchers said those who didn't finish the study had a hard time keeping up with counting bites. As a solution, researchers in BYU's Computer Science department have developed an algorithm that can do the counting for people.

That technology, created with the help of professor Christophe Giraud-Carrier, has now been licensed to local startup company SmartBites, whose team is refining it as an app for wearable devices such as Android Wear and WatchOS devices. Crookston and West believe counting bites is a doable, cost-effective option for the 70 percent of Americans who are overweight.

"We're consuming considerably more calories than we did a generation ago or two generations ago; at the same time we're much less active," Crookston said. "The good news is that you don't have to be extreme calorie cutting. Even a 20 percent reduction in bites makes a difference." The results from the pilot study appear in a recent issue of Advances in Obesity, Weight Management & Control.

http://www.eurekalert.org/pub_releases/2015-10/wtsi-ttf102715.php

Targeted therapy for gastric cancer possible

Genomic fingerprint can highlight which breast, ovarian, pancreatic and gastric cancers are likely to respond to treatment

Gastric cancer, otherwise known as stomach cancer, does not respond well to existing treatments and it is currently the third leading cause of cancer death in the world (after lung and liver cancer). Researchers have discovered that certain drugs, currently used to treat breast, ovarian and pancreatic cancers, could also be used to treat certain gastric cancers with a particular pattern of mutations (genomic molecular fingerprint).

Recent research has shown that a specific genomic molecular fingerprint, called signature 3, is associated with cells that have defective DNA repair mechanisms, for example due to faulty BRCA1 or BRCA2 genes which are linked with breast cancer. Cancer cells harbouring signature 3 have defects that stop them from efficiently repairing damage to their DNA. Due to their inability to repair DNA damage, these cells become vulnerable to platinum drugs and PARP inhibitor drugs, both of which attack DNA, causing it to break. Since the DNA damage cannot then be repaired, the cancer cell dies.

Signature 3 could therefore predict which cancers would be likely to respond to particular drug therapies. Initially found only in some breast, ovarian and pancreatic cancers, signature 3 may be present in other human cancers, and researchers in this latest study aimed to find out which other cancers harboured this clue to drug vulnerability.

"We analysed the cancer genomes of 10,250 patients, performing a large-scale computational screen across 36 different types of tumours, looking for the pattern of Signature 3 in each sample. Not only did we confirm the presence of signature 3 in a significant percentage of breast, ovarian, and pancreatic cancers, we also found this molecular fingerprint in approximately 10% of stomach cancers," said Dr Ludmil Alexandrov, corresponding author and Oppenheimer Fellow at Los Alamos National Laboratory in the USA. "This subset of stomach cancer is likely to have a defective DNA break-repair mechanism, and could therefore be susceptible to existing treatments such as platinum drugs or PARP inhibitor drugs."

In addition to discovering the pattern of signature 3 in gastric cancer, the study quantified its occurrence in other cancer types. It showed that 30% of ovarian, 27% of breast and 8% of pancreatic cancers exhibit this molecular fingerprint, a higher percentage than originally thought. Previous research using whole genome sequencing data showed that pancreatic cancers harbouring the signature 3 fingerprint responded very well to platinum therapy. This suggests that the

presence of signature 3 could be used as a biomarker to guide targeted therapy for not just some gastric cancers, but also for breast, ovarian and pancreatic cancers.

Previous research has shown the importance of two genes, BRCA1 and BRCA2 to breast and ovarian cancer and currently, clinicians target platinum therapy or PARP inhibitor drugs towards breast and ovarian cancer patients who have mutations in their BRCA1 and BRCA2 genes. However, this study shows that these two genes are only part of the story.

"While all the patients with BRCA1 and BRCA2 mutations show this signature 3 fingerprint, there are also many patients who have signature 3 but don't have mutations in BRCA1 and BRCA2. By focusing exclusively on those two genes, clinicians may be missing many cancer patients with the genomic signature 3 who could benefit from PARP inhibitor drugs or platinum therapy." Says Professor Suet Yi Leung, Chair of Gastrointestinal Cancer Genetics and Genomics from the University of Hong Kong "Even just for breast cancer, you could potentially double the population size that could be treated with this therapy."

PARP inhibitor drugs shut down a specific DNA repair enzyme, poly ADP ribose polymerase, and because they are more targeted, they cause far fewer side effects than platinum drugs. Olaparib (trade name Lynparza) is the latest PARP inhibitor drug to be licenced for use against ovarian cancer, but using Signature 3 as a marker, this and future PARP inhibitor drugs could be used to treat other cancer types such as gastric cancers. This would allow doctors to treat more patients, more effectively.

So far, this has only been shown in a laboratory setting using genomics. The next steps would be to clinically test these therapies to see if patients with cancers that have the signature 3 molecular fingerprint really do respond as hoped to these treatments.

It takes many years of research to launch a new drug as not only does any new treatment have to be effective, it also has to be proven to be safe in humans. However, PARP inhibitors are already available and safety tested, which could speed up the process of approving their use for other cancers.

"This is an extremely exciting finding which shows the importance of genomic sequencing for personalised healthcare in the future." says Professor Michael Stratton, corresponding author and Director of the Wellcome Trust Sanger Institute. "In years to come, routine genomic analysis of cancers could show which have the signature 3 fingerprint and inform and transform treatment of thousands of patients with these specific breast, ovarian, pancreatic and gastric cancers."

Notes to Editors

Publications details

Alexandrov LB et al., (2015) A mutational signature in gastric cancer suggests therapeutic strategies. Nature Communications 2015. DOI:10.1038/ncomms9683

Participating Centres

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http://www.eurekalert.org/pub_releases/2015-10/fhcr-ifp102615.php

Immunotherapy for pancreatic cancer boosts survival by more than 75 percent in mice

Human trials are planned within the next year

SEATTLE - A new study in mice by researchers at Fred Hutchinson Cancer Research Center has found that a specialized type of immunotherapy -- even when used without chemotherapy or radiation -- can boost survival from pancreatic cancer, a nearly almost-lethal disease, by more than 75 percent. The findings are so promising, human clinical trials are planned within the next year.

The study, led by Drs. Sunil Hingorani and Phil Greenberg, both members of the Clinical Research Division at Fred Hutch, tested the immunotherapy on mice genetically engineered to grow pancreatic tumors very similar to those of human pancreatic cancer. The mouse model, developed by Hingorani, already has led to a first-in-humans clinical trial that is showing early promise in some patients with advanced pancreatic cancer.

Pancreatic cancer is notoriously difficult to treat, said Hingorani, because it recruits the body's natural systems to construct both a tough physical barrier around tumors as well as an immune-cloaking device that keeps other, disease-fighting immune cells from recognizing the cancer.

