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Recovering from a heart attack? Hold the antibiotics

A healthy gut microbiome is important for recovery after a heart attack

MADISON - The community of microorganisms that live in the human gut has been shown to confer all kinds of health benefits. Now, an international team of researchers has shown in mice that a healthy gut microbiome is important for recovery after a heart attack.

Writing today (Oct. 8, 2018) in the journal *Circulation*, a team led by surgeon Patrick Hsieh of the Institute of Biomedical Sciences at Academia Sinica in Taipei, Taiwan, in collaboration with researchers from the University of Wisconsin-Madison, reports on experiments that show mice recovering from heart attacks are more likely to die if treated with antibiotics, a common intervention in hospitalized patients.

"This is a new thing to add to the list of potential complications" for recovery from a heart attack, says Timothy Kamp, a UW-Madison professor of medicine and cardiologist who contributed to the new study.

It is common, Kamp explains, for hospitalized patients to be dosed with broad spectrum antibiotics to treat a variety of infections, and some of these patients have heart attacks. But antibiotics can be indiscriminate and eliminate not only bad microbial players, but also the microbes we depend on to stay healthy, including the trillions of fungi and bacteria that help make up the gut microbiome.

Working in collaboration with microbiome expert and UW-Madison Professor of Bacteriology Federico Rey, Hsieh and Kamp treated mice with antibiotics to deplete the gut microbiome a week prior to experimentally inducing myocardial infarction or heart attack.

The depleted microbiome, the team found, tamps down the production of a set of three short-chain fatty acids, which are produced as the gut's community of microorganism's metabolizes food and which act as important chemical messengers to the body's immune system. The diminished response, says Hsieh, "impacts the immune response and the repair response after myocardial infarction."

Conversely, when the mouse microbiome is restored through a fecal transplant, the researchers observed an uptick in mouse physiological well-being and survival. And in mice that had their microbiomes boosted through the use of probiotics or other interventions prior to a heart attack, increased cardioprotective effects and survival were the hallmark effects. Previous studies in healthy mice have shown that the microbiome influences gene expression and the deployment of the short-chain fatty acids that help regulate immune response.

The current study showed that production of a small set of short-chain fatty acids was diminished by a depleted microbiome, but there likely are many more players - perhaps thousands - that may also be affected and that play a role in the immune response to a heart attack, says Kamp.

The research also showed that heart attacks themselves influence the health of the microbiome: "We found changes after myocardial infarction even without any antibiotics," notes Rey. "Your microbiome changes as a result of a heart attack."

However, the key finding - that a depleted microbiome and its diminished production of short-chain fatty acids blunts recovery from a heart attack - suggests that clinical intervention to manipulate the microbiome through a more nuanced use of antibiotics and supplementing it with probiotics will help human patients recover faster and more robustly from heart attacks, says Kamp. He adds that the study also identifies the short-chain fatty acids themselves as a potential therapeutic target to bolster a favorable immune response in the context of cardiovascular disease, one of the leading causes of death in industrialized societies. "The immune system and inflammation play a role in repair from a heart attack. We've known

about the relationship between the microbiome and immune response. Now we're getting at how that relationship works after a heart attack."

The study was supported by a grant from the University of Wisconsin-Madison's Microbiome Initiative administered by the Office of the Vice Chancellor for Research and Graduate Education.

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Root extract of Chinese medicinal plant makes worms to live longer

Identification of molecular signalling pathways that could be responsible for the extract's effect

A root extract of the Fallopia multiflora, or Chinese knotweed, ツルドクダミ, 何首烏, has special properties: it enables the nematode *C. elegans* to live longer and protects it from oxidative stress. This has been demonstrated in a new study by nutritional scientists at Martin Luther University Halle-Wittenberg (MLU). The researchers provide scientifically substantiated evidence for the effectiveness of this extract, which is primarily used in traditional Chinese medicine and as a dietary supplement. At the same time, they have identified molecular signalling pathways that could be responsible for the extract's effect. Their study was recently published in the international scientific journal Plants.

The Chinese knotweed is very popular. Many suppliers sell extracts and powders of this plant as dietary supplements and advertise the rejuvenating and particularly health-promoting effect that the products supposedly possess. However only a handful of scientifically based studies have examined its effects. "Most studies have only focused on the primary active ingredient of the plant extract. But it actually contains many different substances whose combined efficacy has not yet been thoroughly researched," says nutritional scientist Professor Wim Wätjen from MLU. His research group has been studying the plant, its ingredients, and their possible effects for several years.

In the current study, the researchers from Halle examined whether the much-praised anti-ageing effects can actually be proven. They administered a high amount of the extract to the nematode *C. elegans*, a model organism frequently used in the bio- and life sciences. "Most earlier studies investigated the effects of the plant on isolated cells or in a test tube; we wanted to study it in a living organism," explains Wätjen. When the highest concentration was administered to the worms, 1,000 micrograms per millilitre, various effects were observed: The lifetime of the worms was extended by almost 19 per cent. For *C. elegans* this corresponds to an increase of about three days. In two further tests, the scientists investigated the extent to which the drug also protects the worms from oxidative stress or heat stress. Even though the extract did not improve the survival rate of worms in hot conditions, it was found to reduce the formation of harmful oxygen radicals and protect the animals significantly better against elevated oxidative stress.

In the next step the researchers repeated the tests with worms whose genetic material had been specifically altered at certain sites. This switched off special proteins that are critical for ageing. "If the genes responsible for producing the proteins DAF-16 or Sir-2.1 were defective, the positive effects of the root extract were also significantly lower," says Wätjen. A longer lifespan could only be observed if all proteins functioned properly. "This confirms that ageing is a complex process that depends on many factors," says Wätjen.

The results of the new study fit in well with previous studies: The primary component of the root extract is a substance that has a similar structure to resveratrol. "This substance is found in grapes, for example, and is known to activate a special class of enzymes

called sirtuins. These have long been considered the most important substances for controlling the body's ageing process," says Wätjen.

The new study provides clues on how plant-based ingredients intervene in basic mechanisms and signalling pathways of ageing which can serve as a basis for further research. However, the findings cannot be transferred directly to humans. Although the basic principles and signalling pathways in other organisms may be similar, says Wätjen, subsequent studies are needed to clarify whether the effects observed in *C. elegans* can also be demonstrated in other organisms. In the future researchers in Halle will investigate the protective effect the extract has on the development of plaques in Alzheimer's disease.

https://wb.md/2CbT8KT

Gout Drug May Protect Against Chronic Kidney Disease

***Allopurinol (multiple brands), used to manage gout, may protect against chronic kidney disease (CKD), according to results of a study published online October 8 in* JAMA Internal Medicine.**

Ricki Lewis, PhD

Only one third of patients with gout in the United States take urate-lowering medication. One factor that may contribute to the low rate is the high prevalence of comorbid CKD of stage 3 or higher and concern that the drugs could hasten kidney failure. CKD affects 20% of people with gout, compared with 5% of those who do not have gout.

