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Fiber Is Good for You. Now Scientists May Know Why.

Experts always say how good dietary fiber is for us, but it's not so clear why *fiber is so great*

Carl Zimmer

A diet of fiber-rich foods, such as fruits and vegetables, reduces the risk of developing diabetes, heart disease and arthritis. Indeed, the evidence for fiber's benefits extends beyond any particular ailment: Eating more fiber seems to lower people's mortality rate, whatever the cause.

That's why experts are always saying how good dietary fiber is for us. But while the benefits are clear, it's not so clear *why* fiber is so great.

"It's an easy question to ask and a hard one to really answer," said Fredrik Bäckhed, a biologist at the University of Gothenburg in Sweden.

He and other scientists are running experiments that are yielding some important new clues about fiber's role in human health. Their research indicates that fiber doesn't deliver many of its benefits directly to our bodies.

Instead, the fiber we eat feeds billions of bacteria in our guts. Keeping them happy means our intestines and immune systems remain in good working order.

In order to digest food, we need to bathe it in enzymes that break down its molecules. Those molecular fragments then pass through the gut wall and are absorbed in our intestines.

But our bodies make a limited range of enzymes, so that we cannot break down many of the tough compounds in plants. The term "dietary fiber" refers to those indigestible molecules.

But they are indigestible only to us. The gut is coated with a layer of mucus, atop which sits a carpet of hundreds of species of bacteria, part of the human microbiome. Some of these microbes carry the enzymes needed to break down various kinds of dietary fiber.

The ability of these bacteria to survive on fiber we can't digest ourselves has led many experts to wonder if the microbes are somehow involved in the benefits of the fruits-and-vegetables diet. Two detailed studies published recently in the journal Cell Host and Microbe provide compelling evidence that the answer is yes.

In one experiment, Andrew T. Gewirtz of Georgia State University and his colleagues put mice on a low-fiber, high-fat diet. By examining fragments of bacterial DNA in the animals' feces, the scientists were able to estimate the size of the gut bacterial population in each mouse.

On a low-fiber diet, they found, the population crashed, shrinking tenfold.

Dr. Bäckhed and his colleagues carried out a similar experiment, surveying the microbiome in mice as they were switched from fiber-rich food to a low-fiber diet. "It's basically what you'd get at McDonald's," said Dr. Bäckhed said. "A lot of lard, a lot of sugar, and twenty percent protein."

The scientists focused on the diversity of species that make up the mouse's gut microbiome. Shifting the animals to a low-fiber diet had a dramatic effect, they found: Many common species became rare, and rare species became common.

Along with changes to the microbiome, both teams also observed rapid changes to the mice themselves. Their intestines got smaller, and its mucus layer thinner. As a result, bacteria wound up much closer to the intestinal wall, and that encroachment triggered an immune reaction.

After a few days on the low-fiber diet, mouse intestines developed chronic inflammation. After a few weeks, Dr. Gewirtz's team observed that the mice began to change in other ways, putting on fat, for example, and developing higher blood sugar levels.

Dr. Bäckhed and his colleagues also fed another group of rodents the high-fat menu, along with a modest dose of a type of fiber called inulin. The mucus layer in their guts was healthier than in mice that

didn't get fiber, the scientists found, and intestinal bacteria were kept at a safer distance from their intestinal wall.

Dr. Gewirtz and his colleagues gave inulin to their mice as well, but at a much higher dose. The improvements were even more dramatic: Despite a high-fat diet, the mice had healthy populations of bacteria in their guts, their intestines were closer to normal, and they put on less weight.

Dr. Bäckhed and his colleagues ran one more interesting experiment: They spiked water given to mice on a high-fat diet with a species of fiber-feeding bacteria. The addition changed the mice for the better: Even on a high-fat diet, they produced more mucus in their guts, creating a healthy barrier to keep bacteria from the intestinal walls.

One way that fiber benefits health is by giving us, indirectly, another source of food, Dr. Gewirtz said. Once bacteria are done harvesting the energy in dietary fiber, they cast off the fragments as waste. That waste — in the form of short-chain fatty acids — is absorbed by intestinal cells, which use it as fuel.

But the gut's microbes do more than just make energy. They also send messages.

Intestinal cells rely on chemical signals from the bacteria to work properly, Dr. Gewirtz said. The cells respond to the signals by multiplying and making a healthy supply of mucus. They also release bacteria-killing molecules.

By generating these responses, gut bacteria help maintain a peaceful coexistence with the immune system. They rest atop the gut's mucus layer at a safe distance from the intestinal wall. Any bacteria that wind up too close get wiped out by antimicrobial poisons.

While some species of gut bacteria feed directly on dietary fiber, they probably support other species that feed on their waste. A number of species in this ecosystem — all of it built on fiber — may be talking to our guts.

Going on a low-fiber diet disturbs this peaceful relationship, the new studies suggest. The species that depend on dietary fiber starve, as do the other species that depend on them. Some species may switch to feeding on the host's own mucus.

With less fuel, intestinal cells grow more slowly. And without a steady stream of chemical signals from bacteria, the cells slow their production of mucus and bacteria-killing poisons.

As a result, bacteria edge closer to the intestinal wall, and the immune system kicks into high gear.

"The gut is always precariously balanced between trying to contain these organisms and not to overreact," said Eric C. Martens, a microbiologist at the University of Michigan who was not involved in the new studies. "It could be a tipping point between health and disease."

Inflammation can help fight infections, but if it becomes chronic, it can harm our bodies. Among other things, chronic inflammation may interfere with how the body uses the calories in food, storing more of it as fat rather than burning it for energy.

Justin L. Sonnenburg, a biologist at Stanford University who was not involved in the new studies, said that a low-fiber diet can cause low-level inflammation not only in the gut, but throughout the body.

His research suggests that when bacteria break down dietary fiber down into short-chain fatty acids, some of them pass into the bloodstream and travel to other organs, where they act as signals to quiet down the immune system.

"You can modulate what's happening in your lung based on what you're feeding your microbiome in your gut," Dr. Sonnenburg said.

Hannah D. Holscher, a nutrition scientist at the University of Illinois who was not involved in the new studies, said that the results on mice need to be put to the test in humans. But it's much harder to run such studies on people.

In her own lab, Dr. Holscher acts as a round-the-clock personal chef. She and her colleagues provide volunteers with all their meals for two weeks. She can then give some of her volunteers an extra source of

fiber — such as walnuts — and look for changes in both their microbiome and their levels of inflammation.

Dr. Holscher and other researchers hope that they will learn enough about how fiber influences the microbiome to use it as a way to treat disorders. Lowering inflammation with fiber may also help in the treatment of immune disorders such as inflammatory bowel disease.

Fiber may also help reverse obesity. Last month in the American Journal of Clinical Nutrition, Dr. Holscher and her colleagues reviewed a number of trials in which fiber was used to treat obesity. They found that fiber supplements helped obese people to lose about five pounds, on average.

But for those who want to stay healthy, simply adding one kind of fiber to a typical Western diet won't be a panacea. Giving mice inulin in the new studies only partly restored them to health.

That's probably because we depend on a number of different kinds of dietary fiber we get from plants. It's possible that each type of fiber feeds a particular set of bacteria, which send their own important signals to our bodies.

"It points to the boring thing that we all know but no one does," Dr. Bäckhed said. "If you eat more green veggies and less fries and sweets, you'll probably be better off in the long term."

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Immune cells play key role in early breast cancer metastasis even before a tumor develops

Macrophages in healthy breast tissue play a major role in helping early breast cancer cells leave the breast for other parts of the body

New York, NY - Mount Sinai researchers have discovered that normal immune cells called macrophages, which reside in healthy breast tissue surrounding milk ducts, play a major role in helping early breast cancer cells leave the breast for other parts of the body, potentially creating metastasis before a tumor has even developed, according to a study published in Nature Communications.

The macrophages play a role in mammary gland development by regulating how milk ducts branch out through breast tissue. Many studies have also proven the importance of macrophages in metastasis, but until now, only in models of advanced large tumors. By studying human samples, mouse tissues, and breast organoids, which are miniaturized and simplified versions of breast tissue produced in the lab, the new research found that in very early cancer lesions, macrophages are attracted to enter the breast ducts where they trigger a chain reaction that brings early cancer cells out of the breast, said lead researcher Julio Aguirre-Ghiso, PhD, Professor of Oncological Sciences, Otolaryngology, Medicine, Hematology and Medical Oncology at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai.

This research shows that macrophages' relationship with normal breast cells is co-opted by early cancer cells that activate the cancer-causing HER2 gene, helping in this newly-discovered role of these immune cells. The findings from this study could eventually help pinpoint biomarkers to identify cancer patients who may be at risk of carrying potential metastatic cells due to these macrophages and potentially lead to the development of novel therapies that prevent early cancer metastasis.

Early treatment of high-risk patients may prevent the formation of deadly metastasis better than the current standard of treating metastatic disease only once it has occurred, said key researcher Miriam Merad, MD, PhD, Director of the Precision Immunology Institute and the Human Immune Monitoring Center and co-leader of the Cancer Immunology program at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai.

"Our study challenges the dogma that early diagnosis and treatment means sure cure," Dr. Aguirre-Ghiso said. "In this study and in our previous studies, we present mechanisms governing early dissemination. This work further sheds light onto the mysterious

process of early dissemination and cancer of an unknown primary tumor."

Researchers hope to build on this study by identifying which macrophages specifically control early dissemination. They also hope to further detail how early disseminated cancer cells interact with macrophages in the lungs where metastases eventually form and how this interaction can be targeted to prevent metastasis.

"Here, we have identified how macrophages and early cancer cells form a 'microenvironment of early dissemination' and show that by disrupting this interaction we can prevent early dissemination and ultimately deadly metastasis," said Dr. Merad. "This sheds light onto the mysterious process of early dissemination and for patients who have metastasis cancer that came from an unknown source."

This study was funded by the following grants and agencies DoD-BCRP BC133807, BC112380, BC132674, NIH/National Cancer Institute CA109182, CA191430, CA196521, CA163131 CA216248 F31CA183185, Samuel Waxman Cancer Research Foundation Tumor Dormancy Program, Human Frontiers Science Program, Schneider-Lesser Foundation Fellow Award, Melanoma Research Alliance (MRA) NCI-K22 (22CA 201054) NIH 1S10RR024745 and S10OD023547-01.

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Restasis: Why US consumers paid billions for drug deemed ineffective in other countries

Why are Americans, paying billions of dollars for a drug whose efficacy is questionable and not approved in the European Union?

Why are Americans, both as patients and taxpayers, paying billions of dollars for a drug whose efficacy is so questionable that it's not approved in the European Union, Australia or New Zealand?

Restasis, a blockbuster drug sold by Allergan to treat chronic dry eye, has done $8.8 billion in U.S. sales between 2009 and 2015, including over $2.9 billion in public monies through Medicare Part D. Restasis and Allergan have been in the news lately due to the company's novel legal strategy of transferring their patents on the drug to the Saint Regis Mohawk Tribe in order to stave off competition posed by generic drugs.

However, in a recently published article in JAMA IM, "A Clear-Eyed View of Restasis and Chronic Dry Eye Disease," Lisa Schwartz and Steven Woloshin, physician-researchers at The Dartmouth Institute for Health Policy and Clinical Practice, argue that a more fundamental question we should be asking is: Does Restasis even work?

The FDA approved Restasis to increase tear production in 2003, after a 1999 application failed when reviewers and a unanimous FDA advisory committee concluded it did not meet efficacy criteria. Even though Restasis did not improve symptoms scores (compared to a placebo) when tested directly in the pivotal trials, the FDA accepted indirect evidence from the validation study in which, at six months, 15% vs. 5% of patients had a response with Restasis vs. placebo in a pooled analysis.

Meanwhile, regulatory agencies in other countries found the evidence of Restasis's efficacy unconvincing. Australia's regulatory agency found that the trials--the same ones submitted to the FDA--showed no convincing or sustained benefit to patients who had been treated with the drug. Although Canada approved Restasis for a narrower group of patients in 2010, its health technology assessment unit was unconvinced of the drug's benefit and recommended Canada not pay for it. Schwartz and Woloshin's research found that no Canadian provincial or federal drug plan currently does.