Unlike any other cancer, pancreatic tumors are able to survive with a significantly decreased blood supply. As a consequence, chemotherapy, commonly administered via the bloodstream, has a difficult time getting inside. The tumors not only commonly grow quite large before patients will ever notice something is wrong, but they are very prone to metastasize, or spread to other sites in the body.

The investigators' new study, published Thursday in Cancer Cell, breaches pancreatic cancer's physical and immunological walls by using immunotherapy, a type of treatment that harnesses or refines the body's own immune system, to recognize and destroy cancer cells. The researchers devised a therapy using T cells, disease-fighting immune cells, that they engineered in the lab to recognize and attack pancreatic cancer.

T-cell therapy is showing promise as a treatment for several types of blood cancers, based on early results from Fred Hutch and other research centers, but aiming these cells at solid tumors like pancreatic cancer has historically proven more difficult, Hingorani said. Part of the challenge comes from the access to tumor cells -- or lack thereof. T-cell therapy is administered through the bloodstream, like chemo. It's easy enough to see why solid tumors may present more of a challenge to treat with this kind of immunotherapy than blood cancers such as leukemia and lymphoma.

The researchers didn't think the engineered T cells would stand a chance against pancreatic cancer on their own. But they needed somewhere to start, Greenberg said.

But to their surprise, the T cells -- engineered to recognize and kill cells bearing a protein called mesothelin, which is overproduced by virtually all pancreatic tumors -- got into the mice's tumors and started attacking them.

In the mouse model of the disease -- which is actually slightly more aggressive than the human version, Hingorani said -- animals that received T cells engineered to recognize a non-cancerous protein survived on average 54 days after their cancer became detectable. Those that received the mesothelin-directed cells lived an average of 96 days, a 78 percent bump.

Although the researchers weren't expecting to take this first version of the T-cell therapy to clinic, that's now their plan. Their team has already built the human version of the special T-cell protein that recognizes mesothelin. They're planning to launch a phase 1 clinical trial to test the therapy's safety in patients with advanced pancreatic cancer within the next year.

"As best we can tell, this would be a better therapy than anything that exists for pancreatic cancer right now," Greenberg said. "It's hard to be this optimistic without ever having treated a pancreatic cancer patient with this [therapy], but the biology of what we're doing looks so remarkably true and good."

The study was funded in part by the National Institutes of Health, the Giles W. and Elise G. Mead Foundation and Juno Therapeutics.

http://www.eurekalert.org/pub_releases/2015-10/uot-pne102915.php

Possible new explanation for ALS

University of Toronto researchers discover RNA-binding proteins play important role

University of Toronto (U of T) researchers are proposing a new way of understanding Amyotrophic Lateral Sclerosis (ALS), the devastating and incurable neurological disease. Their findings, published today in the journal Neuron, could be a major milestone on the path to a treatment for both ALS and dementia.

By delving into a previously overlooked corner of ALS research, Professor Peter St. George-Hyslop and his team discovered a new way in which the disease kills nerve cells.

"These are dreadful diseases -- the more we know about how they work, the faster we'll find treatments or even a cure," says St. George-Hyslop, Director of U of T's Tanz Centre for Research in Neurodegenerative Diseases.

Many cases of ALS are sparked by a toxic build-up of certain proteins, which cause neurons in the brain and spinal cord to die. Paralysis and suffocation result, meaning that few people live more than five years with an ALS diagnosis. Over the last decade, mutations that cause ALS have been found in a growing number of genes that encode RNA-binding proteins. The protein they create commonly builds up inside the diseased brain and spinal cords in ALS patients. Until now, scientists haven't thought this build-up was important to the disease process because it looked different from the types of protein accumulations -- such as tau, amyloid and alpha synuclein -- that are clearly toxic and always found in patients with Alzheimer's, Parkinson's and some forms of dementia.

Several years ago, St. George-Hyslop decided to take a closer look at these seemingly innocuous protein accumulations. Working with Tanz researcher Tetsuro Murakami and with colleagues at the University of Cambridge and Columbia University, they focused initially on the FUS protein, and discovered that these abnormal clumps could actually be a very important player in causing nerve cell damage and ALS.

The FUS protein normally plays a key role in the healthy functioning of neurons, which transmit nerve signals in the brain and spinal cord. However, FUS and other proteins in its RNA-binding class seem to operate differently from many other cellular proteins. St. George-Hyslop's team showed that FUS protein has the very unusual ability to morph from a liquid to a gel that resembles Jell-O. The gel form of FUS allows it to collect other cellular components that are necessary to make new proteins, and delivers them in a compact, concentrated form to the outer edges of the neurons. After reaching its destination, the gel melts into liquid, releasing the cellular components and allowing protein synthesis to occur. Its ability to repeatedly cycle between liquid and gel, allows FUS to rapidly and discreetly control protein synthesis in specific parts of the cell. This ability is key to keeping big cells like spinal cord neurons -- which can be more than a metre long -- in a healthy state.

The research team found that mutations in FUS changed the property of FUS protein so that it tends to form very dense gels that do not easily re-melt and release their cargo appropriately. As a result, it's unable to deliver the tools necessary for the neurons to stay healthy and do their job.

"This kills the nerve by throttling it and preventing it from making new protein in the parts of the cell that desperately need it," says St. George-Hyslop, who is also a Cambridge professor. "The mutations force the gelling process to go further than it should have gone."

The next step is for researchers to find ways to prevent the solidification of the gel, or to reverse the hardening process, offering a key to a future drug to treat ALS and frontotemporal dementia -- another disease in which the protein is active.

The discovery has implications for other, more common forms of ALS that have accumulations of other over-gelled RNA binding proteins.

http://bit.ly/1WoO7Dl

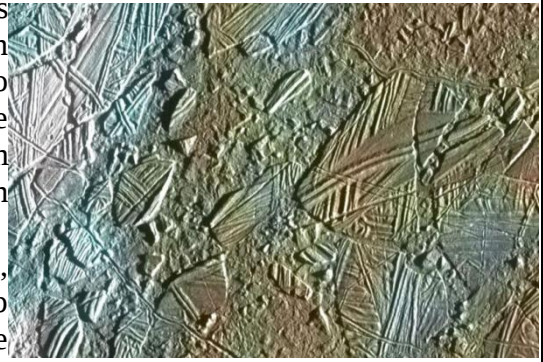
Salt flats on Europa mean moon's ocean may come to surface

Salt flats on Europa mean moon's ocean may come to surface

Forget drilling through the ice – Europa's buried ocean might come to us. In a cracked region of Jupiter's frozen moon (pictured below), salty ice has been spotted that doesn't match anything seen before.

Europa has been a perennial favourite in the search for alien life, thanks to its probable subsurface ocean. NASA plans to send a probe to the moon to study its surface in the 2020s, but what we are learning in the meantime is making it an even more attractive destination.