The American College of Rheumatology has suggested that patients with advanced kidney disease and gout begin treatment with allopurinol at lower starting doses than other patients.

The precaution against use of the drug is largely due to concern about the possibility of allopurinol hypersensitivity syndrome affecting renal function.

In the current study, Ana Beatriz Vargas-Santos, MD, from the State University of Rio de Janeiro, in Brazil, and colleagues investigated whether allopurinol, at a dosage at or above 300 mg/day, is detrimental to renal function in patients with gout.

The team assessed the association of allopurinol use in gout with the risk of developing CKD of stage 3 or higher within a few years among a propensity score–matched prospective cohort composed of 4760 patients newly diagnosed with gout who were taking at least 300 mg/day of allopurinol and the same number of gout patients who were not taking the drug. The patients had been diagnosed from 2000 through 2014. The mean age of the patients was 57 years, and they had normal or near-normal kidney function at baseline.

Using data from the Health Improvement Network, an electronic health records database from general practitioners in the United Kingdom, the researchers found that 579 patients (12.2%) taking allopurinol developed CKD of stage 3 or higher within 5 years, compared with 623 patients (13.1%) in the group that did not receive the drug.

In an adjusted analysis, patients taking allopurinol had a 13% reduced risk of developing CKD of stage 3 or higher compared with those not taking the drug (propensity score-matched hazard ratio, .87; 95% confidence interval, 0.77 - 0.97).

The authors note that at the time of analysis, 70% of each group had stage 2 CKD, and the remainder had stage 1 disease.

They conclude that initiating allopurinol at a dosage of at least 300 mg/day to treat gout was not only safe but possibly protective against the development of CKD.

"Because allopurinol did not appear to be associated with renal function decline, clinicians should consider evaluating other factors when faced with renal function decline in their patients with gout rather than lowering the dose of or discontinuing allopurinol, a

strategy that has contributed to the ongoing suboptimal treatment of gout," they write.

"Ultimately, we hope these results will be disseminated to PCPs [primary care physicians] and internists taking care of patients with gout (since the bulk of patients with gout are managed in primary care) so that allopurinol is not held or stopped when a patient experiences a creatinine bump," said corresponding author and rheumatologist Tuhina Neogi, MD, PhD, professor of medicine and epidemiology at the Boston University School of Medicine and School of Public Health, in a news release,

In an invited commentary, Jonathan Zipursky, MD, and David N. Juurlink, MD, PhD, both from the University of Toronto, Canada, applaud the use of "real-world" observational studies to investigate the current practice of starting patients with gout and CKD on a lower dose of allopurinol. They note that the recommendation initially came from studies in which there was an overrepresentation of patients of Chinese ethnicity. Such patients are at higher risk for allopurinol hypersensitivity.

"The important message from this new study, however, is that allopurinol is unlikely to contribute to progression of CKD; indeed, it might even be protective, presumably by reducing the risk of urate nephropathy," the commentators conclude.

A limitation of the study is a surveillance bias arising from more frequent and extended monitoring of patients who were taking the drug compared to those who were not taking it; this possibly resulted in more rigorous examination of renal function.

Dr Vargas-Santos has received speaker's fees and support for international medical events from Grünenthal. The other investigators and the writers of the commentary have disclosed no relevant financial relationships.

JAMA Int Med. *Published online October 8, 2018.* *Full text*, *Commentary*

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Fields of five-story-high ice blades could complicate landing on Jupiter moon

A mission to explore Europa's ocean could be tricky

By Paul Voosen

Scientists have long wanted to explore Jupiter's frozen moon, Europa, which is home to a vast subsurface ocean that makes it a promising home for extraterrestrial life. Recently, that desire has gained prominent financial backing from the U.S. Congress, which has directed NASA to start to build a robotic lander to follow the Europa Clipper, which will chart the moon from above.

But such a mission could be tricky.

Probes have shown that Europa's ice-bound surface is riven with fractures and ridges, and new work published today in *Nature Geosciences* suggests any robotic lander could face a nasty surprise, in the form of vast fields of ice spikes, each standing as tall as a semitruck is long.

ESO

Such spikes are created on Earth in the frigid tropical peaks of the Andes Mountains, where they are called "penitentes," for their resemblance to devout white-clad monks. First described by Charles Darwin, penitentes are sculpted by the sun in frozen regions that experience no melt; instead, the fixed patterns of light cause the ice to directly vaporize, amplifying minute surface variations that result in small hills and shadowed hollows. These dark hollows absorb more sunlight than the bright peaks around them, vaporizing down further in a feedback loop.

Penitentes have already been seen on Pluto. And by calculating other competing erosional processes on Europa, such as impacts and charged particle bombardment, the new work suggests the vaporization of ice would be dominant in its equatorial belt, forming penitentes 15 meters tall spaced only 7 meters apart. Such formations

could explain, the authors add, why radar observations of the planet dip in energy at its equator, the penitentes scattering the response. But the ultimate proof of whether Europa's belly will be off limits to landing will come when the Clipper arrives in the mid-2020s.

https://wb.md/2ISphIC

Inadequate Thyroid Ultrasound a 'National Epidemic' in US

Glaring problem that is leading to incomplete surgeries, incomplete evaluation, persistent disease, and patient morbidity

Nancy A. Melville

WASHINGTON, DC — Preoperative ultrasound imaging of thyroid nodules of concern for malignancy at diagnostic imaging centers around the United States rarely includes lateral neck imaging, according to research presented here at the 2018 Annual Meeting of the American Thyroid Association (ATA).

This comes despite the accepted gold standard of the comprehensive evaluation of suspicious nodules to include the lateral neck, as well as the thyroid, as critical components of any such ultrasound, reported Gary L. Clayman, MD, of the Clayman Thyroid Surgery Center, Thyroid and Parathyroid Institute of Tampa General Hospital, Florida.

"This is clearly a glaring problem that is leading to incomplete surgeries, incomplete evaluation, persistent disease, and patient morbidity," Clayman told *Medscape Medical News*.

The situation represents a "national epidemic" that needs to be addressed by the collective medical organizations involved in thyroid medicine, he added.

"This is a call to arms to bring about change through national diagnostic imaging organizations."