So why did Americans pay more than $1.5 billion a year in 2016 alone for a drug that potentially does so little, and to treat a condition that many would not even consider to be a disease?

Schwartz and Woloshin point to the extensive marketing campaign to sell chronic dry eye (CDE) as a disease--and Restasis as the only viable treatment option. From 2016-2017, Allergan spent $645 million advertising Restasis, including its mydryeyes.com website. The website, Schwartz and Woloshin say, recasts the merely unpleasant experience of itching or watery eyes (often caused by allergies, weather, or other common irritants) as disease. Visitors to the site and to another Allergan website, Restasis.com, are also warned of

potential health consequences of undiagnosed and/or untreated CDE disease.

Schwartz and Woloshin also note that both websites offer online help locating a doctor, though neither site discloses that participating doctors many have company ties. Allergan paid over $9 million to 24,152 U.S. doctors from 2013-2015, and the "find-a-doctor" feature includes seven of the top 10 payees.

"Disease awareness campaigns--like chronic dry eyes--are an effective way for companies to sell a disease to sell a drug," Woloshin says. "But people shouldn't assume that you even need a drug to treat symptoms--or that the advertised drug actually relieves the symptoms in the quizzes."

Restasis might not have become such a blockbuster drug, Schwartz and Woloshin argue if consumers, doctors, and payers had easy access to independent drug information.

While U.S. and foreign regulatory documents are valuable sources, they are often underutilized. Many doctors, they say, learn about new drugs not from regulatory documents but from company-sponsored promotional efforts.

In addition, although regulators now produce more structured, readable documents, reviews for older drugs, such as Restasis, are often poorly organized, and missing information remains a problem. Reviews may be heavily redacted and some are never released.

Unlike its counterparts in Europe and Australia, the FDA currently does not release reviews for drugs not approved (even when marketing applications are withdrawn prior to final regulatory action). Schwartz and Woloshin argue that they should.

"When you think of all the good that could have been done with the billions spent on Restasis in the U.S., it reminds us how high the stakes are for better independent information about how well drugs work," Schwartz says.

To read the full article:
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2666792

http://bit.ly/2CpWdUB

Blacks' high diabetes risk driven by obesity, not mystery

Study flips belief in 'unexplained' reason for double the rate of midlife diabetes in blacks

CHICAGO --- In a surprising finding, blacks and whites have the same risk of developing diabetes when all biological factors for the disease are considered over time, reports a large new Northwestern Medicine study.

The finding flips long-held beliefs that there is an unexplained or genetic reason why blacks have double the rate of diabetes compared to whites by midlife, which is considered early onset.

"Obesity is driving these differences," said senior study author Mercedes Carnethon, associate professor of preventive medicine at Northwestern University Feinberg School of Medicine. "The findings surprised us, because for the past 20 years there was a narrative that there must be something we haven't found that was causing this higher rate."

Previous studies have found higher rates of diabetes in blacks are still present even when risk factors for diabetes such as obesity and lower socioeconomic status are taken into account.

But this study, for the first time, identified a combination of modifiable risk factors over time -- body mass index, fat around the abdomen, fasting glucose levels, lipids, blood pressure and lung function -- that drive the higher rate of diabetes. When all of these were factored out, there were no disparities between black and white men or women.

Before the authors accounted for the differences in risk factors, black women had nearly three times the risk for developing diabetes as white women.

The study was published in the journal JAMA on Dec. 26.

"Blacks gained more weight over time," Carnethon said. "It was the accumulation of this and other risk factors that eliminated the so-called mysterious cause of the disparity."

In previous studies, researchers measured such health behaviors as obesity, physical activity and diet once during their study participants' lives.

But these factors can change over time, and how much they change may be different in each race group.

For example, a white woman and a black woman may be the same weight at age 35 -- but if that black woman gains more weight over the next 15 years, her risk for developing diabetes goes up. The Northwestern study measured these changes in her weight over time, along with changes in other related health behaviors and health risk factors.

When scientists accounted for these changes in risk factors for diabetes, they did not observe race differences in the development of diabetes.

The findings are particularly important because the incidence of diabetes is rising in black youth ages 10 to 19 years old. Another recent study showed from 2002 to 2012 the incidence of diabetes remained fairly stable for non-Hispanic white youth (ages 10-19) but increased annually by more than 6 percent for non-Hispanic black youth.

There is no easy fix for the problem, which is driven by a combination of biological, neighborhood, psychosocial, socioeconomic and behavioral factors, the authors said.

"To eliminate the higher rate of diabetes, everybody needs to have access to healthy foods, safe spaces for physical activity and equal economic opportunity to have enough money to afford these things and live in communities that offer this," said lead study author Michael Bancks, a postdoctoral fellow in preventive medicine at Feinberg.

Changing risk behaviors in childhood and adolescence is key because that's when risky health behaviors develop and damage begins to accumulate, Bancks said.

The research is part of the observational cohort Coronary Artery Risk Development in Young Adults (CARDIA) Study. CARDIA was started in 1985-1986, enrolling 5,115 black and white men and women who were 18 to 30 years of age from Birmingham, Alabama; Oakland, California; Minneapolis and Chicago.

The Northwestern study sample included 4,251 individuals from the original study. Individuals were followed through 2015 to 2016 for the development of diabetes, which was assessed at eight follow-up examinations over these 30 years using standard diagnostic criteria for diabetes.

"If we could wave a magic wand and get rid of risk factors, then we could eliminate the disparity," Carnethon said. "But we can't do that. Still, we now know there is no mystery to these higher rates. Our efforts to control the traditional risk factors can work to reduce the disparities we observe in diabetes incidence."

Kiarri Kershaw is a Northwestern co-author of the paper.

The CARDIA study is supported by the National Heart, Lung, and Blood Institute (NHLBI) HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, HHSN268200900041C and T32HL069771. CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI grant AG0005, all of the National Institutes of Health.

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New diagnostic criteria and treatment guidelines proposed for thyroid storm

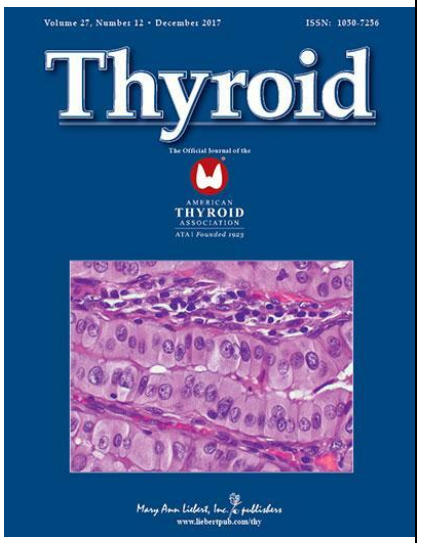
Thyroid storm demands rapid diagnosis and treatment and can benefit from new evidence-based guidelines

New Rochelle, NY - With a mortality rate estimated at 10%, the life-threatening condition known as thyroid storm (TS) demands rapid diagnosis and treatment and can benefit from new evidence-based guidelines for TS developed by researchers in Japan.

The article entitled "Thyroid Storm: A Japanese Perspective" is part of a special section on Japanese Research led by Guest Editor Yoshiharu Murata, Nagoya University, Japan, in the January 2018 issue of Thyroid, a peer-reviewed journal from Mary Ann Liebert, Inc.,

publishers and the official journal of the American Thyroid Association (ATA).

The article is available free on the *Thyroid* website.



In the article, author Takashi Akamizu, Wakayama Medical University, Japan, presents updated diagnostic criteria, extensively revised patient management and treatment guidelines, and newly developed algorithms based on information gathered on patients with TS from hospitals throughout Japan and from the medical literature.

The most common cause of death from thyroid storm was multiple organ failure, followed by congestive heart failure, respiratory failure, and arrhythmia.

Thyroid, the official journal of the American Thyroid Association, publishes original articles and timely reviews that reflect the rapidly advancing changes in our understanding of thyroid physiology and pathology, from the molecular biology of the cell to clinical management of thyroid disorders. **Mary Ann Liebert, Inc., publishers**

Also identified are as yet unanswered clinical questions and the future studies needed to better understand TS and its outcomes and prognosis. "The definition of TS is often somewhat vague, and many reports are of an anecdotal nature. The efforts by our Japanese colleagues to better define the diagnostic criteria and management recommendations are, therefore, highly welcome," says Peter A. Kopp, MD, Editor-in-Chief of Thyroid and Professor of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL. "The proposed framework will serve as a solid foundation for future research and reflection about this challenging clinical entity."

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When a Medical "Cure" Makes Things Much, Much Worse

In 1960s Japan, a bizarre outbreak of hairy green tongues failed to set off alarms around the world

By Jeanne Lenzer, Undark Magazine smithsonian.com

Keiko Yamaguchi's troubles began with diarrhea. After a few weeks, her toes went numb. The numbness and weakness crept up her legs, to her hips, and her vision began to fail. That was in early 1967. By the end of 1968, Yamaguchi, just 22 years old, was blind and paralyzed from the waist down.

She was one of more than 11,000 people in Japan, (with reported cases also occurring in Great Britain, Sweden, Mexico, India, Australia, and several other nations) who were struck by a mysterious epidemic between 1955 and 1970. The outbreak was concentrated in Japan where an estimated 900 died of the disease, which doctors eventually named SMON, for subacute myelo-optic neuropathy—"myelo" from the Greek word referring to the spinal cord; "optic" referring to vision; and neuropathy indicating a disease of the nerves.

The illness usually started with bouts of diarrhea and vomiting. Some patients, like Yamaguchi, became paralyzed and blind. (My efforts to track her down have been unsuccessful.) An uncertain number developed "green hairy tongue": Their tongues sprouted what looked like tiny green hairs. Some of the afflicted developed green urine. Family members, too, came down with the disease, as did doctors and nurses who treated it. Approximately 5 to 10 percent of SMON patients died.

What was causing the outbreak? During the 1960s, Japan—where SMON was concentrated—launched vigorous research efforts to find out. Doctors thought an answer was at hand when a researcher studying SMON patients announced that he'd isolated the echovirus, which is known to cause intestinal problems. But soon other viruses were found in patients, including Coxsackie and a herpes virus. The

herpes finding was compelling, since those viruses are known to affect the nervous system. But one by one, each claim was disproved when independent researchers were unable to replicate earlier laboratory findings.

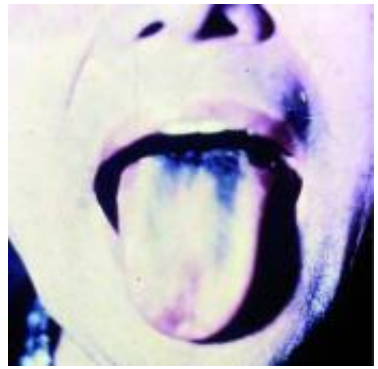
Other possible causes were considered and shot down. No drinking water pathogen was detected. Pesticides? That hypothesis was discarded when a study found that farmers, who would have the greatest exposure, had lower rates of SMON than non-farmers. There was some excitement when researchers found that many victims had taken two types of antibiotics, but it seemed unlikely that two different antibiotics would both suddenly cause the same highly unusual disease. Besides, experts noted, some patients took the antibiotics only *after* developing symptoms of SMON.

Then, in late 1970, three years after the drug theory was dismissed, a pharmacologist made a forehead-slapping discovery. The two presumably different antibiotics, it turned out, were simply different brand names for clioquinol, a drug used to treat amoebic dysentery. The green hairy tongue and green urine, it turned out, had been caused by the breakdown of clioquinol in the patients' systems. One month after the discovery, Japan banned clioquinol, and the SMON epidemic—one of the largest drug disasters in history—came to an abrupt end.

It appeared that the epidemic was concentrated in Japan in part because the drug was routinely used not just for dysentery, but to prevent traveler's diarrhea and various forms of abdominal upset; and in part because Japanese doctors prescribed the drug at far higher doses and for longer periods than was customary in other countries.