Infrared observations from the Galileo spacecraft, which visited the Jupiter system in the 1990s, found that the moon is covered in water ice. Sulphur and oxygen from volcanoes on the nearby moon Io also fall onto Europa's surface, where they combine to make magnesium sulphate – the same chemical found in Epsom salts.



Now a new analysis has found another, unidentified material that only shows up in fractured terrain. This could mean the buried ocean is breaching the surface.

Salt flats on Europa mean moon's ocean may come to surface **NASA/JPL/University of Arizona**

The spectrum of the material – its chemical signature – has so far defied identification. "It looks like the spectrum of water ice except that it's distorted," says Patrick Fischer of the California Institute of Technology. The team hasn't been able to reproduce it using a library of known chemicals – although they can rule out sulphates, which Europa researchers expected to see.

One possibility is an unknown blend of potassium or sodium chloride, which would mean these regions are salt flats left behind when ocean water burbled up and then evaporated, giving us a look at the chemistry hidden within. "We can guess that the spectrum we're seeing is probably evaporate deposits of salt left over from the ocean," Fischer says.

If that's true, there are big implications for Europa's habitability. If the ocean is seasoned with those chloride salts instead of the sulphate salts expected, its overall salinity could be three times lower than thought, making it friendlier to life. "Any information on the salt content of the oceans helps us understand what biology might be possible," says Christopher Chyba of Princeton University.

Life-friendly

"Microbial life on Earth can live in high salt concentrations, but it comes at a cost," he says. "These new observational results make Europa look slightly better from the point of view of the origin of life on Europa and, should life actually exist there, slightly less challenging for microbes to live in the ocean."

And if ocean chemistry is laid bare on the surface, we could see if any of the chemicals that fuel chemosynthetic ecosystems on Earth are present – improving the chances of finding ocean life.

Long before NASA's mission arrives, we should know more. Fischer's team is busy writing proposals to get better spectral data from Europa that will classify the mystery material. At the same time, researchers at the nearby Jet Propulsion Lab are trying to manufacture an ice with a similar spectrum in the lab.

But these faint hints underscore the need to take a close look at Europa, says Chyba. "I admire the wonderful work that the Caltech/JPL group has done," he says. "But their paper is also a reminder of how badly we need a dedicated mission to Europa."

Journal reference: Astronomical Journal, in press

http://nyti.ms/1KPPXB6

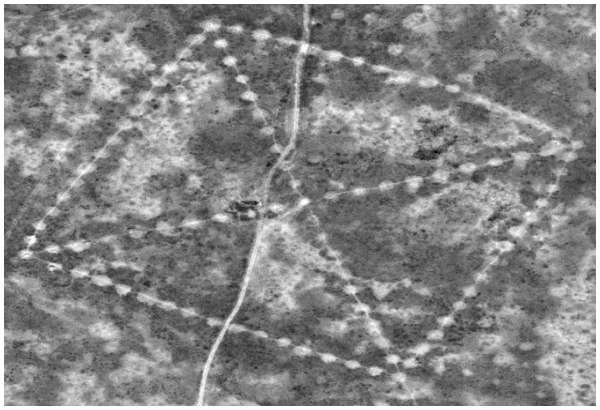
NASA Adds to Evidence of Mysterious Ancient Earthworks

High in the skies over Kazakhstan, space-age technology has revealed an ancient mystery on the ground.

By RALPH BLUMENTHAL OCT. 30, 2015

Satellite pictures of a remote and treeless northern steppe reveal colossal earthworks — geometric figures of squares, crosses, lines and rings the size of several football fields, recognizable only from the air and the oldest estimated at 8,000 years old. The largest, near a Neolithic settlement, is a giant square of 101 raised mounds, its opposite corners connected by a diagonal cross, covering more terrain than the Great Pyramid of Cheops. Another is a kind of three-limbed swastika, its arms ending in zigzags bent counterclockwise.

Described last year at an archaeology conference in Istanbul as unique and previously unstudied, the earthworks, in the Turgai region of northern Kazakhstan, number at least 260 — mounds, trenches and ramparts — arrayed in five basic shapes.

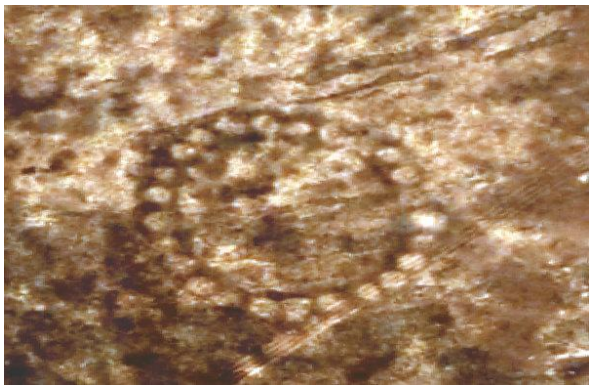


Spotted on Google Earth in 2007 by a Kazakh economist and archaeology enthusiast, Dmitriy Dey, the so-called Steppe Geoglyphs remain deeply puzzling and largely unknown to the outside world.

One of the enormous earthwork configurations photographed from space is known as the Ushtogaysky Square, named after the nearest village in Kazakhstan. Credit DigitalGlobe, via NASA

Two weeks ago, in the biggest sign so far of official interest in investigating the sites, NASA released clear satellite photographs of some of the figures from about 430 miles up.

"I've never seen anything like this; I found it remarkable," said Compton J. Tucker, a senior biospheric scientist for NASA in Washington who provided the archived images, taken by the satellite contractor DigitalGlobe, to Mr. Dey and The New York Times.

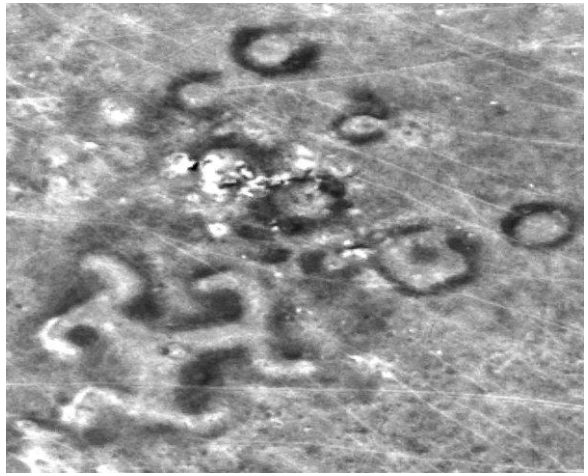


Ronald E. LaPorte, a University of Pittsburgh scientist who helped publicize the finds, called NASA's involvement "hugely important" in mobilizing support for further research.