Asked for comment, Gregory W. Randolph, MD, professor of otolaryngology, Harvard Medical School, in Boston, Massachusetts, noted that not long ago, ultrasound of just the thyroid was the standard.

"It used to be that 20 years ago you would just get a thyroid ultrasound, but then it became clear that a lot of people with papillary thyroid cancer had lymph node involvement and we now know that about a third of patients who have a biopsy-proven thyroid nodule also wind up having lymph node involvement in one or more areas of the neck," Randolph, who is the Claire & John Bertucci Endowed Chair in Thyroid Surgical Oncology, told *Medscape Medical News*.

"So, knowing the importance of the lateral neck, I will get very meticulous neck ultrasounds," he said. "I will even get CT scans of the neck and look at those. But not every center moves along at the same rate, and this paper is helpful in showing that."

Thyroid Nodules and Cancers Diagnosed by Wide Variety of Specialists

Thyroid nodules and cancers are commonly diagnosed by wide-ranging practitioners, often including those outside of the fields of endocrinology, and even endocrinologists often do not perform their own ultrasound evaluations, resulting in varying levels of skill in the evaluations.

Meanwhile, with thyroid cancers commonly involving one or more areas including the lateral neck or lymph nodes, preoperative ultrasound imaging is only considered to be comprehensive if those areas are included — skipping them can and often does result in the need for additional surgery.

To determine how often the comprehensive evaluations of the neck are conducted in thyroid evaluations, Clayman and colleagues identified 217 patients who had been referred to their center in 2017 for management of primary thyroid malignancy and whose preoperative ultrasounds were obtained prior to the patients receiving definitive high-resolution ultrasound at their center.

Of the patients, 66 were men and 151 were women. They were a median age of 41 years (range 14 to 87).

The information the researchers received about the patients, which included ultrasound, histopathologic details, and cancer staging, showed that only four — just 2% — of the ultrasound studies obtained prior to referral included analysis of any lateral neck lymph nodes.

Among the patients, 101 (46%) were diagnosed with smaller nodules (T1), 39 (18%) were T2, and 77 (35%) were T3 or T4 malignancies. Further comprehensive evaluation of the nodules with the center's own high-resolution preoperative ultrasound identified 39 lateral neck metastases (18%), central compartment lymph node disease in 60 (28%) patients, and contralateral second primary thyroid disease in four (2%) patients, which had not been previously detected.

"None of those that we found were in the ultrasounds that we'd received," Clayman said.

"These patients would have had the wrong surgical procedures. They very well could have had a lobectomy, for instance, without even addressing the central compartment lymph nodes."

Action by National Organizations Urged

A big part of the problem is that many community ultrasound centers — which are tasked with a wide variety of ultrasounds ranging from the breast to liver to abdominal — are not adequately set up for comprehensive thyroid ultrasounds, Clayman explained.

"You need the right machine, you need the right transducers, you need to have the equipment calibrated to image the thyroid, and you need an experienced technician and experienced diagnostician," he said. "If any of those are poor quality, it makes the entire process poor quality."

Meanwhile, current procedural terminology (CPT) codes used in reimbursement for thyroid ultrasound only indicate ultrasound of the thyroid, and not a comprehensive evaluation including the neck, adding to the common omission, Clayman noted.

To improve awareness and uniformity in thyroid nodule imaging, Clayman is calling on medical organizations to take action.

"We propose that the ATA and American Academy of Clinical Endocrinology jointly address the American College of Radiology, American Society of Neuroradiology, and American Society of Radiology to evolve structured guidelines for clearly establishing the need for comprehensive cervical ultrasound evaluation in the analysis of the thyroid gland," he urged.

"Ultrasound analysis of the thyroid must only be considered an inadequate analysis, and CPT codes for such should be eliminated through appropriate legal and organizational pursuits."

Comprehensive Imaging Standard at Top Centers — Not Elsewhere

Mabel Ryder, MD, of the Mayo Clinic, Rochester, Minnesota, agrees with both Clayman and Randolph, describing a recent case that perfectly underscores the potential consequences of inadequate ultrasound imaging.

"I just had a patient come in for a second opinion after surgery for thyroid cancer, and it was discovered that she did indeed have suspicious lymph nodes in the lateral neck," Ryder, who is cochair of the ATA meeting program committee, told *Medscape Medical News*.

"The patient had to unfortunately undergo a subsequent surgery to remove the disease from the lateral neck, so this is a common problem in the field."

Ryder said for that reason, the Mayo Clinic requires lateral neck ultrasound in the referral of thyroid cancer patients.

"We require everyone referred to Mayo to have comprehensive neck ultrasound before they see us if there is a question about thyroid

cancer because of the common lymph node involvement in this disease."

"But the challenge is that most people aren't coming to us at the Mayo Clinic," she said.

"There are far more surgeries being done in the community outside of medical centers, so it's important to try to help practices understand that it's best practice for the patient to have lymph node ultrasound preoperatively."

2018 Annual Meeting of the American Thyroid Association. October 5, 2018; Washington, DC. Abstract 19.

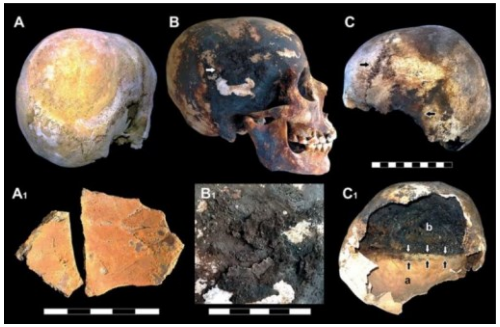
http://bit.ly/2Ej7rQc

Extreme heat of Vesuvius eruption vaporized body fluids, exploded skulls

New analysis of human remains shows many victims didn't suffocate from gas or ash.

Jennifer Ouellette - 10/9/2018, 9:43 PM

The catastrophic eruption of Mount Vesuvius in 79 AD wiped out several nearby towns and killed thousands of people. It has long been supposed that the vast majority died from asphyxiation, choking on the thick clouds of noxious gas and ash. But a recent paper by Italian archaeologists concludes that at least some of the Vesuvian victims died instantaneously from the intense heat of fast-moving lava flows, with temperatures high enough to boil brains and explode skulls.