The illusion that SMON was an infectious disease was compelling: When patients with abdominal upset or diarrhea were treated with clioquinol and developed SMON, family members, doctors and nurses often took the drug thinking it would protect them—inadvertently creating the very disease they feared. The resulting cluster outbreaks made SMON look like an infectious disease. In short, what people thought was a cure for SMON was in fact its cause.

Few doctors know the story of SMON, and perhaps even fewer use the catchphrase "cure as cause." Yet the phenomenon is more relevant today than ever. A study published last year suggests that medical interventions, including problems with prescribed drugs and implanted medical devices—from cardiac stents to artificial hips and birth control devices—are now the third leading cause of death in the U.S.



The green tongue fur of a patient with SMON, rendered as blue in this image.
(Visual by Proceedings of the Japan Academy, Series B)

Examples abound in virtually every specialty, from cardiology to psychiatry to cancer care. Jerome Hoffman, an emeritus professor of medicine at UCLA, says it isn't surprising: Because drugs and medical devices target disordered body systems, it's all too easy to overshoot and make the disorder worse.

In the 1980s and 1990s, for instance, patients were widely treated with heart rhythm drugs to prevent the abnormal heartbeats called premature ventricular contractions (PVCs) from triggering deadly ventricular fibrillation.

The drugs were quite good at reducing the abnormal beats, and doctors prescribed them widely, believing they were saving lives. But in 1989, the Cardiac Arrhythmia Suppression Trial, or CAST, sponsored by the National Institutes of Health, demonstrated that although the drugs effectively suppressed PVCs, when they did occur they were much more likely to trigger deadly rhythms.

Treated patients were 3.6 times as likely to die as patients given a placebo.

The drugs could fix the PVCs but kill the patient; as the old joke goes, the operation was a success but the patient died.

The problem was invisible for more than a decade because doctors assumed that when a patient died suddenly it was from the underlying heart condition—not the treatment they prescribed.

In another case of cure as cause, a landmark study of Prozac to treat adolescent depression found that it *increased* overall suicidality—the very outcome it is intended to prevent. In the study, 15 percent of depressed adolescents treated with Prozac became suicidal, versus 6 percent treated with psychotherapy, and 11 percent treated with placebo.

These numbers were not made obvious by Eli Lilly, the manufacturer, or the lead researcher who claimed that Prozac was "the big winner" in the treatment of depressed teens. Doctors, unaware that the drug could increase suicidality, often increased the dosage when teens became more depressed in treatment, thinking the underlying depression — not the drug — was at fault.

Studies of other drugs in the same class as Prozac, selective serotonin reuptake inhibitors, or SSRIs, have shown similar problems.

There are many other instances of cure as cause: cardiac stents that caused clots in the coronary arteries; implanted pacemaker-defibrillators that misfired or failed to fire, causing deadly heart rhythms; and vagus nerve stimulators to treat seizures that instead have led to increased seizures.

One of SMON's lessons is the danger of perverse financial incentives. Japanese doctors were paid for each prescription they wrote, a practice considered unethical in most peer nations. Doctors in some prefectures in Japan can still sell drugs to their patients. No wonder they prescribed such high doses of clioquinol for prolonged periods.

More than half of doctors in the U.S. receive money or other blandishments from Big Pharma and device manufacturers. The amounts can be stupendous: Some doctors have received tens of millions of dollars to implant certain devices or to promote certain drugs. Such influence takes a toll on the humans exposed to harmful treatments.

The nonprofit group Institute for Safe Medication Practices conducted a study to quantify drug harms and concluded that prescribed medicines are "one of the most significant perils to human health resulting from human activity."

With the rise of the medical-industrial complex and its extraordinary profits, industry has a vested interest in blaming bad outcomes on a patient's underlying disease and not on their own products.

Industry claims often mislead doctors and patients alike. Ciba-Geigy, the main manufacturer of clioquinol, said the drug was safe because it couldn't be absorbed into the bloodstream from the intestines. Yet legal filings from a lawsuit against the company show that Ciba-Geigy was aware of the drug's harmful effects for years. As early as 1944, clioquinol's inventors said the drug should be strictly controlled and limited to 10 to 14 days' use.

In 1965, after a Swiss veterinarian published reports that dogs given clioquinol developed seizures and died, Ciba was content to issue a warning that the drug shouldn't be given to animals.

In the U.S., pharma's influence over what doctors and the public believe about drugs and devices has increased by orders of magnitude, as virtually all research is now conducted by industry and genuinely independent research has all but vanished.

In 1977, industry sponsorship provided 29 percent of funding for clinical and nonclinical research. Estimates today suggest that figure has increased to around 60 percent. Even most "independent" research, such as that conducted by the National Institutes of Health, is now "partnered" with industry, making our reliance on industry claims nearly complete.

Stemming the tide of medical interventions that do more harm than good will require a deep examination of cure as cause—and a willingness to stop depending on the industry that perversely promotes it.

http://bit.ly/2lXr7wH

Caffeine level in blood may help diagnose people with Parkinson's disease

Testing the level of caffeine in the blood may provide a simple way to aid the diagnosis of Parkinson's disease

MINNEAPOLIS - Testing the level of caffeine in the blood may provide a simple way to aid the diagnosis of Parkinson's disease, according to a study published in the January 3, 2018, online issue of Neurology®, the medical journal of the American Academy of Neurology.

The study found that people with Parkinson's disease had significantly lower levels of caffeine in their blood than people without the disease, even if they consumed the same amount of caffeine.

"Previous studies have shown a link between caffeine and a lower risk of developing Parkinson's disease, but we haven't known much about how caffeine metabolizes within the people with the disease," said study author Shinji Saiki, MD, PhD, of Juntendo University School of Medicine in Tokyo, Japan.

People in the study with more severe stages of the disease did not have lower levels of caffeine in the blood, suggesting that the decrease occurs from the earliest stages of the disease, according to David G. Munoz, MD, of the University of Toronto in Canada, who wrote an editorial accompanying the study.

"If these results can be confirmed, they would point to an easy test for early diagnosis of Parkinson's, possibly even before symptoms are appearing," Munoz said. "This is important because Parkinson's disease is difficult to diagnose, especially at the early stages."

The study involved 108 people who had Parkinson's disease for an average of about six years and 31 people of the same age who did not have the disease. Their blood was tested for caffeine and for 11 byproducts the body makes as it metabolizes caffeine. They were also tested for mutations in genes that can affect caffeine metabolism.

The two groups consumed about the same amount of caffeine, with an average equivalent to about two cups of coffee per day. But the people with Parkinson's disease had significantly lower blood levels of caffeine and nine of the 11 byproducts of caffeine in the blood. The caffeine level was an average of 79 picomoles per 10 microliters for people without Parkinson's disease, compared to 24 picomoles per 10 microliters for people with the disease. For one of the byproducts, the level was below the amount that could be detected in more than 50 percent of the people with Parkinson's disease.

In the statistical analysis, the researchers found that the test could be used to reliably identify the people with Parkinson's disease, with a score of 0.98 where a score of 1 means that all cases are identified correctly.

In the genetic analysis, there were no differences in the caffeine-related genes between the two groups.

Limitations of the study include that people with severe Parkinson's disease were not included, which could affect the ability to detect an association between disease severity and caffeine levels. Munoz also noted that all of the people with Parkinson's were taking Parkinson's medication and it's possible that these drugs could affect the metabolism of caffeine.

The study was supported by the Japan Agency for Medical Research and Development, Japan Society for the Promotion of Science, and the Japanese Ministry of Education, Culture, Sports, Science and Technology.

http://bit.ly/2CHjmVT

Agricultural parasite takes control of host plant's genes

Dodder, a parasitic plant, inserts microRNAs into the host that can silence the expression of host

Dodder, a parasitic plant that causes major damage to crops in the U.S. and worldwide every year, can silence the expression of genes in the host plants from which it obtains water and nutrients.

This cross-species gene regulation, which includes genes that contribute to the host plant's defense against parasites, has never before been seen from a parasitic plant. Understanding this system could provide researchers with a method to engineer plants to be resistant to the parasite.

A paper describing the research by a team that includes scientists at Penn State and Virginia Tech appears January 4, 2018 in the journal Nature.

"Dodder is an obligate parasite, meaning that it can't live on its own," said Michael J. Axtell, professor of biology at Penn State and an author of the paper.

"Unlike most plants that get energy through photosynthesis, dodder siphons off water and nutrients from other plants by connecting itself to the host vascular system using structures called haustoria. We were able to show that, in addition to the nutrients that flow into dodder from the host plant across the haustoria, dodder passes microRNAs into its host plant that regulate the expression of host genes in a very direct way."

MicroRNAs are very short bits of nucleic acid -- the material of DNA and RNA -- that can bind to messenger RNAs that code for protein. This binding of microRNA to messenger RNA prevents the protein from being made, either by blocking the process directly or by triggering other proteins that cut the messenger RNA into smaller pieces.

Importantly, the small remnants of the messenger RNA can then function like additional microRNAs, binding to other copies of the messenger RNA, causing further gene silencing.

"Dodder seems to turn on the expression of these microRNAs when it comes into contact with the host plant," said James H. Westwood, professor of plant pathology, physiology, and weed science at Virginia Tech and another author of the paper. "What was really interesting is that the microRNAs specifically target host genes that are involved in the plant's defense against the parasite."

When a plant is attacked by a parasite it initiates a number of defense mechanisms. In one of these mechanisms, similar to blood clotting after a cut, the plants produce a protein that clots the flow of nutrients to the site of the parasite.

MicroRNA from dodder targets the messenger RNA that codes for this protein, which then helps to maintain a free flow of nutrients to the parasite.

The gene that codes for this clotting protein has a very similar sequence across many plant species, and the researchers showed that the microRNA from dodder targets regions of the gene sequence that are the most highly conserved across plants. Because of this, dodder can probably silence this clotting protein in, and therefore parasitize, a wide variety of plant species.

The researchers sequenced all of the microRNAs in tissue from the parasite alone, the host plant alone, and a combination of two. By comparing the sequencing data from these three sources, they were able to identify microRNAs from dodder that had entered the plant tissue.

They then measured the amount of messenger RNA of genes that were targeted by the dodder microRNAs and saw that the level of messenger RNA from the host was reduced when the dodder microRNAs were present.

"Along with previous examples of small RNA exchange between fungi and plants, our results imply that this cross-species gene regulation may be more widespread in other plant-parasite interactions," said Axtell. "So, with this knowledge, the dream is that we could eventually use gene editing technology to edit the microRNA target sites in the host plants, preventing the microRNAs from binding and silencing these genes. Engineering resistance to the parasite in this way could reduce the economic impact of the parasite on crop plants."

In addition to Axtell and Westwood, the research team includes Saima Shahid, Nathan R. Johnson, Eric Wafula, Feng Wang, Ceyda Coruh, and Claude W. dePamphilis at Penn State; Gunjune Kim and Vivian Bernal-Galeano at Virginia Tech; and Tamia Phifer at Knox College. The research was funded by the U.S. National Science Foundation and the U.S. National Institute of Food and Agriculture. Additional support was provided by the Penn State Huck Institutes of the Life Sciences.

http://bit.ly/2qyuVd9

11,000-year-old child's skeleton tells tale of Native American origins

Suggests a human population was isolated in Beringia during the last ice age.

John Timmer - 1/4/2018, 2:12 AM

Where did Native Americans come from? Over the years, lots of ideas have been considered, but genetic data eventually came down decisively in favor of one of them.

Native Americans are most closely related to East Asians and must have come across a land bridge that was present between Siberia and Alaska during the last glacial period.

Enlarge / Excavations at the Upward Sun River site. **Ben Potter**

But that big-picture answer has raised all sorts of additional questions about the details. There has been a long-running argument over their mode of travel, which only recently seems to have been decided in favor of boats. There are still arguments over how many waves of migration took place. And a weak genetic affinity for Eurasian populations, strengthened by an ancient Siberian genome, raises questions about how that DNA ended up in Native American genomes.