The Bestamskoe Ring is among the so-called Steppe Geoglyphs in Kazakhstan — at least 260 earthwork shapes made up of mounds, trenches and ramparts, the oldest estimated at 8,000 years old, recognizable only from the air. **DigitalGlobe, via NASA**

This week, NASA put space photography of the region on a task list for astronauts in the International Space Station. "It may take some time for the crew to take imagery of your site since we are under the mercy of sun elevation angles, weather constraints and crew schedule," Melissa Higgins of Mission Operations emailed Dr. LaPorte.

The archived images from NASA add to the extensive research that Mr. Dey compiled this year in a PowerPoint lecture translated from Russian to English. "I don't think they were meant to be seen from the air," Mr. Dey, 44, said in an interview from his hometown, Kostanay, dismissing outlandish speculations involving aliens and Nazis. (Long before Hitler, the swastika was an ancient and near-universal design element.) He theorizes that the figures built along straight lines on elevations were "horizontal observatories to track the movements of the rising sun."



Kazakhstan, a vast, oil-rich former Soviet republic that shares a border with China, has moved slowly to investigate and protect the finds, scientists say, generating few news reports.

"I was worried this was a hoax," said Dr. LaPorte, an emeritus professor of epidemiology at Pittsburgh who noticed a report on the finds last year while researching diseases in Kazakhstan.

The earthworks, including the Turgai Swastika, were spotted on Google Earth in 2007 by Dmitriy Dey, a Kazakh archaeology enthusiast. **DigitalGlobe, via NASA**

With the help of James Jubilee, a former American arms control officer and now a senior science and technology coordinator for health issues in Kazakhstan, Dr. LaPorte tracked down Mr. Dey through the State Department, and his images and documentation quickly convinced them of the earthworks' authenticity and importance. They sought photos from KazCosmos, the country's space agency, and pressed local authorities to seek urgent Unesco protection for the sites — so far without luck.

In the Cretaceous Period 100 million years ago, Turgai was bisected by a strait from what is now the Mediterranean to the Arctic Ocean. The rich lands of the steppe were a destination for Stone Age tribes seeking hunting grounds, and Mr. Dey's research suggests that the Mahandzhar culture, which flourished there from 7,000 B.C. to 5,000 B.C., could be linked to the older figures. But scientists marvel that a nomadic population would have stayed in place for the time required to fell and lay timber for ramparts, and to dig out lake bed sediments to construct

the huge mounds, originally 6 to 10 feet high and now 3 feet high and nearly 40 feet across.

Persis B. Clarkson, an archaeologist at the University of Winnipeg who viewed some of Mr. Dey's images, said these figures and similar ones in Peru and Chile were changing views about early nomads.

"The idea that foragers could amass the numbers of people necessary to undertake large-scale projects — like creating the Kazakhstan geoglyphs — has caused archaeologists to deeply rethink the nature and timing of sophisticated large-scale human organization as one that predates settled and civilized societies," Dr. Clarkson wrote in an email.

"Enormous efforts" went into the structures, agreed Giedre Motuzaite Matuzeviciute, an archaeologist from Cambridge University and a lecturer at Vilnius University in Lithuania, who visited two of the sites last year.

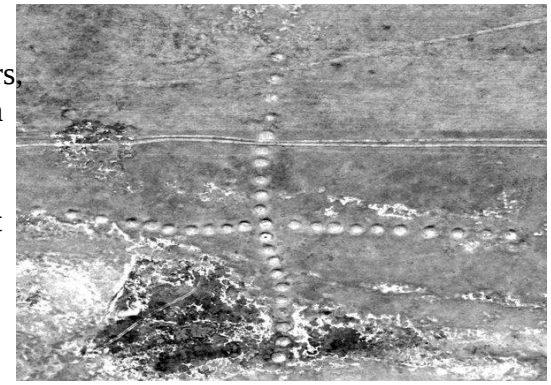
She said by email that she was dubious about calling the structures geoglyphs — a term applied to the enigmatic Nazca Lines in Peru that depict animals and plants — because geoglyphs "define art rather than objects with function."

Dr. Matuzeviciute and two archaeologists from Kostanay University, Andrey Logvin and Irina Shevnina, discussed the figures at a meeting of European archaeologists in Istanbul last year.

With no genetic material to analyze — neither of the two mounds that have been dug into is a burial site — Dr. Matuzeviciute said she used optically stimulated luminescence, a method of measuring doses from ionizing radiation, to analyze the construction material, and came up with a date from one of the mounds of around 800 B.C.

Other preliminary studies push the earliest date back more than 8,000 years, which could make them the oldest such creations ever found. Other materials yield dates in the Middle Ages.

Mr. Dey said some of the figures might have been solar observatories akin, according to some theories, to Stonehenge in England and the Chankillo towers in Peru.



Researchers are hoping to marshal support for investigating the earthen mounds that make up figures like this one, the Big Ashutastinsky Cross. **DigitalGlobe, via NASA**

"Everything is linked through the cult of the sun," said Mr. Dey, who spoke in Russian via Skype through an interpreter, Shalkar Adambekov, a doctoral student at the University of Pittsburgh.

The discovery was happenstance.

In March 2007, Mr. Dey was at home watching a program, "Pyramids, Mummies and Tombs," on the Discovery Channel. "There are pyramids all over the earth," he recalled thinking. "In Kazakhstan, there should be pyramids, too."

Soon, he was searching Google Earth images of Kostanay and environs.

There were no pyramids. But, he said, about 200 miles to the south he saw something as intriguing — a giant square, more than 900 feet on each side, made up of dots, crisscrossed by a dotted X.

At first Mr. Dey thought it might be a leftover Soviet installation, perhaps one of Nikita S. Khrushchev's experiments to cultivate virgin land for bread production.

But the next day, Mr. Dey saw a second gigantic figure, the three-legged, swastikalike form with curlicue tips, about 300 feet in diameter.

Before the year was out, Mr. Dey had found eight more squares, circles and crosses.

By 2012, there were 19. Now his log lists 260, including some odd mounds with two drooping lines called "whiskers" or "mustaches."

Before setting out to look for the figures on the ground, Mr. Dey asked Kazakh archaeologists whether they knew of such things. The answer was no.

In August 2007, he led Dr. Logvin and others to the largest figure, now called the Ushtogaysky Square, named after the nearest village.

"It was very, very hard to understand from the ground," he recalled. "The lines are going to the horizon. You can't figure out what the figure is."

When they dug into one of the mounds, they found nothing. "It was not a cenotaph, where there are belongings," he said. But nearby they found artifacts of a Neolithic settlement 6,000 to 10,000 years old, including spear points.

Now, Mr. Dey said, "the plan is to construct a base for operations."

"We cannot dig up all the mounds. That would be counterproductive," he said. "We need modern technologies, like they have in the West."

Dr. LaPorte said he, Mr. Dey and their colleagues were also looking into using drones, as the Culture Ministry in Peru has been doing to map and protect ancient sites.