***Enlarge* / Italian scientists detected red and black mineral incrustations in victims' skulls—the iron from human blood. P. Petrone et al.**

As bioarchaeologist Kristina Killgrove notes over at Forbes, this new analysis, led by Pierpaolo Petrone of the University of Naples, builds on the Italian team's short 2001 paper in *Nature*. This is when they first broached their hypothesis, noting that the body postures of many victims unearthed in waterfront chambers in the town of Herculaneum, near the foot of Vesuvius, showed evidence of thermal shock. There were telltale flexed body parts, like curled toes and charred bones, indicating sudden death from a blast of extreme heat. It is estimated that the eruption of Vesuvius released 100,000 times the thermal energy of the atomic bombs dropped on Hiroshima and Nagasaki in 1945, ejecting many tons of molten rock, pumice, and hot ash over the course of two days. In the first phase, immediately after the eruption, a long column of ash and pumice blanketed the surrounding towns, most notably Pompeii and Herculaneum. By late night or early morning, pyroclastic flows (fast-moving hot ash, lava fragments, and gases) swept through and obliterated what remained, leaving the bodies of the victims frozen in seeming suspended action. The only surviving eyewitness account is that of Pliny the Younger, who wrote two letters to his friend, the historian Tacitus, describing the cataclysmic event. He described "broad sheets of flame" visible from Vesuvius and a rain of ash blanketing the area like snow. He and his uncle, Pliny the Elder, also witnessed a dense cloud "filled with earth and cinders" rising above the mountain like a pine tree, "for it shot up to a great height in the form of a tall trunk, which spread out at the top as though into branches."

Archaeologists have made casts from the impressions victims' bodies left in the ash deposits around Pompeii (roughly 1,044) and collected bones from another 100 victims. A little over a third are believed to have been killed by roof collapses or falling rocks. Archaeologists also recovered the remains of around 332 bodies in the ash fall deposits at the Herculaneum site, located closer to the crater than Pompeii, likely killed by the pyroclastic surges.

It got hot

Most scientists assumed the Pompeii victims not killed by falling debris suffocated from the thick clouds of ash and gas, believing the temperatures of the material spewed forth by Vesuvius would not have been hot enough to cause outright death. There was good cause to think so, given the state of the bodies, the outline of clothing still visible on some. But a 2010 study by volcanologists estimated that the temperatures of the pyroclastic surge that destroyed Pompeii could have been as high as 572°F, killing the populace in fractions of a second. "The contorted postures are not the effects of a long agony, but of the cadaveric spasm, a consequence of heat shock on corpses," lead author Giuseppe Mastrolorenzo told *National Geographic* at the time.

The victims at Herculaneum appear to have met a similar horrid fate, according to Petrone and his colleagues. Archaeologists believe the shoreline site used to hold boathouses, given the overhead crossbeams and arched vaults within the chambers. They surmise that those unable to evacuate in time sought shelter from the open beach in the boathouses, only to be caught in the dense, hot flows that wiped out the town. Those 100 or so skeletons were removed for laboratory analysis in the 1980s. (There are fiberglass reproductions at the site itself for tourists to get some sense of the impact.)

Petrone and his colleagues were intrigued by the strong red and black residue on some of the bones that could not have come from coins or other metal artifacts, since there were none near this particular site. They used Raman micro spectroscopy to analyze samples for iron and other remnants of blood. There was a very high concentration of iron, most likely derived from victims' bodily fluids, although they could not say definitively that the source was human blood.

Most of the bones were also fractured—another indicator of being exposed to sudden extreme high heat. They especially noted "cracking and explosion" of the skullcaps of many of the skeletons, consistent with forensic cases of bursting skulls, when "expelled brain matter may form a circular pattern around the head." Essentially, the hot pyroclastic flows boiled the soft brain tissue and evaporated the bodily fluids of the unfortunate victims, raising the internal pressure so severely that the skulls quite literally exploded. That is not a nice way to go, to say the least. But perhaps it was faster than suffocating to death.

DOI: PLOS One, *2018.* *10.1371/journal.pone.0203210* *(About DOIs).*

https://bbc.in/2A7Wo8p

Pioneering CJD treatment to be used on British patient

Doctors have been given permission to give a British man with CJD a pioneering treatment, in a world first.

By Alex Therrien Health reporter, BBC News

There is currently no treatment for the rare but lethal brain disease, known as the human version of "mad cow disease".

Doctors in London were given permission for the trial use on a human for the first time by the Court of Protection. Scientists say lab testing of the man-made antibody has been encouraging, but they admit they do not know how their patient will respond.

'Extreme caution'

The patient in this case, who has not been named, has sporadic CJD, the most common form of the disease in humans.

This is different from variant CJD, the version linked to eating beef infected by bovine spongiform encephalopathy, or BSE.

Sporadic CJD happens when healthy proteins in the human body - prions - become spontaneously misshapen and build up in the brain.

The man-made antibody treatment, called PRN100, aims to prevent abnormal prions from being able to attach themselves to healthy proteins, meaning that they cannot grow and cause devastation throughout the brain.

University College London Hospitals NHS Foundation Trust (UCLH) is set to use it in a patient for the first time after a judge from

the Court of Protection confirmed on Monday that it was lawful and in the patient's best interests to receive it.

Prof John Collinge, director of the Medical Research Council Prion Unit at University College London, who led the development of the treatment, said: "As this is the first time this treatment has been used in humans we cannot predict what the outcome will be, but laboratory testing has shown the potential to treat prion infection.

"A key issue will be whether a sufficient quantity of the drug is able to cross the blood brain barrier to reach the brain tissue where it needs to work. "We will proceed with extreme caution in very tightly-controlled conditions.

"A team of experts from a range of disciplines will make collective decisions in the best interests of the patient."

'The diagnosis was devastating'

Colin Beatty's wife, Annie, died in 2010 after she was diagnosed with sporadic CJD. Annie was 70 and the couple had been married for 40 years. "The diagnosis was devastating. It was like a bomb had gone off in our family," said Colin.

Colin, 75, from Dorset, said the illness made Annie vacant in the beginning. Then her speech became muddled and she would wander off without warning, which he said was "terrifying".

"It was heartbreaking to watch Annie deteriorate.

"I nursed her at home initially but she became very difficult to care for, so we had to admit her to a nursing home."

Colin said if the PRN100 antibody had been available at the time, he would have wanted Annie to have had the opportunity to be treated with it. "It's true that the treatment carries potential risks, and the benefits are not yet certain, but without it, there is no hope. The only certainty with CJD is death."

'Important step forward'

UCLH's National Prion Clinic sees about 120 patients with sporadic CJD each year.

The patient, who together with his family supported the UCLH's court application, will initially receive the treatment via a drip into a vein in the arm. The hospital trust said it was preparing for a range of possible outcomes, from the treatment having no measurable effect to slowing or halting the progression of the disease. It is not expected to reverse any brain damage that has already occurred.