Now, a large team of researchers is saying they have data that clarifies a lot of these questions. It comes in the form of a genome obtained from a child's skeleton found in Alaska. The skeleton has been dated to 11,500 years ago, and the genome now suggests it represents a member of a now-lost population that occupied the Beringian land bridge at the peak of the last glacial period—and gave rise to Native Americans.

Meet the ancestors

The skeleton was found at a site called Upward Sun River and was one of two child skeletons found buried there (the second did not yield any DNA that could be sequenced). The site is located in the Alaskan interior, along a river that flows into the Yukon. It would have been north of the massive ice sheets that formed during the last glaciation.

The genome itself looks almost exactly like you'd expect given a migration along the land bridge, either by foot or boat, prior to the end of the glaciation. It's equally related to all Native American populations but lies closer to the base of that branch of the human family tree. In other words, it is more similar to what we'd predict the ancestor of all Native Americans would look like, genetically.

So, it's located in a spot on the family tree that's very informative. Plus, it comes with a precise date, which allow us to determine the timing of various events, like migrations and interbreeding. Using that information, the authors reconstruct the history of Native Americans.

The data suggest that the ancestors of Native Americans branched off from other East Asian lineages starting at about 35,000 years ago, although the groups continued to interbreed for another 10,000 years. At about the time that stopped, the Native American ancestors started interacting with a Eurasian population in Siberia. That stopped by about 18,000 years ago. From then on, the population was isolated.

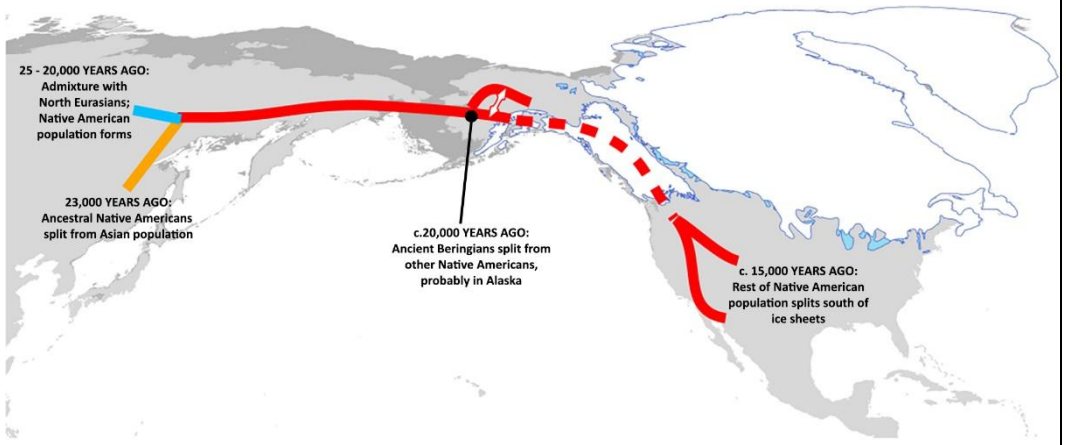
From Beringia to the Americas

How did this isolation take place? The authors argue that the separation from East Asian populations occurred due to the onset of the Last Glacial Maximum 24,000 years ago. This was the final exceptionally cold period before the glaciation came to an end. It would have led to expanded ice sheets in Siberia that could have closed the Native American ancestors off on the east side of an icy wall, and indications are that human presence in Siberia dropped during this time. Although there are small regions of Siberia that would have been habitable, the authors argue that it's likely that this population was already occupying the land bridge but was blocked

from continuing beyond Alaska by other ice sheets. (This "isolation on the land bridge" hypothesis has been called the "Beringian standstill.") All indications are that Native Americans had made their way to the North American interior by 15,000 years ago, and the new data suggest they started to split off from other Beringians as early as 20,000 years ago.

Since the new Beringian genome is equally related to both northern and southern groups of Native Americans, the authors argue that the migration into the interior probably took place in a single wave by an ancestral Native American population.

The split into northern and southern groups would have happened once they were in the interior, since the team calculates the split at somewhere between 17,500 and 14,500 years ago.



Enlarge / The research team's model for the process that brought Native Americans to their current home. **Victor Moreno Mayar**

The authors' favored model isn't definitive. It's possible that the Beringians remained in northeast Siberia, rather than expanding through the land bridge and into Alaska, until relatively recently. It's also possible that the northern and southern Native Americans had already diverged before they made their way into the interior of the Americas.

But the researchers persuasively argue that their model is the simplest explanation for all the data we have at the moment.

Epilogue

The child's burial took place in the Alaskan interior, north of the ice sheets, after the ancestors of Native Americans had already made their way south. But there's no sign of any Beringian heritage among modern-day Alaskans. Instead, Alaskan natives all appear to be derived from a group of Native Americans who migrated back north after the ice sheets collapsed (some of this population would go on to interact with Siberians and Inuit, complicating the picture somewhat).

All of which indicates that the child was probably one of the last of her lineage. After having survived the Last Glacial Maximum on the harsh tundra of Alaska, the Beringian lineage came to an end as the climate warmed up.

Nature, *2017. DOI: 10.1038/nature25173 (About DOIs).*

http://bit.ly/2CS2756

Hotly debated 3.5 billion-year-old microbe fossils get another look

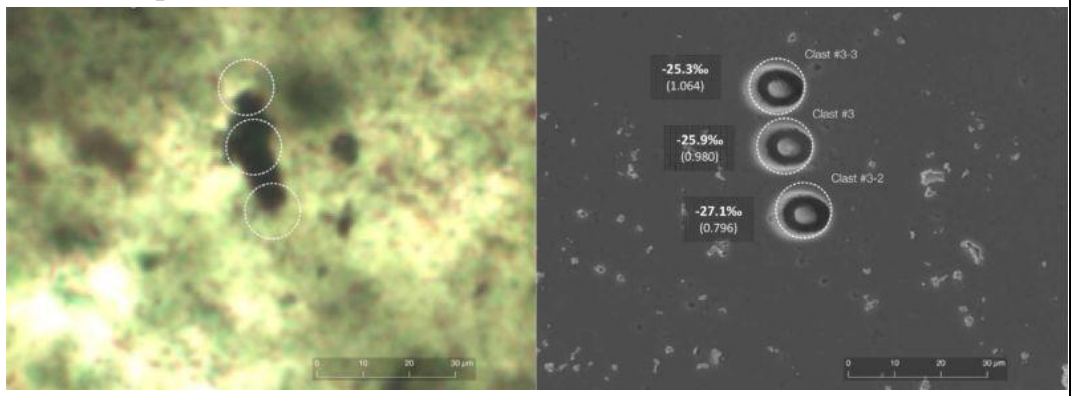
Carbon isotopes seem to show ancient samples really are living in origin.

Scott K. Johnson - 1/4/2018, 4:50 AM

The title of “oldest evidence of life” has been provisionally claimed by a growing and confusing crowd of discoveries recently. At least until the last few years, the crown rested comfortably on a 3.47 billion-year-old rock from Western Australia called the Apex Chert. First described in the early 1990s, this rock contained a variety of microscopic structures that looked for all the world like the fossilized remains of microbial life.

Like other finds in this category, the Apex Chert has seen its fair share of controversy as researchers skeptically poked and prodded. Just two years ago, we covered a study that concluded these microfossils were simply clever lookalikes created by minerals crystallizing near a hydrothermal vent. In that version of events, some carbon (which may or may not have come from living things) stuck to vaguely microbe-shaped mineral crystals.

A recent study led by William Schopf—who discovered the Apex Chert in the first place—brings newer tools to bear on the question. And the researchers believe the results show that these microfossils are not impostors.



Optical microscope image of one of the purported microfossils on the left, and a Scanning Electron Microscope image of the same spot after carbon isotopes were measured in three pits on the right. **Schopf et al./PNAS**

Schopf and his team subjected 11 purported fossils from the original sample to an incredibly precise spot-measurement instrument that can determine the mix of carbon isotopes that are present. (It's the same instrument that we once visited, in fact.)

The first question is simply whether the carbon in the fossils—and the random carbon particles that can be found around them—matches the isotope signature of carbon from living organisms. Biology is somewhat choosy when it comes to isotopes of carbon. The extra neutron in carbon-13 causes organisms to prefer its lighter version; non-biological chemical reactions are typically more indiscriminate. So an unusually low share of carbon-13 is an indicator of biological carbon. All the carbon in the samples passes this test. And the carbon inside the fossils contained even less carbon-13 than the random bits of carbonaceous stuff outside the fossils.

But the most interesting comparison is *between* the relevant fossil specimens. In the original study, Schopf identified five different types of fossils in the Apex Chert, which he suggested corresponded to five different species or types of microbial organisms. It turns out they each had distinct carbon isotope signatures. If these fossils were just lookalike mineral crystals coated in carbon, you would expect to see no consistent carbon isotope pattern—they should all be roughly the same. But if these were different types of organisms subsisting on different chemical fuels, it would make sense to see variations in the carbon isotopes.

The isotope signatures can actually hint at what these organisms would have been like. Two of them are within the range of photosynthetic, single-celled life.

The other three would match up with an interesting pair: methane-producing archaea and methane-consuming bacteria. That would be pretty cool, as the existence of these two types of life have been guessed at from carbon isotope measurements of very old rocks but never pinned to specific microbial fossils. Their presence would hint at the diversity of life, even in the early days. Then again, recent studies have claimed to find evidence of life from 3.7 or even 3.95 billion years ago—and that would make 3.47 billion-year-old lifeforms comparative spring chickens.

But as for the truth about the Apex Chert, the authors argue there is simply too much consistent evidence supporting the conclusion that these are real microbial fossils. The multiple lines of evidence make it more difficult to find a plausible non-biological explanation. They'll now probably keep their place in an exclusive VIP section unless a better objection comes along.

Proceedings of the National Academy of Sciences, *2017. DOI: 10.1073/pnas.1718063115*

http://bbc.in/2D3ed8I

Common virus used to help fight incurable brain cancer

Scientists are optimistic that they may have found a new treatment to help people with incurable brain cancer.

By Michelle Roberts Health editor, BBC News online

Ten patients so far in the UK have received the therapy, which is a virus that causes mild flu-like symptoms. The virus can cross the

blood-brain barrier and appears to help "switch on" the body's defence systems to attack the tumour, early studies suggest.

Experts at University of Leeds and four other centres now plan to treat more patients with reovirus therapy.

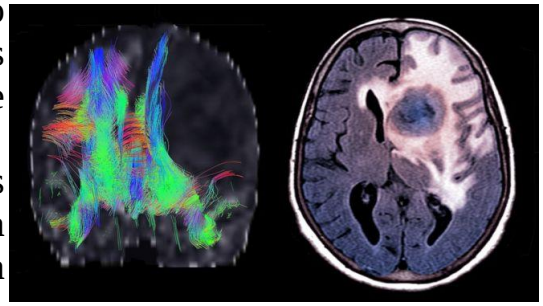


Image copyright SPL

Although not a cure, the scientists hope it could be a useful add-on to traditional treatments, like chemotherapy and radiotherapy and newer immunotherapy drugs to buy patients more weeks, months or perhaps even years of life. It is too early to know what impact, if any, reovirus treatment has on survival, but researchers are hopeful that with more studies they will be able to find out.

Dr Colin Watts, Cancer Research UK's brain tumour expert, told the BBC it was "an exciting first step along the journey towards clinical use". He added: "Scientists working with surgeons and oncologists have proven that the virus penetrates into the tumour and does what it is supposed to do - wake up the immune system to see the cancer.

"Now clinical trials are seeing if that wake-up call is sufficient to kill the cancer cells and help to improve survival of patients with brain tumours."

How it works

The virus can be injected into a person's bloodstream rather than directly into the brain, which doctors say should be less risky and more convenient for the patients who receive it. Reovirus tends to infect cancer cells and largely leaves healthy cells alone, say researchers. Patients receiving the treatment reported only mild flu-like side-effects.

Until now, scientists thought it was unlikely that the virus would be able to pass from the blood into the brain because of the protective membrane that surrounds the brain - the blood-brain barrier.

The first-ever patient trial of the treatment - in nine volunteers with fast-growing gliomas that had regrown despite surgery and chemo and radiotherapy, or advanced cancers that had spread to the brain from other sites - showed reovirus crossed successfully to reach its target.