But time is an enemy, Mr. Dey said. One figure, called the Koga Cross, was substantially destroyed by road builders this year. And that, he said, "was after we notified officials."

http://www.eurekalert.org/pub_releases/2015-10/rb-wmu103015.php

Working memory: Underlying processes are more complex than we thought

Rhythmic brain activity in hippocampus is the key

In order to retain a piece of information for a short time, working memory is required. The underlying processes are considerably more complex than hitherto assumed, as researchers from the Ruhr-Universität Bochum and Bonn University report in the journal "Cell Reports". Two brain states must alternate rhythmically in order for a piece of information to be successfully maintained.

Working memory: maintaining new information for a short time

When we want to remember a new piece of information for a short time, for example a phone number, working memory is called upon. Different brain regions are involved in this process, including the hippocampus, which is known for its crucial role in long-term memory.

The team headed by Prof Dr Nikolai Axmacher from the Institute of Cognitive Neuroscience in Bochum and Marcin Leszczynski, researcher in Bochum and at the Department of Epileptology at Bonn University, studied rhythmic activity patterns in the hippocampus while the subjects memorised sequences of numbers or faces.

Two activity states at semi-second intervals

To this end, the team worked with epilepsy patients who had electrodes implanted into the hippocampus for the purpose of surgical planning. Those electrodes enabled the researchers to measure the activity of the region embedded deeply in the brain.

While the patients memorised sequences of faces or numbers, the researchers observed two activity states in the hippocampus, which alternated twice per second: an excited and a less excited state.

Seemingly simple tasks require highly complex processes

If the rhythmic pattern did not occur in the hippocampus, the patients tended to make mistakes during the task. Based on the activity patterns, the researchers were also able to estimate how many numbers or faces the test subjects could reliably memorise.

"The results show that the brain performs highly complex processes even during seemingly simple tasks," says Prof Nikolai Axmacher. "Our subjective feeling if something is simple or complex is not a reliable marker for how the brain actually solves a task."

M. Leszczynski, J. Fell, N. Axmacher (2015): Rhythmic working memory activation in the human hippocampus, Cell Reports, DOI: 10.1016/j.celrep.2015.09.081

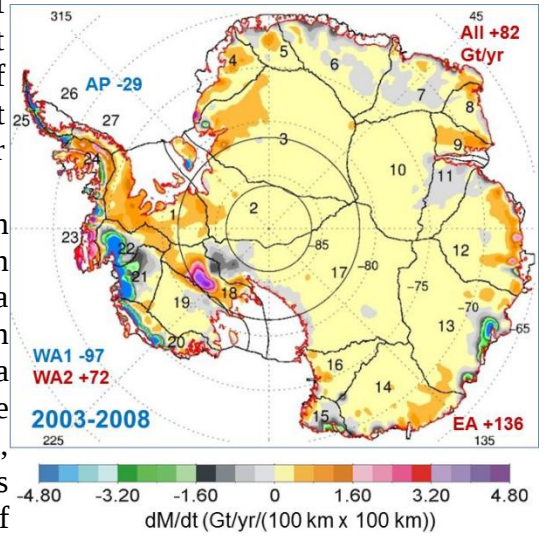
http://www.eurekalert.org/pub_releases/2015-10/nsfc-nsm103015.php

NASA study: Mass gains of Antarctic Ice Sheet greater than losses

A new NASA study says that an increase in Antarctic snow accumulation that began 10,000 years ago is currently adding enough ice to the continent to outweigh the increased losses from its thinning glaciers.

The research challenges the conclusions of other studies, including the Intergovernmental Panel on Climate Change's (IPCC) 2013 report, which says that Antarctica is overall losing land ice.

According to the new analysis of satellite data, the Antarctic ice sheet showed a net gain of 112 billion tons of ice a year from 1992 to 2001. That net gain slowed to 82 billion tons of ice per year between 2003 and 2008.



"We're essentially in agreement with other studies that show an increase in ice discharge in the Antarctic Peninsula and the Thwaites and Pine Island region of West Antarctica," said Jay Zwally, a glaciologist with NASA Goddard Space Flight Center in Greenbelt, Maryland, and lead author of the study, which was published on Oct. 30 in the Journal of Glaciology.

This map shows the rates of mass changes from ICESat 2003-2008 over Antarctica. Sums are for all of Antarctica: East Antarctica (EA, 2-17); interior West Antarctica (WA2, 1, 18, 19, and 23); coastal West Antarctica (WA1, 20-21); and the Antarctic Peninsula (24-27). A gigaton (Gt) corresponds to a billion metric tons, or 1.1 billion U.S. tons. **Credits: Jay Zwally/ Journal of Glaciology**

"Our main disagreement is for East Antarctica and the interior of West Antarctica - there, we see an ice gain that exceeds the losses in the other areas." Zwally added that his team "measured small height changes over large areas, as well as the large changes observed over smaller areas."

Scientists calculate how much the ice sheet is growing or shrinking from the changes in surface height that are measured by the satellite altimeters. In locations where the amount of new snowfall accumulating on an ice sheet is not equal to the ice flow downward and outward to the ocean, the surface height changes and the ice-sheet mass grows or shrinks.

But it might only take a few decades for Antarctica's growth to reverse, according to Zwally. "If the losses of the Antarctic Peninsula and parts of West Antarctica continue to increase at the same rate they've been increasing for the last two decades, the losses will catch up with the long-term gain in East Antarctica in 20 or 30 years -- I don't think there will be enough snowfall increase to offset these losses."

The study analyzed changes in the surface height of the Antarctic ice sheet measured by radar altimeters on two European Space Agency European Remote Sensing (ERS) satellites, spanning from 1992 to 2001, and by the laser altimeter on NASA's Ice, Cloud, and land Elevation Satellite (ICESat) from 2003 to 2008.

Zwally said that while other scientists have assumed that the gains in elevation seen in East Antarctica are due to recent increases in snow accumulation, his team used meteorological data beginning in 1979 to show that the snowfall in East Antarctica actually decreased by 11 billion tons per year during both the ERS and ICESat periods. They also used information on snow accumulation for tens of thousands of years, derived by other scientists from ice cores, to conclude that East Antarctica has been thickening for a very long time.

"At the end of the last Ice Age, the air became warmer and carried more moisture across the continent, doubling the amount of snow dropped on the ice sheet," Zwally said.

The extra snowfall that began 10,000 years ago has been slowly accumulating on the ice sheet and compacting into solid ice over millennia, thickening the ice in East Antarctica and the interior of West Antarctica by an average of 0.7 inches (1.7 centimeters) per year. This small thickening, sustained over thousands of years and spread over the vast expanse of these sectors of Antarctica, corresponds to a very large gain of ice - enough to outweigh the losses from fast-flowing glaciers in other parts of the continent and reduce global sea level rise.