UCLH said it would see how the first patient responded before considering using it in a second person.

UCLH's chief executive, Prof Marcel Levi, said: "At present, caring for patients with CJD involves trying to use medicines to alleviate symptoms only, but sadly the disease always results in the rapid death of the patient. "The court's confirmation is an important step forward in tackling this devastating illness."

http://bit.ly/2QM5zAU

Vaccinating humans to protect mosquitoes from malaria

For decades, scientists have been trying to develop a vaccine that prevents mosquitoes from spreading malaria among humans.

by Cory Nealon

This unique approach—in which immunized humans transfer anti-malarial proteins to mosquitoes when bitten—is called a transmission-blocking vaccine (TBV). A few malarial TBVs have shown promise but they have not been widely tested due to unwanted side effects or limited effectiveness.

That could change.

A biotechnology advancement reported Monday, Oct. 8, in the journal *Nature Nanotechnology* describes how a University at Buffalo-led research team has devised a simple way to boost the efficacy of malarial TBVs.

If successful, it could help reduce the spread of the disease, which kills more than 400,000 people annually, mostly small children in sub-Saharan Africa.

"Malaria is a huge global problem. This approach—using a transmission-blocking vaccine—could be part of a suite of tools that we use to tackle the disease," says the study's lead author, Jonathan Lovell, PhD, associate professor of biomedical engineering, a joint program of UB's School of Engineering and Applied Sciences and the Jacobs School of Medicine and Biomedical Sciences at UB.

Co-authors include researchers from Walter Reed Army Institute of Research, the National Institutes of Health, McGill University and the PATH Malaria Vaccine Initiative.

How malaria is spread

Utilizing TBVs to fight malaria stems, in part, from how the disease is spread. Here is how it works: a mosquito carrying the disease bites a child and transmits the malaria parasite to her. Later, a non-infected mosquito bites the child, and this time it's the girl who passes the parasite to the mosquito. That mosquito later bites a new victim and infects them with the parasite.

The development of effective TBVs—combined with bug nets, insecticides, anti-parasitic drugs and others types of vaccines—could help break this vicious cycle, proponents say. While a TBV would not directly prevent an immunized person from getting infected, the vaccine would reduce the odds that people living in that community get malaria, hopefully to zero.

Prior research in this area has focused on techniques like genetic engineering and chemical binding of toxin proteins to boost TBV responses. Each strategy has potential, but they're also time- and resource-consuming. The biotechnology created by the UB-led research team differs in its relative ease of assemble and overall effectiveness, Lovell says.

The malaria parasite's life cycle includes numerous stages. Different malaria proteins represent the best vaccine target antigens, which are proteins that a vaccine mounts an immune response against. To purify these antigens for a vaccine, they are often modified with a small chain of amino acids called a polyhistidine-tag.

The research team's discovery

Researchers discovered that the antigens could be mixed with nanoparticles containing small amounts of cobalt-porphyrin and phospholipid. The cobalt-porphyrin, which is similar in structure to vitamin B12, is responsible for binding the nanoparticle to the antigens.

The resulting structure is a next-generation adjuvant, which is an immunological agent that enhances the efficacy of vaccines. The vaccine works by inducing humans to make malaria-attacking antibodies, which are then transmitted to the mosquito as it bites the immunized human.

In tests involving mice and rabbits, researchers showed that antibodies from a protein called Pfs25 effectively blocked the development of malaria-causing parasites inside the gut of mosquitoes. Additional tests paired the adjuvant with multiple malaria antigens, suggesting its promise for blocking the spread of malaria at numerous stages of the disease.

The research team's next step is to prepare additional experiments that will justify moving the technology into human trials.

More information: *Wei-Chiao Huang et al. A malaria vaccine adjuvant based on recombinant antigen binding to liposomes, Nature Nanotechnology (2018). DOI: 10.1038/s41565-018-0271-3*

Journal reference: *Nature Nanotechnology*

http://bit.ly/2pPX2S7

Scoliosis linked to essential mineral

Children with severely curved spines may be unable to use manganese

Nobody knows why some children's backs start to curve to one side just as they hit puberty. Most children diagnosed with scoliosis, or curvature of the spine, have no known risk factors.

A new study suggests that the body's inability to fully utilize the essential dietary mineral manganese might be to blame for some cases of severe scoliosis. Researchers at Washington University School of Medicine in St. Louis have found that children with severe scoliosis are twice as likely as children without the disease to carry a gene variant that makes it hard for their cells to take in and use manganese. Manganese is required for growing bones and cartilage.

"Our study links a common disease - scoliosis - to something that's potentially modifiable in the diet," said senior author Christina Gurnett, MD, PhD, a professor of neurology, of orthopedic surgery and of pediatrics. "But we don't want people to go out right now and start manganese supplements, because we already know that too much manganese can be harmful."

Zebrafish that lacked a manganese-related gene grew curved spines. An inability to properly use the essential mineral manganese could be to blame for some cases of severe scoliosis, according to a new study from Washington University School of Medicine in St. Louis. **Gabriel Haller**

The study is published Oct. 9 in Nature Communications.

About 3 million new cases of scoliosis are diagnosed every year. Most are mild and require only that doctors keep a watchful eye on the condition. Children who develop a moderate bend to their spine may need to wear a back brace until they finish growing. In rare cases, the curvature is so pronounced that it requires surgery to correct.

Cases of scoliosis tend to cluster in families, but not in a simple way, which suggests that many different genes each play a small role in increasing the risk of the disease. To identify such genes, Gurnett and a research team including Matthew Dobbs, MD, the Dr. Asa C and Mrs. Dorothy W. Jones Professor of Orthopaedic Surgery, and postdoctoral researcher and first author Gabriel Haller, PhD, scanned all the genes in 457 children with severe scoliosis and 987 children without scoliosis.

They found a variant in the gene SLC39A8 in only 6 percent of the healthy children but 12 percent of the children with severe scoliosis. A second analysis in a separate group of 1,095 healthy children and 841 children with moderate to severe scoliosis also found that children with scoliosis were about twice as likely to carry the variant.

When the researchers bred zebrafish with a disabled SLC39A8 gene, the fish developed movement and skeletal abnormalities, including curves in their spines.

This gene hasn't been studied much, but there are some reports that it helps cells take in minerals such as zinc, iron and manganese. Haller and Gurnett found that human cells with the gene variant successfully took up zinc and iron but failed to take in manganese. They also discovered that children with the gene variant had significantly lower levels of manganese in their blood than those with the more common form - although both groups were still within the normal range.