Analysis of tumour samples suggested that the virus helped alert and ramp up the body's immune system to attack the cancerous tissue.

Prof Alan Melcher from the Institute of Cancer Research, who is co-author of the study published in the journal Science Translational Medicine, said: "Our immune systems aren't very good at 'seeing' cancers, partly because cancer cells look like our body's own cells, and partly because cancers are good at telling immune cells to turn a blind eye. But the immune system is very good at seeing viruses.

"In our study, we were able to show that reovirus could infect cancer cells in the brain. And, importantly, brain tumours infected with reovirus became much more visible to the immune system."

The findings have prompted other doctors to recruit more patients to try out a full course of the treatment.

Susan Short, professor of clinical oncology at the University of Leeds, has already started treating one patient in her care. The man, who was only recently diagnosed with a very aggressive type of brain tumour called glioblastoma, is receiving multiple doses of reovirus treatment alongside standard therapy to see what effect it will have.

Prof Short said: "Brain cancer is a devastating disease. For a long time, there have not been many new developments that we could offer patients. "We do not yet know how much of a difference the treatment will make because this is a new method that has not been available before. It's a paradigm change."

She said there were early hints that other "relatively harmless" viruses might work even better to prime the body to fight harder against these very aggressive cancers. "We hope it might ultimately lead to a therapy that has a big impact, but we just don't know yet."

Sarah Lindsell, chief executive of The Brain Tumour Charity which co-funded the research, said: "Brain tumours cost too many lives. The

only way to change that is through research. This news from the University of Leeds and the Institute of Cancer Research will be welcomed by all of those who know only too well the devastation caused by this cruel disease."

According to figures from Cancer Research UK, almost 11,000 new cases of primary brain cancers are diagnosed in the UK each year. Only 14% of patients survive for 10 years or more following a diagnosis of a primary or malignant brain tumour.

http://bit.ly/2ACOSPM

Study links asthma and allergic rhinitis with cataracts

In a study that investigated the association between allergic diseases and ophthalmologic diseases in 14,776 adults, asthma and allergic rhinitis were each associated with a 50% increased likelihood of having cataracts. Atopic dermatitis was not linked with cataracts in the *Journal of Dermatology* study, however. The findings indicate that efforts should be made to reduce the risk of ophthalmologic complications when treating patients with certain allergic diseases.

http://bit.ly/2COTPKD

Dark Age people lived much longer than you thought

Dental remains indicate Anglo Saxon septuagenarians were very common.

Andrew Masterson reports.

The idea that people in the Dark Ages died around the age of 40 is not supported by the evidence, according to a study of human remains in three English cemeteries.

The study, by anthropologists Christine Cave and Marc Oxenham of the Australian National University in Canberra, focussed on tooth condition instead of bone development when examining remains of people buried between the years 475 and 625 CE.

The idea that most people during that period didn't make it much past 40 is a product of classification rather than evidence, says Cave.

"Once people are fully grown it becomes increasingly difficult to determine their age from skeletal remains, which is why most studies just have a highest age category of 40-plus or 45-plus," she says.

"So effectively they don't distinguish between a fit and healthy 40-year-old and a frail 95-year-old."

Dark Age dentition provides a more accurate insight into death than bone development. **ANU**

Tracking dental wear provided a much more graduated measure of age at death, and the central finding was surprising.

"For people living traditional lives without modern medicine or markets the most common age of death is about 70, and that is remarkably similar across all different cultures," reveals Cave.

Studying the burial conditions in the three cemeteries – Greater Chesterford in Essex, Mill Hill in Kent, and Worthy Park in Hampshire – also exploded another romantic myth – that in pre-industrial English society old women were revered as wise matriarchs.

In fact, Cave and Oxenham report, old women were often given "non-normative" and "deviant" burials. Ageing in Anglo Saxon England, they conclude in their paper, "was a gendered process".

"Women were more likely to be given prominent burials if they died young, but were much less likely to be given one if they were old," says Cave.

"The higher status men are generally buried with weapons, like a spear and a shield or occasionally a sword. Women were buried with jewellery, like brooches, beads and pins. This highlights their beauty, which helps explain why most of the high-status burials for women were for those who were quite young."

The study is published in the *Journal of Anthropological Archaeology*.

http://bit.ly/2F8zqHu

NASA study: First direct proof of ozone hole recovery due to chemicals ban

For the first time, scientists have shown through direct satellite observations of the ozone hole that levels of ozone-destroying chlorine are declining, resulting in less ozone depletion.

Measurements show that the decline in chlorine, resulting from an international ban on chlorine-containing manmade chemicals called chlorofluorocarbons (CFCs), has resulted in about 20 percent less ozone depletion during the Antarctic winter than there was in 2005 -- the first year that measurements of chlorine and ozone during the Antarctic winter were made by NASA's Aura satellite.

"We see very clearly that chlorine from CFCs is going down in the ozone hole, and that less ozone depletion is occurring because of it," said lead author Susan Strahan, an atmospheric scientist from NASA's Goddard Space Flight Center in Greenbelt, Maryland.

CFCs are long-lived chemical compounds that eventually rise into the stratosphere, where they are broken apart by the Sun's ultraviolet radiation, releasing chlorine atoms that go on to destroy ozone molecules. Stratospheric ozone protects life on the planet by absorbing potentially harmful ultraviolet radiation that can cause skin cancer and cataracts, suppress immune systems and damage plant life.

Two years after the discovery of the Antarctic ozone hole in 1985, nations of the world signed the Montreal Protocol on Substances that Deplete the Ozone Layer, which regulated ozone-depleting compounds. Later amendments to the Montreal Protocol completely phased out production of CFCs.

Past studies have used statistical analyses of changes in the ozone hole's size to argue that ozone depletion is decreasing. This study is the first to use measurements of the chemical composition inside the ozone hole to confirm that not only is ozone depletion decreasing, but that the decrease is caused by the decline in CFCs.

The study was published Jan. 4 in the journal Geophysical Research Letters.

The Antarctic ozone hole forms during September in the Southern Hemisphere's winter as the returning sun's rays catalyze ozone destruction cycles involving chlorine and bromine that come primarily from CFCs. To determine how ozone and other chemicals have changed year to year, scientists used data from the Microwave Limb Sounder (MLS) aboard the Aura satellite, which has been making measurements continuously around the globe since mid-2004. While many satellite instruments require sunlight to measure atmospheric trace gases, MLS measures microwave emissions and, as a result, can measure trace gases over Antarctica during the key time of year: the dark southern winter, when the stratospheric weather is quiet and temperatures are low and stable.

The change in ozone levels above Antarctica from the beginning to the end of southern winter -- early July to mid-September -- was computed daily from MLS measurements every year from 2005 to 2016. "During this period, Antarctic temperatures are always very low, so the rate of ozone destruction depends mostly on how much chlorine there is," Strahan said. "This is when we want to measure ozone loss."

They found that ozone loss is decreasing, but they needed to know whether a decrease in CFCs was responsible. When ozone destruction is ongoing, chlorine is found in many molecular forms, most of which are not measured. But after chlorine has destroyed nearly all the available ozone, it reacts instead with methane to form hydrochloric acid, a gas measured by MLS. "By around mid-October, all the chlorine compounds are conveniently converted into one gas, so by measuring hydrochloric acid we have a good measurement of the total chlorine," Strahan said.

Nitrous oxide is a long-lived gas that behaves just like CFCs in much of the stratosphere. The CFCs are declining at the surface but nitrous oxide is not. If CFCs in the stratosphere are decreasing, then over time, less chlorine should be measured for a given value of nitrous oxide.

By comparing MLS measurements of hydrochloric acid and nitrous oxide each year, they determined that the total chlorine levels were declining on average by about 0.8 percent annually.

The 20 percent decrease in ozone depletion during the winter months from 2005 to 2016 as determined from MLS ozone measurements was expected. "This is very close to what our model predicts we should see for this amount of chlorine decline," Strahan said. "This gives us confidence that the decrease in ozone depletion through mid-September shown by MLS data is due to declining levels of chlorine coming from CFCs. But we're not yet seeing a clear decrease in the size of the ozone hole because that's controlled mainly by temperature after mid-September, which varies a lot from year to year."

Looking forward, the Antarctic ozone hole should continue to recover gradually as CFCs leave the atmosphere, but complete recovery will take decades. "CFCs have lifetimes from 50 to 100 years, so they linger in the atmosphere for a very long time," said Anne Douglass, a fellow atmospheric scientist at Goddard and the study's co-author. "As far as the ozone hole being gone, we're looking at 2060 or 2080. And even then there might still be a small hole."

To read the study, visit: http://onlinelibrary.wiley.com/doi/10.1002/2017GL074830/abstract

http://bit.ly/2CAKaUM

Cancer mortality in the US continues decades-long drop

Nearly 2.4 million fewer deaths as a result of dropping rates

ATLANTA - The cancer death rate dropped 1.7% from 2014 to 2015, continuing a drop that began in 1991 and has reached 26%, resulting in nearly 2.4 million fewer cancer deaths during that time.

The data is reported in Cancer Statistics 2018, the American Cancer Society's comprehensive annual report on cancer incidence, mortality, and survival.

It is published in *CA: A Cancer Journal for Clinicians* and is accompanied by its consumer version: Cancer Facts and Figures 2018.

The report estimates that there will be 1,735,350 new cancer cases and 609,640 cancer deaths in the United States in 2018.

The cancer death rate dropped 26% from its peak of 215.1 per 100,000 population in 1991 to 158.6 per 100,000 in 2015.

A significant proportion of the drop is due to steady reductions in smoking and advances in early detection and treatment.

The overall decline is driven by decreasing death rates for the four major cancer sites:

Lung (declined 45% from 1990 to 2015 among men and 19% from 2002 to 2015 among women);
female breast (down 39% from 1989 to 2015),
prostate (down 52% from 1993 to 2015),
and colorectal (down 52% from 1970 to 2015).

Over the past decade, the overall cancer incidence rate was stable in women and declined by about 2% per year in men.

The report also finds that while the racial gap in cancer mortality continues to narrow, this mainly reflects progress in older age groups, and masks stark persistent inequalities for young and middle-aged black Americans.

Among all ages combined, the cancer death rate in 2015 was 14% higher in non-Hispanic blacks than in non-Hispanic whites, down from a peak of 33% in 1993.

However, while the gap narrowed to 7% in those 65 or older, likely in part due to universal health care access for seniors through Medicare, mortality rates were 31% higher in blacks than in whites under 65, with much larger disparities in many states.

While the new report also finds that death rates were not statistically significantly different between whites and blacks in 13 states, a lack of racial disparity is not always indicative of progress.

For example, cancer death rates in Kentucky and West Virginia were not statistically different by race, but are the highest of all states for whites.

Other highlights from the report:

- ***The overall estimate of 1,735,350 cases for 2018 equals more than 4,700 new cancer diagnoses each day.***

- ***Prostate, lung, and colorectal cancers account for 42% of all cases in men, with prostate cancer alone accounting for almost one in five new diagnoses.***
- ***For women, the three most common cancers are breast, lung, and colorectal, which collectively represent one-half of all cases; breast cancer alone accounts for 30% all new cancer diagnoses in women.***
- ***The most common causes of cancer death are lung, prostate, and colorectal cancers in men and lung, breast, and colorectal cancers in women. These four cancers account for 45% of all cancer deaths, with one in four cancer deaths from lung cancer.***
- ***The lifetime probability of being diagnosed with cancer is slightly higher for men (39.7%) than for women (37.6%). Adult height has been estimated to account for one-third of the difference.***
- ***Liver cancer incidence continues to increase rapidly in women, but appears to be plateauing in men. The long-term, rapid rise in melanoma incidence appears to be slowing, particularly among younger age groups. Incidence rates for thyroid cancer also may have begun to stabilize in recent years, particularly among whites, in the wake of changes in clinical practice guidelines.***
- ***The decline in cancer mortality, which is larger in men (32% since 1990) than in women (23% since 1991), translates to approximately 2,378,600 fewer cancer deaths (1,639,100 in men and 739,500 in women) than what would have occurred if peak rates had persisted.***

"This new report reiterates where cancer control efforts have worked, particularly the impact of tobacco control," said Otis W. Brawley, M.D., chief medical officer of the American Cancer Society.