Zwally's team calculated that the mass gain from the thickening of East Antarctica remained steady from 1992 to 2008 at 200 billion tons per year, while the ice losses from the coastal regions of West Antarctica and the Antarctic Peninsula increased by 65 billion tons per year.

"The good news is that Antarctica is not currently contributing to sea level rise, but is taking 0.23 millimeters per year away," Zwally said. "But this is also bad news. If the 0.27 millimeters per year of sea level rise attributed to Antarctica in the IPCC report is not really coming from Antarctica, there must be some other contribution to sea level rise that is not accounted for."

"The new study highlights the difficulties of measuring the small changes in ice height happening in East Antarctica," said Ben Smith, a glaciologist with the University of Washington in Seattle who was not involved in Zwally's study.

"Doing altimetry accurately for very large areas is extraordinarily difficult, and there are measurements of snow accumulation that need to be done independently to understand what's happening in these places," Smith said.

To help accurately measure changes in Antarctica, NASA is developing the successor to the ICESat mission, ICESat-2, which is scheduled to launch in 2018. "ICESat-2 will measure changes in the ice sheet within the thickness of a No. 2 pencil," said Tom Neumann, a glaciologist at Goddard and deputy project scientist for ICESat-2. "It will contribute to solving the problem of Antarctica's mass balance by providing a long-term record of elevation changes."

http://www.eurekalert.org/pub_releases/2015-10/asfm-ntc102915.php

New technique could prevent biofilms on catheters and medical implants

Coating implants with tPA can prevent Staphylococcus aureus from forming biofilms

Washington, DC - Biofilms--mats of bacteria similar to the plaque that grows on teeth--frequently coat the surfaces of catheters, and of various medical implants and prostheses, where they can threaten lives or lead to failure of the implants. Antibiotics are impotent against biofilms. Now Jakub Kwiecinski, PhD, Tao Jin, MD, PhD, and collaborators show that coating implants with "tissue plasminogen activator" can prevent Staphylococcus aureus, the leading cause of hospital-acquired infections, from forming biofilms. The research is published 30 October in Applied and Environmental Microbiology, a journal of the American Society for Microbiology.

A growing biofilm requires anchoring, and in earlier research, this team, led by Jin, an Associate Professor of Rheumatology and Inflammation Research, the University of Gothenburg, Gothenburg, Sweden, had discovered that S. aureus hijacks the human clotting system to create a scaffold of micro-clots to support the growing biofilm. "We hypothesized that if we forced the human body to start dissolving those clots, we could prevent the biofilm from developing," said Kwiecinski, a post-doctoral researcher in Jin's laboratory.

To encouraging the clot-busting, the investigators coated the surfaces with tissue plasminogen activator (tPA), which activates the clot-dissolving protein, plasminogen. "This deprives S. aureus of a scaffold for biofilm formation and prevents infection," said Kwiecinski. After performing the research under laboratory conditions, they confirmed that it works by coating catheters that they then implanted into laboratory mice.

A key to the team's success was their decision to look beyond the bacteria, the stopping place for most previous research, to the human body's involvement in the

infections, said Kwiecinski. The clot-busting, he said, could be applied to biofilms of pathogens other than S. aureus.

Biofilm-related infections afflict around 1.7 million in the US alone, killing nearly 100,000 annually, according to the Center for Disease Control and Prevention. "With increasing numbers of prosthetic devices used in modern medicine, this number is only going to increase," said Kwiecinski. Thus, the research could lead to a major reduction in hospital-acquired disease and death.

http://www.eurekalert.org/pub_releases/2015-10/uoc--ncs103015.php

New computational strategy finds brain tumor-shrinking molecules

Computer modeling identifies first-ever molecule to inhibit a transient cellular event that drives glioblastoma, and the molecule shrinks glioblastoma in mice

Patients with glioblastoma, a type of malignant brain tumor, usually survive fewer than 15 months following diagnosis.

Since there are no effective treatments for the deadly disease, University of California, San Diego researchers developed a new computational strategy to search for molecules that could be developed into glioblastoma drugs.

In mouse models of human glioblastoma, one molecule they found shrank the average tumor size by half. The study is published October 30 by Oncotarget.

The newly discovered molecule works against glioblastoma by wedging itself in the temporary interface between two proteins whose binding is essential for the tumor's survival and growth.

This study is the first to demonstrate successful inhibition of this type of protein, known as a transcription factor.

"Most drugs target stable pockets within proteins, so when we started out, people thought it would be impossible to inhibit the transient interface between two transcription factors," said first author Igor Tsigelny, PhD, research scientist at UC San Diego Moores Cancer Center, as well as the San Diego Supercomputer Center and Department of Neurosciences at UC San Diego. "But we addressed this challenge and created a new strategy for drug design -- one that we expect many other researchers will immediately begin implementing in the development of drugs that target similar proteins, for the treatment of a variety of diseases."

Transcription factors control which genes are turned "on" or "off" at any given time. For most people, transcription factors labor ceaselessly in a highly orchestrated system.

In glioblastoma, one misfiring transcription factor called OLIG2 keeps cell growth and survival genes "on" when they shouldn't be, leading to quick-growing tumors.

In order to work, transcription factors must buddy up, with two binding to each other and to DNA at same time.

If any of these associations are disrupted, the transcription factor is inhibited.

In this study, Tsigelny and team aimed to disrupt the OLIG2 buddy system as a potential treatment for glioblastoma.

Based on the known structure of related transcription factors, study co-author Valentina Kouznetsova, PhD, associate project scientist at UC San Diego, developed a computational strategy to search databases of 3D molecular structures for those small molecules that might engage the hotspot between two OLIG2 transcription factors.

The team used the Molecular Operation Environment (MOE) program produced by the Chemical Computing Group in Montreal, Canada and high-performance workstations at the San Diego Supercomputer Center to run the search.

With this approach, the researchers identified a few molecules that would likely fit the OLIG2 interaction.

They then tested the molecules for their ability to kill glioblastoma tumors in the Moores Cancer Center lab of the study's senior author, Santosh Kesari, MD, PhD.

The most effective of these candidate drug molecules, called SKOG102, shrank human glioblastoma tumors grown in mouse models by an average of 50 percent.

"While the initial pre-clinical findings are promising," Kesari cautioned, "it will be several years before a potential glioblastoma therapy can be tested in humans. SKOG102 must first undergo detailed pharmacodynamic, biophysical and mechanistic studies in order to better understand its efficacy and possible toxicity."

To this end, SKOG102 has been licensed to Curtana Pharmaceuticals, which is currently developing the inhibitor for clinical applications.

Kesari is a co-founder, has an equity interest in and is chair of the scientific advisory board for Curtana Pharmaceuticals.

Co-authors Rajesh Mukthavaram, PhD, and Wolfgang Wrasidlo, PhD, also own stock in Curtana Pharmaceuticals.