"Our goal in studying the genetics of this disorder was to see if there was anything we could learn that might change how we treat patients," said Gurnett, who is also director of the Division of Pediatric and Developmental Neurology and neurologist-in-chief at St. Louis Children's Hospital. "And we came across this gene variant that affects the level of manganese in the body. That tells me maybe we should start thinking about studying nutritional treatments for some children at risk."

Manganese is both an essential mineral and a toxin. High doses can cause manganism, a permanent neurological condition characterized by tremors and difficulty walking, as well as psychiatric symptoms such as aggression and hallucinations. The mineral also has been linked to Parkinson's disease, schizophrenia and high blood pressure. Too little manganese, on the other hand, can cause manganese

deficiency - although this is rarely seen in people because the human body needs only trace amounts that are easily obtained from food.
But animal studies show that lack of manganese can result in problems metabolizing fat and sugar, impaired growth, difficulty walking and curvature of the spine.
The children with the genetic variant did not have manganese deficiency, but they may be unable to use manganese as efficiently as others.
"The genetic variant does not stop the gene from working entirely, it's just not working optimally," Haller said. "So maybe most people need a certain level of manganese in their blood, but if you have a bad gene variant like this one, you need more."
Any manganese supplementation would have to be carefully measured to avoid raising the risk for other serious diseases, the researchers cautioned.
"We've started doing these studies in zebrafish by adding manganese to their water," Gurnett said. "But we still need to do human studies to figure out how much exactly is both safe and effective."

http://bit.ly/2yjwnSa

Planned intermittent fasting may help reverse type 2 diabetes, suggest doctors

And cut out need for insulin while controlling blood glucose

Planned intermittent fasting may help to reverse type 2 diabetes, suggest doctors writing in the journal BMJ Case Reports after three patients in their care, who did this, were able to cut out the need for insulin treatment altogether.
Around one in 10 people in the US and Canada have type 2 diabetes, which is associated with other serious illness and early death. It is thought to cost the US economy alone US$245 billion a year.
Lifestyle changes are key to managing the disease, but by themselves can't always control blood glucose levels, and while bariatric surgery (a gastric band) is effective, it is not without risk, say the authors. Drugs can manage the symptoms, and help to stave off complications, but can't stop the disease in its tracks, they add.
Three men, aged between 40 and 67, tried out planned intermittent fasting to see if it might ease their symptoms. They were taking various drugs to control their disease as well as daily units of insulin. In addition to type 2 diabetes, they all had high blood pressure and high cholesterol.
Two of the men fasted on alternate days for a full 24 hours, while the third fasted for three days a week. On fast days they were allowed to drink very low calorie drinks, such as tea/coffee, water or broth, and to eat one very low calorie meal in the evening.
Before embarking on their fasting regime, they all attended a 6-hour long nutritional training seminar, which included information on how diabetes develops and its impact on the body; insulin resistance; healthy eating; and how to manage diabetes through diet, including therapeutic fasting.
They stuck to this pattern for around 10 months after which fasting blood glucose, average blood glucose (HbA1c), weight, and waist circumference were re-measured.
All three men were able to stop injecting themselves with insulin within a month of starting their fasting schedule. In one case this took only five days.
Two of the men were able to stop taking all their other diabetic drugs, while the third discontinued three out of the four drugs he was taking.
They all lost weight (by 10-18%) as well as reducing their fasting and average blood glucose readings, which may help lower the risk of future complications, say the authors.
Feedback was positive, with all three men managing to stick to their dietary schedule without too much difficulty.
This is an observational study, and refers to just three cases-all in men. As such, it isn't possible to draw firm conclusions about the

wider success or otherwise of this approach for treating type 2 diabetes.

"The use of a therapeutic fasting regimen for treatment of [type 2 diabetes] is virtually unheard of," write the authors. "This present case series showed that 24-hour fasting regimens can significantly reverse or eliminate the need for diabetic medication," they conclude.

http://bit.ly/2yesVsq

Statins no good for non-cardiovascular conditions, major review concludes

Claims that statins can be used to treat dementia, cancer, and other diseases are not supported by evidence.

Andrew Masterson reports.

Statins are valuable in the fight against heart disease, but there is no firm evidence they can treat non-cardiovascular conditions.

There is no convincing evidence to support claims that statins can be used to manage non-cardiovascular health conditions, an extensive review has concluded.

The review was conducted by a large team of researchers led by geneticist Yazhou He from the University of Edinburgh. It was prompted by a number of studies conducted over the past decade or so that suggested possible roles for statins in the treatment or prevention on non-cardiac conditions, including vascular dementia, cancer, Parkinson's disease and multiple sclerosis.

To test the strength of these claims, He and his colleagues identified 112 meta-analyses of observational studies and 144 meta-analyses of random controlled trials, which together identified 278 unique non-CVD conditions. All the studies had been included on either of two standard medical archives -- MEDLINE and EMBASE – before a cut-off date of May 2018.

Analysing the observational studies, the researchers found "no convincing evidence" of replicated benefits for non-CVD conditions. They did, however, find two "highly suggestive" outcomes indicating, but not unambiguously so, that statins may have a positive effect in decreasing mortality in cancer patients and easing obstruction in patients with chronic obstructive pulmonary disease.

The analysis of the random controlled trials produced only one significant result – an indication of decreased all-cause mortality in patients with chronic kidney disease.

The observational results also suggested that statins could produce adverse affects in the form of diabetes and myopathy, or muscle weakness. However, the random controlled trial data did not throw up matching statistical evidence.

Over all, the researchers conclude that there is no strong evidence to warrant widening the range of conditions for which statins are prescribed.

"We report a dearth of convincing evidence that statins had a major role in the 278 unique non-CVD outcomes assessed," they write.

The report is published in the journal *Annals of Internal Medicine*.

https://go.nature.com/2OY5psX

First report of antimicrobial resistance pre-dates penicillin

Antimicrobial resistance was first reported four years before Alexander Fleming's discovery of penicillin

Dov Stekel

Clinical antimicrobial resistance was first reported four years before Alexander Fleming's discovery of penicillin in 1928. The antimicrobial in question was known as Salvarsan (S. Silberstein *Arch. Derm. Syph.* **147**, 116–130; 1924).

An antibiotic was originally defined as an agent that microorganisms produce to kill competing bacteria (S. A. Waksman *Mycologia* **39**, 565–569; 1947). This has been extended to include synthetic drugs, including sulfonamides and quinolones. Salvarsan was one such drug, from a group of compounds known as arsphenamines. It was used to

treat syphilis from 1910 until the 1940s, when penicillin took over because it was more readily available, safer and more effective.