"A decline in consumption of cigarettes is credited with being the most important factor in the drop in cancer death rates. Strikingly though, tobacco remains by far the leading cause of cancer deaths today, responsible for nearly three in ten cancer deaths."

Citation: Cancer Statistics, 2018, CA Cancer J Clin 2018; 10.3322/caac.21442
URL upon publication: http://onlinelibrary.wiley.com/doi/10.3322/caac.21442/full

http://go.nature.com/2FccVZB

A dark side to omega-3 fatty acids

The molecule 19,20-dihydroxydocosapentaenoic acid, formed by the metabolism of a fatty acid involved in normal brain function, promotes the development of a diabetes-associated form of blindness in a mouse model.

Keisuke Yanagida & Timothy Hla

Diabetes can have many dangerous complications, including the progressive deterioration of blood vessels in the retina, which can lead to visual impairment. Despite the fact that this condition, called diabetic retinopathy, is a major cause of blindness in middle age, the pathways that mediate its development and progression are poorly understood. In a paper online in *Nature*, Hu *et al.*[1] report that a derivative of the omega-3 fatty acid docosahexaenoic acid (DHA) has a role in diabetic retinopathy.

Dietary intake of DHA is associated with several health benefits, including normal brain and eye function[2]. Moreover, mice that lack the protein Mfsd2a, which transports DHA across the blood–brain barrier into the brain, develop severe retinal and brain dysfunction[3–5]. Omega-3 fatty acids such as DHA have key functions in cell membranes, where they provide membrane fluidity and flexibility, and promote the membranes' role as barriers, allowing the selective transport of molecules into and out of cells[6].

In addition, omega-3 fatty acids can have signalling roles. DHA is highly susceptible to oxidation, producing 'lipid mediator' molecules that can regulate cell–cell signalling — for instance, to orchestrate the return to normal conditions following an inflammatory reaction[7]. One class of lipid mediator produced by DHA oxidation is epoxide molecules. These metabolites are rapidly degraded by the enzyme soluble epoxide hydrolase (sEH) to form dihydroxy derivatives such as 19,20-dihydroxydocosapentaenoic acid (19,20-DHDP)[8]. Indeed, 19,20-DHDP is the major product of DHA metabolism in the retina[9].

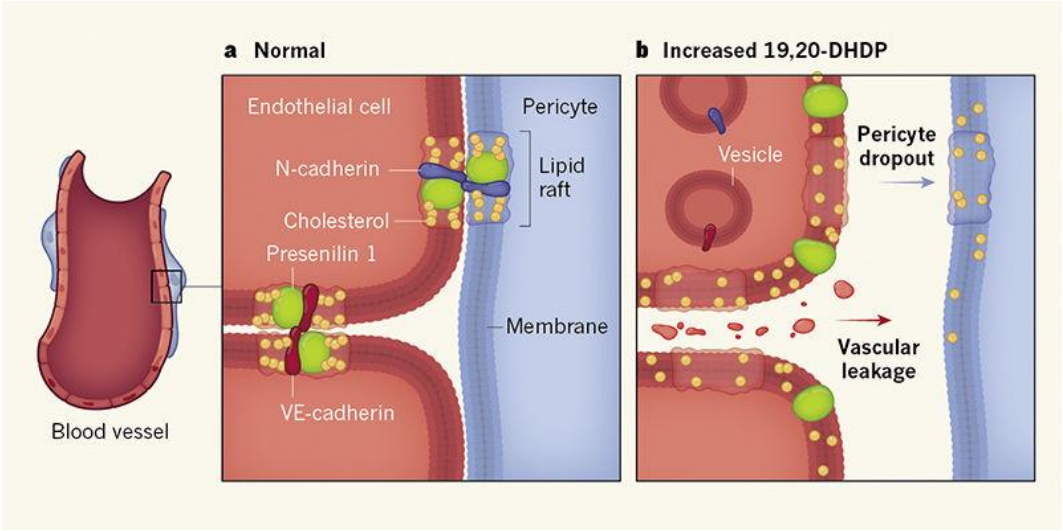
Given that DHA and epoxide metabolites are associated with beneficial retinal effects, might sEH play a part in diabetic retinopathy by reducing the levels of these molecules? Hu *et al.* set out to examine this possibility using a mouse model of the disease. They found that increases in sEH expression in Müller glia cells (which support neuronal function in the retina) correlated with the onset of several early signs of diabetic retinopathy. Such changes included: the degeneration of pericyte cells, which wrap around and provide support for the endothelial cells that make up the blood-vessel wall; an increase in the number of acellular capillaries, which have abnormal transport and barrier properties; and leakage of plasma out of vessels into the surrounding retinal tissue. These defects eventually lead to poor circulation in the retina, abnormal and uncontrolled blood-vessel formation, retinal bleeding and visual impairment[10].

Importantly, the authors demonstrated that pharmacological inhibition of sEH or genetic suppression of the gene encoding sEH prevented these pathological events, suggesting that sEH has a causal role in diabetic retinopathy. How might it exert these effects? Hu and colleagues showed that it is the production of 19,20-DHDP, rather than the reduction in DHA or epoxide molecules, that is the key trigger of vascular degeneration.

Next, the group found that the mechanism of pathogenesis involves interactions between three proteins — presenilin 1, vascular endothelial (VE)-cadherin and neural (N)-cadherin. The two cadherins are an essential part of protein complexes called adherens junctions, which anchor cell–cell adhesion sites on cell surfaces to the cell interior. VE-cadherin is found at junctions between pairs of endothelial cells, and N-cadherin is located at junctions between endothelial cells and pericytes.

The authors showed that presenilin 1 and the cadherins associated with cholesterol in clusters called lipid rafts in cell membranes (Fig. 1a). However, increased levels of 19,20-DHDP altered the biophysical properties of membranes, leading to decreased interactions between presenilin 1 and cadherins in lipid rafts, presumably by changing the distribution of cholesterol[9] (Fig. 1b). This, in turn, led to internalization of cadherins into the cell, disrupting adherens junctions. Ultimately, this process weakened cell–cell adhesion, causing pericyte 'dropout' from the blood vessel and breaching of the vascular barrier.

Figure 1 | Abnormal lipid dynamics in diabetic retinopathy. Hu et al.[1] have shown that increases in levels of the molecule 19,20-DHDP promote the development and progression of a form of visual impairment called diabetic retinopathy in mice. a, Under normal conditions, the endothelial cells that line



blood vessels in the retina are connected to one another and to supporting cells called pericytes through adhesion molecules known as cadherins in cell membranes. These connections rely on associations between the cadherins and the protein presenilin 1, which are, in turn, facilitated by clustering of cholesterol on 'lipid rafts'. b, The authors show that, during the early stages of diabetic retinopathy, increases in 19,20-DHDP in cell membranes (not shown) alter the distribution of presenilin 1, perhaps by disrupting the distribution of cholesterol molecules. Presenilin 1, no longer restrained to lipid rafts, does not associate with cadherins, leading to cadherin internalization in vesicles. This destabilizes cell–cell contacts, resulting in pericyte 'dropout' from around vessels, and vascular leakage.

Together, Hu and colleagues' results indicate that 19,20-DHDP acts through a different mechanism from that of another player in retinopathy — vascular endothelial growth factor (VEGF). This protein is induced under low-oxygen conditions and acts through receptors on vascular endothelial cells to induce proliferation, resulting in fragile new blood vessels prone to bleeding. Furthermore, the authors demonstrated that overexpression of sEH in the retinas of wild-type mice led to increased levels of 19,20-DHDP, vascular leakage and pericyte dropout, suggesting that sEH activation alone is sufficient to induce retinal-vessel defects, without VEGF-mediated mechanisms. Inhibiting VEGF halts the progression of diabetic retinopathy[10] and that of another vision disorder caused by changes in retinal blood vessels: wet age-related macular degeneration[11]. But not all patients respond to anti-VEGF therapy, and those who do often become insensitive to treatment over time, making Hu and colleagues' discovery of an alternative pathway valuable.

Previous work[12] has shown that a different lipid mediator that acts on endothelial cells, the molecule sphingosine 1-phosphate, induces the formation of adherens junctions and promotes the development of blood vessels. Hu and colleagues' newly discovered role for omega-3 derivatives thus adds to the list of crucial lipid signalling pathways known to be involved in retinal vascular diseases. It is possible that both pathways could be targeted therapeutically.

Hu and co-workers' study raises interesting avenues for future research. First, what triggers increases in sEH production in diabetic retinopathy? Dysregulated metabolic control of blood glucose can cause oxidative stress (an inability to deal with free radicals produced during metabolism) in the retina, which might be a key factor. However, a molecular mechanism by which this could lead to increased sEH remains to be elucidated. Second, it is unclear how 19,20-DHDP is transported from Müller glia cells to endothelial cells or pericytes. The apparent specificity of 19,20-DHDP among all omega-3 fatty acid derivatives as a mediator of diabetic retinopathy is also not understood at the molecular level. Perhaps 19,20-DHDP relies on specific targets, such as particular cell-surface or nuclear receptors, for its functions. Such targets could be a part of separate pathways to the membrane-lipid effects uncovered by the authors

In summary, Hu and colleagues' findings suggest that the metabolism of DHA to 19,20-DHDP by sEH is one of the key regulatory systems that disrupt endothelial junctions at the blood–retinal barrier. The authors' work might help to guide the development of therapeutic approaches that block the activity of sEH to control diabetic retinopathy and wet age-related macular degeneration. The study might even point to ways of treating neurological disorders, including stroke and neurodegenerative diseases, that are characterized by a compromised blood–brain barrier — similar mechanisms might be expected to operate in these diseases.

Read the paper: Inhibition of soluble epoxide hydrolase prevents diabetic retinopathy

http://bbc.in/2m8w4mn

Sharp rise in flu hospital admissions in England

There was a sharp rise in hospital admissions in England for confirmed flu cases in the last week of December, Public Health England figures show.

There were 114 admissions to intensive care with confirmed flu and a further 421 people admitted to general wards - up from 61 and 66 the week before. Prof Paul Cosford, medical director at PHE, said the rises were "significant" but not unexpected. And he said it was still not too late to be vaccinated.

Adults aged over 65, pregnant women and those with underlying health conditions are advised to get a free flu jab. A flu nasal spray is available free to children aged two to eight, who are thought to be the main spreaders of flu. NHS bosses had previously warned of a bad flu season in the UK after Australia experienced its worst flu season for a number of years during their winter.

But Prof Cosford said it was too early to say exactly how severe the flu season would be this year. "Our data shows that more people are

visiting GPs with flu symptoms and we are seeing more people admitted to hospitals with the flu. "This is contributing to the pressure that we see the NHS under."

He said there were simple steps people could take to help prevent flu spreading. "People suffering with flu-like symptoms should catch coughs or sneezes in tissues and bin them immediately, wash their hands regularly with soap and warm water and frequently clean regularly-used surfaces to stop the spread of flu. "Avoid having unnecessary contact with other people if you or they have symptoms of flu."

The PHE figures show there was also a rise in the number of reported flu-like cases seen by GPs. Because of bank holidays, GP surgeries were open for three days in the last week of December, but in this period the consultation rate was 21 per 100,000 in England, compared to 18.9 per 100,000 the previous week. This is above the baseline level of 13.1 per 100,000 but still classed as "low". In the last severe flu outbreak in 2010-11 the consultation rate rose to more than 120 per 100,000.

How do I know if I have flu?	**Symptoms can include:**
a sudden fever - a temperature of 38C or above	***aching body***
feeling tired or exhausted	***dry, chesty cough***
sore throat	***headache***
difficulty sleeping	***loss of appetite***
diarrhoea or tummy pain	***nausea and being sick***
	Source: NHS Choices

Increases in GP consultation rates for flu were also seen across the UK, with rates in Scotland increasing the most.