Additional co-authors of this study include Ying Chao, Ivan Babic, Sandra Pastorino, Pengfei Jiang, Miriam Scadeng, Sandeep C. Pingle, Milan T. Makale, UC San Diego; Elmar Nurmemmedov, The Scripps Research Institute; David Calligaris, Nathalie Agar, Harvard Medical School and Brigham and Women's Hospital.

This research was funded, in part, by the National Institutes of Health (grant 3P30CA023100-25S8), Voices Against Brain Cancer Foundation, Christopher and Bronwen Gleeson Family Trust and American Brain Tumor Association Drug Discovery Grant.

Full study: http://doi.org/10.18632/oncotarget.5633

http://nyti.ms/1RnXDQx

Bubonic Plague Found in Oregon Teenager

The authorities in Oregon have confirmed a case of the bubonic plague in a teenage girl who was believed to have contracted the disease from a flea bite.

By CHRISTINE HAUSER OCT. 30, 2015

Plague is rare and treatable with antibiotics if caught early, but federal authorities have been puzzled by an increase in cases this year.

In a statement, state and local health officials in Oregon said they thought the girl was infected during a hunting trip on Oct. 16 near Heppner, a city located at the foothills of the Blue Mountains in the northeastern region of the state. She fell ill on Oct. 21 and was hospitalized days later. She is now in the intensive care unit.

There have been no other reported recent cases, the statement said.

Plague is an infectious bacterial disease that is carried by wild rodents and transmitted to their fleas, who then carry the infection to other animals or humans through bites. Symptoms include fever, chills, headache, weakness and a cough.

Bubonic plague affects the lymph nodes. Two other types of plague are septicemic, a blood infection, and the most contagious form, pneumonic, which infects the lungs. It is not transmitted from human to human unless the patient also has a lung infection and is coughing. Antibiotics can beat all forms of plague if an infection is caught early. Untreated, it is fatal in 66 percent to 93 percent of cases. With treatment, mortality has been reduced to about 16 percent, according to the Centers for Disease Control and Prevention.

In recent decades, an average of seven human plague cases have been reported each year, according to the disease centers. Since April 1, there have been at least 11 cases in the United States of plague in humans, three of them fatal, affecting residents of Arizona, California, Colorado, Georgia, New Mexico, and Oregon, the C.D.C. said in August. "It is unclear why the number of cases in 2015 is higher than usual," a statement from the disease centers said.

Two of the reported cases were linked to Yosemite National Park.

The statement from Oregon's health authorities said only eight human cases had been diagnosed in the state since 1995, and no deaths have been reported.

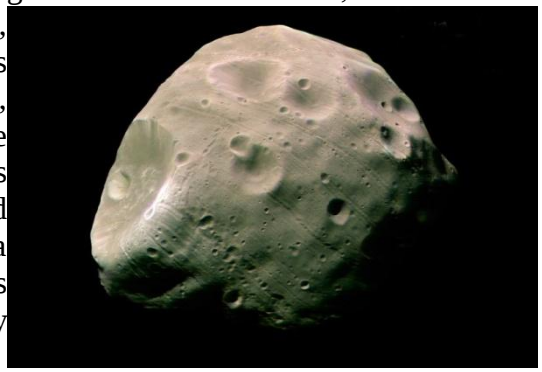
http://bit.ly/1PfI91R

Mars is ripping its beanbag moon Phobos apart

Phobos is falling apart. A set of enigmatic grooves on the surface of Mars's larger moon suggests that the gravity of its parent planet is slowly tearing it to shreds.

We already knew that Phobos was doomed to destruction. It is so close to Mars that the planet's tidal pull drags on the satellite, slowing it down and shrinking its orbit. In tens of millions of years, those forces are expected to rip Phobos apart before it can crash into Mars.

But Phobos now seems to be showing signs of wear. In the 1970s, the Mariner 9 and Viking orbiters uncovered long, often parallel grooves 100 to 200 metres wide and 10 to 30 metres long, stretching across parts of Phobos. At the time, researchers assumed that Phobos was a homogeneous lump of rock, and thought the grooves were cracks from a giant impact, or rows of small craters formed by debris blasted into space by impacts on the Martian surface.



SA/DLR/FU Berlin, CC BY-SA IGO 3.0

But in 2008, the Mars Express spacecraft showed that Phobos is actually a pile of rubble held together by a stronger outer layer of dust 50 to 100 metres thick. That means Phobos looks a bit like a beanbag: easily deformed, but held together by a covering.

Using that model, Terry Hurford of the NASA Goddard Space Flight Center in Maryland and colleagues calculated what stress tidal forces would cause on Phobos – and found that most grooves are perfectly aligned with the regions of greatest stress.

"The grooves are the first sign of tearing it apart," Hurford says. He will present the results on 4 November at a meeting of the Geological Society of America. "I find the results very interesting," says Alexander Basilevsky of the Vernadsky Institute of Geochemistry and Analytical Chemistry in Moscow, who has written a review of the surface features of Phobos. He agrees that the grooves could be faults, and thinks this could explain why some of them appear to criss-cross each other.

The moon is in no immediate danger, Hurford says – it could still survive for millions of years. "We have not looked how far we can go before it completely fails," he says, and no one knows the strength of the beanbag's shell or how well it can hold Phobos together. Finding out may mean landing there – gingerly.

http://nyti.ms/1NLRfSm

Book Review: 'Ending Medical Reversal' Laments Flip-Flopping

"Ending Medical Reversal" is a subtly subversive book in need of a considerably snappier title. "OOPS!" perhaps, or "Are You Kidding Me?"

By ABIGAIL ZUGER, M.D.

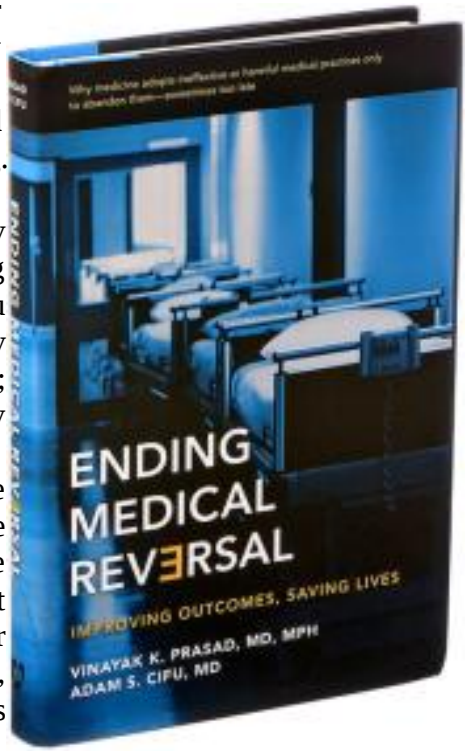
This last was the reaction of a diabetic patient described by the authors who, after years spent dutifully following the most spartan of diets in order to keep his blood sugar in check, just learned he needn't have bothered. The goal his doctor (and

doctors everywhere) were routinely setting for their patients had just been proven by a new study to be far too stringent.