Bacterial resistance to Salvarsan started to emerge about halfway through that period, despite the drug's limited use by comparison with modern antibiotics. The 1924 paper was cited by several groups during the 1930s (see, for example, W. Beckh and G. V. Kulchar *Arch. Derm. Syphilol.* **40**, 1–12; 1939), but has long since been forgotten.

Nature ***562****, 192 (2018) doi: 10.1038/d41586-018-06983-0*

http://bit.ly/2A7zHBd

Do not give decongestants to young children for common cold symptoms, say experts

No evidence that they alleviate symptoms such as a blocked or runny nose, and their safety is unclear

Decongestants should not be given to children under 6 - and given with caution in children under 12 - as there is no evidence that they alleviate symptoms such as a blocked or runny nose, and their safety is unclear, say experts in *The BMJ* today.

Instead, they advise doctors to reassure patients that a cold is distressing but symptoms should pass in a few days.

The common cold is usually caused by viruses and is mostly self limiting (symptoms clear in 7 to 10 days) but it can have a substantial impact on work, school, use of health services, and money spent on medications. Children have around 6-8 colds per year and adults have 2-4.

So Professor Mieke van Driel and colleagues analysed published evidence on the effectiveness of treatments for the common cold.

For adults, the evidence suggests that using decongestants alone, or with antihistamines or analgesics, for a maximum of 3 to 7 days can have a small effect on nasal symptoms.

However, side effects can include an increased risk of insomnia, drowsiness, headache, or stomach upset - and long term use of decongestants can lead to chronic nasal congestion, which is difficult to treat.

Paracetamol and anti-inflammatory drugs (NSAIDs) are sometimes prescribed for pain relief, but they do not appear to improve nasal congestion or runny nose. Other treatments, such as steam inhalation, echinacea, vapour rub, eucalyptus oil, and increased fluid intake, are either not effective or have not been studied at all.

Trials are also lacking for children, especially those under 12 who carry the highest burden of common colds.

Decongestants or medicines containing antihistamine should not be given to children under 6, say the authors, and they advise caution between 6 and 12 years. "There is no evidence that these treatments alleviate nasal symptoms and they can cause adverse effects such as drowsiness or gastrointestinal (stomach) upset," they write. In children under 2 they have been associated with convulsions, rapid heart rate and death.

None of the other commonly used over-the-counter and home treatments, such as heated humidified air, analgesics, eucalyptus oil, or echinacea, are supported by adequate evidence, they add.

"If parents are concerned about their child's comfort, saline nasal irrigations or drops can be used safely, but this may not give the desired relief," they write.

Finally, they say ongoing research is unlikely to provide relevant evidence or address the uncertainty surrounding treatments for the common cold. "Based on the currently available evidence, reassurance that symptoms are self limiting is the best you can offer patients, although short term use of decongestants in adults can provide some relief from a blocked nose," they conclude.

Externally peer-reviewed? Yes
Type of evidence: Recommendations based on systematic reviews of randomised controlled trials
Subjects: Adults and children

https://ind.pn/2QLHCcU

‘Catastrophic collapse’ of Mount Etna could trigger tsunami, scientists warn

Danger that Europe’s biggest active volcano could ‘form a landslide that moves really fast into the sea’, although researchers have no idea when

Josh Gabbatiss Science Correspondent

Europe’s biggest active volcano is slipping into the ocean, and it’s feared the recent discovery could trigger a tsunami.

Scientists are concerned the slow movements that have been measured on Mount Etna’s southeastern flank could escalate and result in part of it collapsing into the water.

Such an event would put neighbouring communities in Sicily at risk as debris enters the surrounding ocean, possibly causing devastating waves.

However, researchers monitoring the site say all they can do for now is “keep an eye” on the active volcano as there is no way of telling whether this acceleration will come within years or centuries.

Previous work suggested Etna’s movement was the result of magma swirling inside the volcano, meaning the movement would be confined to its summit.

However, careful monitoring of the seafloor around the site has revealed that Etna’s gradual sliding movements affected a far wider area – a finding the scientists say increases the risk of “catastrophic collapse”.

“Mount Etna is huge. It’s over 3,000m high and it rises up from below sea level,” said Dr Morelia Urlaub from Geomar Helmholtz Centre for Ocean Research. “It’s really heavy, and it grows continuously.”

Past work has only focused on Etna’s above-ground component, but gathering the new underwater measurements confirmed the movement is due to gravity acting on its growing, and unstable, flank.

“You can think of a slow landslide at the moment – we had 4cm in 15 months, so it moves really slowly, but there is a danger that it could accelerate and form a landslide that moves really fast into the sea,” Dr Urlaub told *The Independent*.

There are historic accounts of such collapses happening on smaller volcanoes, but the geological record has evidence of it affecting large areas in Hawaii and the Canary Islands millions of years ago.

To understand whether something similar was going on in real-time at Etna, the scientists collected data from pressure sensors over several months, publishing their results in the journal *Science Advances*.

While this data gives them a better idea of the volcano’s movements, Dr Urlaub said that it is difficult to calculate the risk of disaster from these measurements given its immense age.

Indonesia volcano Mount Soputan erupts on same island as earthquake-stricken city of Palu

“We have been monitoring Etna on shore for around 30 years now, but 30 years is nothing compared to the age of Etna, which is 500,000 years old,” she said.

“It could happen in 10 or 100 or 100,000 years – we can’t tell.”

With this in mind, she said for now it is very important to keep monitoring the volcano and try to get an idea of what level of movement could indicate an imminent collapse.

“There is much more research to be done,” Dr Urlaub said, noting they would try “to be aware there is a hazard, and keep an eye on Etna’s flank”.

http://bit.ly/2yzbPod

Hundreds of patients with undiagnosed diseases find answers, study reports

Diagnosed through a network of detective-doctors who investigate unidentified diseases

More than 100 patients afflicted by mysterious illnesses have been diagnosed through a network of detective-doctors who investigate unidentified diseases, reports a study conducted by scientists at the Stanford University School of Medicine and multiple collaborating institutes.

The long-awaited diagnoses are the fruits of the Undiagnosed Disease Network, a program created by the National Institutes of Health in 2014.

"Our goal is to take on the hardest cases in medicine -- to find patients and families with conditions that no one has been able to solve," said Euan Ashley, MD, professor of medicine at Stanford. "We wanted to provide a place that these people could come, so the Undiagnosed Disease Network came together to try to answer that need."

The group, made up of hundreds of doctors across the United States, has so far sleuthed out 132 of 382 previously unknown ailments -- roughly 35 percent. "Some of these patients had been waiting decades to put a name to their illness. They tell us how much of a relief it is simply to know what they were up against," Ashley said.