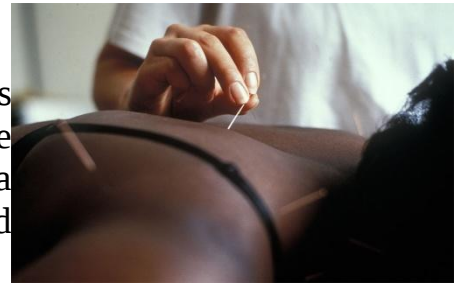
Data from Health Protection Scotland shows that the number of people suffering from flu in Scotland has more than doubled compared to the same time last year. Early tests suggest that just over half of the circulating strains of flu match those in the 2017/18 vaccine, the Scottish government said.

http://go.nature.com/2AFcm7b

Acupuncture in cancer study reignites debate about controversial technique

Large study suggests acupuncture could help women stick with unpleasant cancer treatments.

Jo Marchant



One of the largest-ever clinical trials into whether acupuncture can relieve pain in cancer patients has reignited a debate over the role of this contested technique in cancer care.

Acupuncture may be effective in easing pain for people with breast cancer, according to results from a large, multi-site trial. **UIG via Getty**

Oncologists who conducted a trial of real and sham acupuncture in 226 women at 11 different cancer centres across the United States say their results — presented on 7 December at the San Antonio Breast Cancer Symposium in Texas — conclude that the treatment significantly reduces pain in women receiving hormone therapy for breast cancer. They suggest it could help patients stick to life-saving cancer treatments, potentially improving survival rates. But sceptics say it is almost impossible to conduct completely rigorous double-blinded trials of acupuncture.

Interest in acupuncture has grown because of concerns over the use of opioid-based pain-relief drugs, which can have nasty side effects and are extremely addictive. Many cancer centres in the United States therefore offer complementary therapies for pain relief. Almost 90% of US National Cancer Institute-designated cancer centres suggest that patients try acupuncture, and just over 70% offer it as a treatment for side effects[1]. That horrifies sceptics such as Steven Novella, a neurologist at Yale University School of Medicine and founder of the blog Science-Based Medicine. Acupuncture has no scientific basis, he says; recommending it is “telling patients that magic works”.

But Dawn Hershman, an oncologist at Columbia University Medical Centre in New York City, decided to investigate whether acupuncture could help to reduce the pain caused by aromatase inhibitors, one of the most commonly used treatments for breast cancer. These drugs lower oestrogen levels and, when taken over five to ten years, they reduce the risk that the cancer will recur. But they cause side effects, especially arthritis-like pain, which can cause up to half of women to take the medication irregularly, or to stop taking it altogether.

Meaningful relief

After a small trial at Columbia showed positive results[2], Hershman and her colleagues conducted a larger one. The 226 women were placed into one of three groups: one that received acupuncture; another that got a sham treatment in which needles were inserted at non-acupuncture points, less deeply into the skin; and a third that received no treatment. The researchers trained the acupuncturists to deliver consistent treatments[3]. The women were asked to record their pain levels.

After a six-week course of treatment, 'worst pain' in the true-acupuncture group was about one point lower on a scale from zero to ten than in either the sham or no-treatment groups. This is a statistically significant effect, and larger than is seen with alternatives such as duloxetine, an antidepressant used to help reduce pain in people with cancer[4]. Meanwhile, the percentage of participants whose pain improved by at least two points (which Hershman describes as a "clinically meaningful" change) almost doubled, from around 30% in both control groups to 58% in the true-acupuncture group. Unlike with duloxetine, the benefits persisted after the acupuncture course had finished. Hershman concludes that acupuncture is a "reasonable alternative" to prescription medications such as duloxetine or opiates, neither of which were part of this study.

Rollin Gallagher, director of pain-policy research at the University of Pennsylvania in Philadelphia, and editor-in-chief of the journal *Pain Medicine*, welcomes the trial. "These are careful methodologists," he says. "There is moderate to good evidence in clinical trials for acupuncture now, and this is another contribution."

Placebo effect?

But sceptics have criticized the research. Regardless of how rigorous the trial was in other respects, the acupuncturists knew whether they were delivering real or sham treatment, says Edzard Ernst, emeritus professor of complementary medicine at the University of Exeter, UK. This could have influenced how the recipients responded, he says. "I fear that this is yet another trial suggesting that acupuncture is a 'theatrical placebo'."

But Jun Mao, chief of integrative medicine at the Memorial Sloan Kettering Cancer Centre in New York City, says that acupuncture trials such as Hershman's are better blinded than studies of approaches such as palliative care, cognitive behavioural therapy or exercise, in which participants inevitably know what treatment they are receiving. Sceptics "accept trial results from those fields readily, but they make a special case against acupuncture", he says. "It's not fair to use that single argument to shut down the whole field."

Gallagher says that many studies suggest that acupuncture triggers neurophysiological changes that are relevant to pain, in conditions from carpal tunnel syndrome to fibromyalgia[5]. Integrating acupuncture into mainstream medical care, rather than outsourcing it to independent, and perhaps unregulated, acupuncturists, minimizes the risk of lending authority to unscientific practitioners, he says. "That's why we need to bring it in."

For Hershman, the sceptics' concerns risk losing sight of what's best for patients. "To say that something that is pharmacologic is better, when it causes horrible toxicities, is also problematic," she says. With acupuncture, "we tried to do the most rigorous study we could. At the end of the day, if it keeps somebody on their medication or improves the quality of their life, then it's worth it."

doi: 10.1038/d41586-017-08309-y

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http://bit.ly/2qHiv2Z

A nonaddictive opioid painkiller with no side effects

What if scientists could develop an opioid-based painkiller that is not addictive and has limited side effects?

That is possible based on new findings by an international team of scientists that included contributions from top researchers at the USC Michelson Center for Convergent Bioscience.

The international team captured the crystal structure of the kappa opioid receptor—critical for providing pain relief—in action on the surface of human brain cells. The researchers also made another important discovery: a new opioid-based compound that, unlike current opioids, activates only the kappa opioid receptor, raising hopes that they may develop a painkiller that has no risk of addiction and, therefore, none of the devastating consequences and side effects that accompany it.

The findings were published Jan. 4 in the journal *Cell*. They are an example of how USC Michelson Center scientists collaborate with a range of experts in multiple disciplines to conduct groundbreaking research, including the opioid addiction.

First, do no harm

The current challenge facing scientists in drug research and development is twofold: develop new alternatives to ease pain while minimizing side effects. Amid an opioid addiction crisis, this is a tall order, and it is urgent. More than 1 in 10 Americans suffer chronic pain, according to the National Institutes of Health. At the same time, millions of Americans are addicted to opioids.

Captained by researchers at the University of North Carolina at Chapel Hill, the team of 24 scientists on this latest study included three USC Michelson Center scientists who are among the most-recognized names in research on the special receptors found on the surface of the neuron: Raymond C. Stevens, Vadim Cherezov and Vsevolod "Seva" Katritch. All three are affiliated with the USC Dornsife College of Letters, Arts and Sciences.

The G protein-coupled receptors, found on the surface of the membrane, are the gatekeepers of communication with cells and are therefore the intended target of most therapeutics. The solution to pain, disease and other conditions begins with understanding—and seeing very clearly—the structure of the receptors when they are inactive and when they are active, interacting with a drug compound.

Typically, scientists determine the structure of receptors by forcing the proteins into a crystal lattice that they then expose to X-rays. Essentially, they want to create an accurate model of the receptor when it does and does not interact with a drug compound.

However, these G protein-coupled receptors are challenging to capture in a stabilized state with traditional X-ray crystallography. Like ill-behaving toddlers, they are highly dynamic, move frequently and very fragile. That is why Stevens, Cherezov and Katritch developed some breakthrough techniques for this special class of proteins that have led to more accurate crystallography.

At a cellular level, their work has led to a greater understanding of the receptors and their behaviors. From a holistic perspective, their research is explaining how humans respond to drugs. Furthermore, they have set the foundation for a new wave of therapeutics that are much more precisely targeted than their predecessors to address illnesses and conditions with fewer unintended side effects.

The power of three

Stevens is a molecular biologist and chemist hailed as a pioneer in solving the structures of G protein-coupled receptors. He developed a method of experimenting known as "high-throughput crystallography" in structural biology, which uses robotics, data processing and management software, as well as liquid handling devices and detectors to conduct millions of tests.

Cherezov is a structural biologist who developed new ways to herd capricious membrane proteins like the G protein-coupled receptors into well-behaved crystals. He uses lipids similar to those found in cell membranes to form a special "cubic phase." This technique ensures that the receptors behave as if they had never left their home on the membrane, even as they form crystals.

The Lipidic Cubic Phase technology has been successfully applied to a majority of the GPCRs that have been solved, including the previous kappa opioid receptor structure in its inactive state, according to Cherezov. By adding a stabilizing nanobody, the researchers are able to capture the structure in a fully active state, he said.

Katritch, a biophysicist and computational biologist, has developed computer models of receptor interactions with ligands that activate or inactivate receptors. This allows scientists to quickly test the receptor interactions with millions of ligands in a virtual lab—his computer—so that they may select the molecules that have the most beneficial therapeutic properties for more testing.

In the case of the kappa opioid receptor, his computer analyses enabled the scientists to modify the chemistry of the ligands so that eventually they developed ligands that affected only the kappa opioid receptor.

Currently, most opioids bind to several opioid receptors on the membrane of brain cells, which has its share of drawbacks. They alleviate pain but cause a range of side effects, from nausea to numbness, constipation, anxiety, severe dependency, hallucinations and even death by respiratory depression.

In this study, the computer models revealed the formulations that would create the strongest bond between the ligand and the kappa opioid receptor without affecting other receptors.

Katritch said the latest research may pave the way for a major drug breakthrough.

"We have already found the structure of the inactive kappa opioid receptor highly useful for discovering potential candidates for a new painkiller," Katritch said. "Now with the structure of the active receptor, we have a template for designing new types of pain medications that have no disruptive side effects for patients and would reduce the burden that opioid addiction has placed on society."

More information: *Tao Che et al. Structure of the Nanobody-Stabilized Active State of the Kappa Opioid Receptor, Cell (2018). DOI: 10.1016/j.cell.2017.12.011*

Read more at: https://phys.org/news/2018-01-nonaddictive-opioid-painkiller-side-effects.html#jCp

http://bit.ly/2Fei5Ex

Immune response to Zika virus contributes to fetal harm

***The same proteins that mount a potent immune response to Zika viral infection can also harm the placenta and fetal development, according to a Yale-led study published in* Science Immunology.**

New Haven, Conn. - Zika researchers had established that these antiviral proteins, known as type I interferons, were required to fight Zika infection in mothers. But it was not clear what role interferons played in providing an immune defense for the fetus.

To investigate, the team led by immunobiologist Akiko Iwasaki studied two different types of mouse models. One type lacked the receptor for type 1 interferon altogether, and the other had only one copy of the interferon receptor gene. Only the latter showed signs of abnormal placental development, restricted fetal growth and death, the researchers said.

The finding demonstrates that the damaging effects of the immune response to Zika virus can outweigh the benefits for fetuses, said the researchers, noting that although type 1 interferon is critical to blocking replication of the virus, too much of it can be detrimental during pregnancy. The study results may have implications for other infection-related pregnancy complications and possible interventions.

Other authors are Laura J. Yockey, Kellie A. Jurado, Nitin Arora, Alon Millet, Tasfia Rakib, Kristin M. Milano, Andrew K. Hastings, Erol Fikrig, Yong Kong, Tamas L. Horvath, Scott Weatherbee, Harvey J. Kliman, and Carolyn B. Coyne.

This study was supported in part by the National Institutes of Health.

For a copy of the paper, please contact immunopak@aaas.org.

http://bit.ly/2D6Li3C

Scientists uncover why sauna bathing is good for your health

Over the past couple of years, scientists at the University of Eastern Finland have shown that sauna bathing is associated with a variety of health benefits.

Using an experimental setting this time, the research group now investigated the physiological mechanisms through which the heat exposure of sauna may influence a person's health. Their latest study with 100 test subjects shows that taking a sauna bath of 30 minutes reduces blood pressure and increases vascular compliance, while also increasing heart rate similarly to medium-intensity exercise.