All that broiled fish, all those unbuttered green beans, all that willpower, all for nothing. Oops. (Read an excerpt.)

This kind of medical whiplash is increasingly common and every bit as scary and damaging as the physical kind. What was good for you yesterday is useless or even bad for you today (and may be good for you again tomorrow; who knows). Medical gospel is rewritten daily on the evening news.

The incremental progress of ordinary science is one thing, as individual treatments are progressively replaced by better variants. We all happily accept that kind of revision. But medical reversal, the authors' sober term for sudden flip-flops in standards of care, unnerves and demoralizes everyone, doctors no less than their patients.



Credit Alessandra Montalto/The New York Times

Dr. Vinayak K. Prasad and Dr. Adam S. Cifu, of Oregon Health & Science University and the University of Chicago, have set themselves the task of figuring out how often modern medicine reverses itself, analyzing why it happens, and suggesting ways to make it stop. If this short list of objectives explodes into a breathless and somewhat unwieldy critique of all of Western medicine, you still have to appreciate both their ambition and their argument.

An old saw has long held that 50 percent of everything a student learns in medical school is wrong. Actual calculations suggest that number is not too far off base — Dr. Prasad and Dr. Cifu extrapolate from past reversals to conclude that about 40 percent of what we consider state-of-the-art health care is likely to turn out to be unhelpful or actually harmful.

Recent official flip-flops include habits of treating everything from lead poisoning to blood clots, from kidney stones to heart attacks. One reversal concerned an extremely common orthopedic procedure, the surgical repair of the meniscus in the knee, which turns out to be no more effective than physical therapy alone. The interested reader can plow through almost 150 disproved treatments in the book's appendix.

Some of the glitches that allowed these flawed approaches to enter and persist in medical practice will be familiar. Adequate scientific study is often prohibitively complicated and expensive, forcing us to rely on less definitive work. Financial interests tend to distort scientific results.

More surprising, though, is an odd paradox: Often it is the treatments that make the most theoretical sense that fail.

The single thing that all the abandoned drugs and treatments on the authors' list have in common is that they are all reasonable, logical and scientifically appealing. Every one of them should work.

The authors write that we know enough about human physiology — all the little molecules scooting around in our bodies at the behest of those dictators, our genes — that we are now able to come up with elaborate, well-defended notions of how to help them all along. But "the human body is so complicated, and our understanding of it so superficial, that what we believe should work often does not."

What could make more sense, after all, than finding some cancers early, fixing a piece of torn cartilage, closing a hole in the heart, and propping open blood vessels that have become perilously narrow? And yet not one of these helpful interventions has been shown to make a difference in the health or survival of patients who obediently line up to have them done.

As Dr. Prasad and Dr. Cifu point out, it all forces a careful, critical look at the scientific paradigm that rules medicine these days.

Basic science still lays the foundation for medical training in most schools. Long before students meet actual patients, they learn the minutiae of the theory behind the practice. In fact, that part of their training is generally far more rigorous and methodical than training in patient care, which can be remarkably slipshod.

"Often the study of the study of how therapies should work is much more extensive and comes before the study of whether therapies do work," the authors write. Thus a medical culture based on "should work" rather than "does work" is condemned to constantly correct itself when the science is finally evaluated for outcomes that matter.

To fix this constant backtracking would require nothing less than a revolution in how doctors are trained, with an emphasis on the proven and practical rather than the theoretical. (It would also require a second revolution in how doctors practice, with less prestige and remuneration for coming up with new ideas and more for validating old ones.)

Until the revolution comes, how can the average patient avoid becoming a victim of medical whiplash? It's not easy, particularly since common sense often won't help distinguish good treatment from bad.

Dr. Prasad and Dr. Cifu offer a five-step plan, including pointers for determining if a given treatment is really able to do what you want it to do, and advice on finding a like-minded doctor who won't object to a certain amount of back-seat driving. Of course, there are no guarantees that their tips will endure forever, but they probably have a longer shelf life than most medical advice.

http://www.eurekalert.org/pub_releases/2015-11/aaoo-ot102815.php

'Water on the knee' could be early sign of Lyme disease

Spontaneous knee effusion, also known as "water on the knee," can be a primary symptom of Lyme disease, even when patients do not exhibit a "bull's eye" rash, another common Lyme disease symptom

ROSEMONT, Ill.-. According to a literature review appearing in the November issue of The Journal of the American Academy of Orthopaedic Surgeons (JAAOS), early diagnosis and antibiotic treatment can prevent the development of Lyme disease's more severe symptoms.

Lyme borreliosis, or Lyme disease--the most common vector-borne illness transmitted by insects--is prevalent in the Northeast and upper Midwest regions of the United States. Over 30,000 cases are reported to the Centers for Disease Control and Prevention (CDC) each year and likely over 300,000 new cases occur but go unreported.

"It is important to catch and treat Lyme disease early because the symptoms get progressively worse over time," said Elizabeth Matzkin, MD, lead study author and assistant professor of orthopaedic surgery at Harvard Medical School. "However, the lab tests used to diagnose Lyme disease can take time to process, and there are certain circumstances in which immediate antibiotic treatment may be recommended before the lab results are complete." If symptoms have been present for less than two weeks, the Lyme test may need to be repeated as the test can remain negative the first two weeks of an infection.

The current standard of care for the diagnosis of Lyme disease is a two-tier blood test. Antibiotic treatments are successful in 99 percent of patients who are diagnosed early and in 90 percent of patients who are diagnosed later. If left untreated, 60 percent of patients eventually develop Lyme arthritis, with the most severe cases having higher risks of permanent joint damage.

"Half of patients do not recall a tick bite or observe a rash, and early symptoms are not always detected when a physician diagnoses a knee effusion," said Dr. Matzkin. "One of the most notable differentiating factors is, while septic or arthritic knees usually come with significant pain, knee effusions caused by Lyme disease are often very large, not activity-related, and mostly pain-free."

Early symptoms of Lyme disease, which include fatigue, chills, fever, headache, muscle and joint aches, and swollen lymph nodes, occur three to 30 days after exposure and are not always present.

In areas where Lyme disease is common, physicians should always consider whether a spontaneous knee effusion might be caused by the disease and test accordingly. In areas of low prevalence, the clinician should ask if the patient has traveled to such an area before making a diagnosis.

Disclosures: Dr. Matzkin or an immediate family member has received research or institutional support from Zimmer. Neither of her co-authors nor any immediate family member has received any form of compensation for their research on this topic.