Previously, the research group has published findings from a population-based study indicating that regular sauna bathing is associated with a reduced risk of coronary diseases and sudden cardiac death1, hypertension2 and Alzheimer's disease and dementia3. Frequent sauna bathing has also been associated with a reduced disk of respiratory diseases4 and lower CRP levels5.

The experimental study carried out in the Sauna and Cardiovascular Health project provides new insight into changes that take place in the human body during and after having a sauna. The study analysed the effects of a 30-minute sauna bath in 100 test subjects. In particular, the objective was to analyse the role of vascular compliance and reduced blood pressure in the health benefits caused by sauna bathing.

Vascular compliance was measured from the carotid and femoral artery before sauna, immediately after sauna, and after 30 minutes of recovery. These vascular compliance measurements carried out in the experimental study constitute a new assessment method in a sauna setting.

Immediately after 30 minutes of sauna bathing, test subjects' mean systolic blood pressure reduced from 137 mmHg to 130 mmHg, and their diastolic blood pressure from 82 mmHg to 75 mmHg. Furthermore, their systolic blood pressure remained lower even after 30 minutes of sauna bathing. Test subjects' mean carotid-femoral pulse wave velocity, which is an indicator of vascular compliance, was 9.8 m/s before sauna, decreasing to 8.6 m/s immediately after. During sauna bathing, test subjects' heart rate increased similarly to medium-intensity exercise, and their body temperature rose by approximately 2°C. The findings shed light on the physiological mechanisms through which health benefits, which have been observed at the population level and are caused by the heat exposure of sauna, may develop.

The findings on the effects of sauna bathing on the human body were published in the *Journal of Human Hypertension*, and the findings relating to the carotid-femoral pulse wave velocity measurements were published in the European Journal of Preventive Cardiology. The study was funded by the Finnish Funding Agency for Innovation, Tekes, and it was carried out by Professor Jari Laukkanen's research group at the University of Eastern Finland. The project partners were Harvia Ltd., Velha Ltd., Pihlajalinna, Fintravel Ltd. and the Finnish Sauna Culture Association. The test subjects were 100 clients of the Pihlajalinna health care service provider. Their background information was collected by extensive surveys and interviews, and their physical health was measured by a clinical exercise test. The study was carried out in experimental saunas provided by the sauna stove and sauna heater manufacturer Harvia Ltd. The experimental sauna setting was a careful simulation of the way people in Finland take a sauna in their own homes.

Research indicates that regular physical exercise and a healthy lifestyle promote cardiac health and prevent disease, but not all of the risk and protective factors are yet known. The benefits of regular sauna bathing on cardiac health observed in the population-based study can, according to this experimental study, be explained by the fact that sauna bathing reduces blood pressure and increases vascular compliance. However, further research data from experimental

settings relating to the physiological mechanisms of sauna bathing that promote cardiac health is still needed.

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Original articles relating to the experimental study: *Journal of Human Hypertension*
http://www.nature.com/articles/s41371-017-0008-z doi:10.1038/s41371-017-0008-z
European Journal of Preventive Cardiology
http://journals.sagepub.com/doi/abs/10.1177/2047487317737629

http://bit.ly/2CG8AfH

Repeated influenza vaccination helps prevent severe flu in older adults

Repeated vaccination for influenza in older adults reduced the severity of the virus and reduced hospital admissions, found new research published in CMAJ (Canadian Medical Association Journal)

A team of Spanish researchers looked at the effect of repeated influenza vaccinations in the current and 3 previous seasons in people aged 65 years and older admitted to 20 Spanish hospitals in 2013/14 and 2014/15 to determine whether repeat vaccination reduced severe influenza.

They found repeated influenza vaccination was twice as effective in preventing severe influenza in people admitted to hospital for the virus, compared with nonsevere cases, and that this effect was consistent regardless of flu season, virus subtypes or age of patient.

"Repeated vaccination for influenza was highly effective in preventing severe and fatal infection caused by influenza in older adults," write Dr. Itziar Casado and Dr. Jesús Castilla, Instituto de Salud Pública de Navarra, Pamplona, Spain, with coauthors.

The study adds to findings from previous research that shows influenza vaccination reduces severity of the illness.

"Because severe cases of influenza may be prevented by 2 mechanisms, the effectiveness of vaccination against severe influenza may be greater than that for mild cases, and the benefit of influenza vaccination may be greater than that estimated in previous studies. The prevention of severe and fatal infection caused by influenza was observed mainly in patients who were vaccinated in both the current and previous seasons, which reinforces the recommendation of annual vaccination for influenza in older adults," the authors conclude.

http://bit.ly/2CEVcZ2

Middle-aged couch potatoes may reverse heart effects of a sedentary life with exercise training

Two years of regular aerobic exercise training may reduce or reverse the risk of heart failure associated with years of sitting

DALLAS - Middle-aged couch potatoes may reduce or reverse the risk of heart failure associated with years of sitting if they participate in two years of regular aerobic exercise training, according to a new study in the American Heart Association's journal *Circulation*.

Study participants who adhered to the aerobic exercise regimen had significant improvements in how their body used oxygen and had decreased cardiac stiffness after two years, both markers of a healthier heart.

Aerobic exercises are sustained activities, such as walking, swimming, running and others that strengthen the heart and other muscles and help the body use oxygen effectively.

"The key to a healthier heart in middle age is the right dose of exercise, at the right time in life," said study author Benjamin D. Levine, M.D., lead author of the study and the founder and director of the Institute for Exercise and Environmental Medicine, a joint program between Texas Health Resources and UT Southwestern Medical Center Dallas, Texas.

"We found what we believe to be the optimal dose of the right kind of exercise, which is four to five times a week, and the 'sweet spot' in time, when the heart risk from a lifetime of sedentary behavior can be improved -- which is late-middle age. The result was a reversal of decades of a sedentary lifestyle on the heart for most of the study participants," he said.

The researchers analyzed the hearts of 53 adults ages 45-64 who were healthy but sedentary at the start of the study - meaning they tended to sit most of the time.

Study participants received either two years of training, including high- and moderate-intensity aerobic exercise four or more days a week (exercise group), or they were assigned to a control group, which engaged in regular yoga, balance training and weight training three times a week for two years.

The exercise group committed to a progressive exercise program which monitored participants' recorded heart rates. People in this group worked up to doing exercises, such as four-by-fours -4 sets of four minutes of exercise at 95 percent of their maximum heart rate, followed by three minutes of active recovery at 60 percent to 75 percent peak heart rate.

In this study, maximum heart rate was defined as the hardest a person could exercise and still complete the four-minute interval. Active recovery heart rate is the speed at which the heart beats after exercise.

They found:

- ***Overall, the committed exercise intervention made people fitter, increasing VO2max, the maximum amount of energy used during exercise, by 18 percent. There was no improvement in oxygen uptake in the control group.***
- ***The committed exercise program also notably decreased cardiac stiffness. There was no change in cardiac stiffness among the controls.***

Sedentary behaviors - such as sitting or reclining for long periods of time - increase the risk of the heart muscle shrinking and stiffening in late-middle age and increases heart failure risk.

Previous studies have shown that elite athletes, who spent a lifetime doing high-intensity exercise, had significantly fewer effects of aging on the heart and blood vessels, according to Levine.

However, the six to seven days a week of intense exercise training that many elite athletes perform throughout their life isn't a reality for many middle-aged adults, which led Levine and colleagues to study different exercise doses, including casual exercise at two to three days a week and "committed exercise" at four to five days a week.

"We found that exercising only two or three times a week didn't do much to protect the heart against aging. But committed exercise four to five times a week was almost as effective at preventing sedentary heart aging as the more extreme exercise of elite athletes," he said. "We've also found that the 'sweet spot' in life to get off the couch and start exercising is in late-middle age, when the heart still has plasticity."

People need to make an exercise program part of their personal routine, just like they brush their teeth every day, according to Levine. "I recommend that people do four to five days a week of committed exercise as part of their goals in preserving their health," he said.

The program, according to Levine, should be similar to the one studied, including at least one long session a week, (such as an hour of tennis, cycling, running, dancing, brisk walking, etc.); one high-intensity aerobic session, such as the four-by-four interval training described previously; two or three days a week of moderate intensity exercise, where exercisers break a sweat but can still carry on a conversation; and at least one weekly strength training session.

"That's my prescription for life, and this study really reinforces that it has quite extraordinary effects on the structure and function of the heart and blood vessels," he said.

One of the study's limitations is the researchers selected volunteers who were willing and able to participate in an intensive exercise regimen, so results might not apply to the general adult population. Another potential limitation is that study participants were for the most part Caucasian, which questions whether these results would apply to other racial groups.

Co-authors are Erin Howden, Ph.D.; Sarma Satyam, M.D.; Justin Lawley, Ph.D.; William Cornwell, M.D.; Douglas Stoller, M.D.; Marcus Urey, M.D.; and Beverley Adams-Huet, M.S. Author disclosures are on the manuscript.

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http://bit.ly/2m8CuSr

Chemists discover plausible recipe for early life on Earth

Chemists at The Scripps Research Institute (TSRI) have developed a fascinating new theory for how life on Earth may have begun.

LA JOLLA, CA - Their experiments, described today in the journal *Nature Communications*, demonstrate that key chemical reactions that support life today could have been carried out with ingredients likely present on the planet four billion years ago.

"This was a black box for us," said Ramanarayanan Krishnamurthy, PhD, associate professor of chemistry at TSRI and senior author of the new study. "But if you focus on the chemistry, the questions of origins of life become less daunting."

For the new study, Krishnamurthy and his coauthors, who are all members of the National Science Foundation/National Aeronautics and Space Administration Center for Chemical Evolution, focused on a series of chemical reactions that make up what researchers refer to as the citric acid cycle.

Every aerobic organism, from flamingoes to fungi, relies on the citric acid cycle to release stored energy in cells. In previous studies, researchers imagined early life using the same molecules for the citric acid cycle as life uses today. The problem with that approach, Krishnamurthy explains, is that these biological molecules are fragile and the chemical reactions used in the cycle would not have existed in the first billion years of Earth--the ingredients simply didn't exist yet.

Leaders of the new study started with the chemical reactions first. They wrote the recipe and then determined which molecules present on early Earth could have worked as ingredients.

The new study outlines how two non-biological cycles--called the HKG cycle and the malonate cycle--could have come together to kick-start a crude version of the citric acid cycle. The two cycles use reactions that perform the same fundamental chemistry of a-ketoacids and b-ketoacids as in the citric acid cycle. These shared reactions include aldol additions, which bring new source molecules into the cycles, as well as beta and oxidative decarboxylations, which release the molecules as carbon dioxide (CO_2).

As they ran these reactions, the researchers found they could produce amino acids in addition to CO2, which are also the end products of the citric acid cycle. The researchers think that as biological molecules like enzymes became available, they could have led to the replacement of non-biological molecules in these fundamental reactions to make them more elaborate and efficient.

"The chemistry could have stayed the same over time, it was just the nature of the molecules that changed," says Krishnamurthy. "The molecules evolved to be more complicated over time based on what biology needed."

"Modern metabolism has a precursor, a template, that was non-biological," adds Greg Springsteen, PhD, first author of the new study and associate professor of chemistry at Furman University.

Making these reactions even more plausible is the fact that at the center of these reactions is a molecule called glyoxylate, which studies show could have been available on early Earth and is part of the citric acid cycle today (called the "Glyoxylate shunt or cycle").

Krishnamurthy says more research needs to be done to see how these chemical reactions could have become as sustainable as the citric acid cycle is today.

In addition to Krishnamurthy and Springsteen, authors of the study, "Linked Cycles of Oxidative Decarboxylation of Glyoxylate as Protometabolic Analogs of the Citric Acid Cycle," were Jayasudhan Reddy Yerabolu of The Scripps Research Institute and the National Science Foundation (NSF)/National Aeronautics and Space Administration (NASA) Center for Chemical Evolution; and Julia Nelson and Chandler Joel Rhea of Furman University.

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