But what's most exciting, he said, was that for 80 percent of the network's diagnoses, they distilled actionable information, such as changes to patient therapy, adjustments to future diagnostic testing and recommendations for family screening.

"Our findings underscore the impact that establishing a clear diagnosis can have on clinical decision-making for previously undiagnosed patients," said Kimberly Splinter, associate director of research operations for the network's coordinating center and a genetic counselor at Harvard Medical School. "We hope that the results of this analysis will provide a compelling case for adopting some of the network's diagnostic approaches more broadly in an attempt to clarify diagnoses and refine treatment for patients with rare conditions."

A paper describing the study will publish online Oct. 11 in The New England Journal of Medicine. Ashley is the senior author and Splinter is the lead author.

Cracking the cases

The effort sprung to life four years ago when the NIH tapped Ashley to co-chair a consortium of cross-disciplinary doctors who would work to crack some of medicine's most perplexing cases -- at no charge to the patient. Of the 1,519 applications from patients, 601 were accepted based on the likelihood that the network would be able to help them, given their past medical records and available data. The network continues to accept applications; to date, they've received 2,780 applications, accepted 1,179 and reviewed 907.

Now, Ashley and the team of physicians have seen more than half of those patients, combining traditional medicine with increasingly cutting-edge diagnostic tests.

"We do this Sherlock Holmes-like detective work-up by carefully observing, gathering information, and asking pointed questions, but we're also pairing that with the most advanced genomic technologies to try to solve their case," Ashley said.

Every patient had their genome sequenced, even those whose genomes had been previously sequenced. The field of genetic and genomic testing moves so quickly, Ashley explained, that even patients who've had their genome sequenced six months ago benefit from another look. In coordination with genome sequencing, the physicians looked at patients' RNA profiles, analyzing precursor molecules to the proteins found in their bodies. They also broke down a collection of molecules called metabolites, which form as a product of metabolism and can hint at where metabolic processes go wrong.

"Some cases are solved simply because we know more today than we did a year ago," Ashley said.

Among those diagnosed, most exhibited rare versions of known diseases, broadening the symptomatic information doctors can look for when evaluating patients for those particular diseases in the future. But in 31 patients, the network identified previously unknown syndromes.

One that sticks out to study co-author Matthew Wheeler, MD, assistant professor of medicine at Stanford and executive director of the Stanford Center for Undiagnosed Diseases, is the case of a patient who the network followed for multiple years. The patient had mysterious and life-threatening episodes of something called lactic acidosis, a dangerous buildup of lactic acid in the body.

"It's sort of like an extreme version of when you exercise intensely, and you feel that burn from the lactate buildup -- only it's your whole body that feels that way," Wheeler said. "Lactic acidosis can also cause your acid-base balance to be out of whack, and when people have severe acid-base disturbances, they're at high risk for arrhythmia or death."

It wasn't clear why the patient was experiencing these symptoms, which seemed to be prompted by a cold or flu. After giving the patient the full gamut of tests and analyzing sequencing information, a team of Stanford scientists found the culprit: a single mutation in the gene ATP5F1D, which is involved in the function of mitochondria, the cell's powerhouse. The genetic oddity and symptoms had never been classified together officially, but from connections within the network and in some instances word of mouth, the scientists found that other doctors around the world had patients plagued by this syndrome. In verifying that the mutation causes the syndrome -- called mitochondrial complex V deficiency, nuclear type 5 -- network collaborators on the study developed animal models to show causality.

Continuing the search

"This is a new type of scientific odyssey," Ashley said. "We're learning about biology in a way that could help not just one family, but potentially dozens, even hundreds, of families who suffer that same rare condition. That's the biggest benefit of this network effect -- the impact of identifying one patient's disease could end up being global."

Even the patients who did not receive a diagnosis benefit from knowing that a team continues to investigate their conditions and that the future may hold an answer even if the present does not.

"We've had patients tell us that just knowing that there is a team looking into their condition, that there is someone in the world who has not given up on them, scientists continuing to keep an eye on the literature -- that provides hope," Ashley said.

Now, Ashley and his colleagues are moving into the second phase as they expand network sites and continue to accept applications and see patients.

"Let's face it, solving a third of these cases in the first phase was great -- when they came in the door it was 0 percent. So to get to more than 30 percent -- we are happy with that, but that still leaves the majority of cases unsolved and many patients still suffering, so we need to do better," Ashley said.

Other Stanford authors of the study are Jonathan Bernstein, MD, PhD, professor of pediatrics; and genetic counselor Chloe Reuter.

Ashley is a member of the Stanford Cardiovascular Institute, Stanford Bio-X and the Stanford Child Health Research Institute.

Researchers from Harvard University, the NIH Clinical Center, Baylor University, University of Maryland, Vanderbilt University, HudsonAlpha Institutes for Biotechnology, University of Oregon, Brigham and Women's Hospital, Pacific Northwest National Laboratory, the University of California, Los Angeles, Duke University, Massachusetts General Hospital and the National Human Genome Research Institute contributed to the study.

The study was funded by the NIH (grants U01HG007709, U01HG007672, U01HG007690, U01HG007708, U01HG00773, U01HG007674, U01HG007942, U01HG007943, U01TR001395, U54NS093793 and R01GM113230).

Stanford's Department of Medicine also supported the work.

http://bit.ly/2NCoGLH

UCI researchers discover molecular mechanisms of ancient herbal remedies

Components of leaf extract prove highly effective at preventing life-threatening seizures

Irvine, CA - Researchers in the Department of Physiology & Biophysics at the University of California, Irvine School of Medicine have discovered the molecular basis for a therapeutic action of an ancient herbal medicine used across Africa to treat various illnesses, including epilepsy.

The herbal medicine, a leaf extract from the shrub *Mallotus oppositifolius*, was previously found to be effective in controlling seizures but the mechanism was unknown. The discovery, published in *Nature Communications*, found that two components of the Mallotus leaf extract activate KCNQ2/3, a potassium ion channel essential for controlling electrical activity in the brain. The two components were somewhat effective alone, but in combination were highly effective both at activating KCNQ2/3 channels and at preventing life-threatening seizures.

The UCI research team, comprising postdoctoral fellow Rían Manville, PhD and principal investigator Geoffrey Abbott, MSc, PhD, screened individual compounds from the leaf extract for channel opening activity, and then combined the two most active compounds to discover the therapeutic synergy contained in an African folk remedy used for centuries. Strikingly, one of the two compounds identified, isovaleric acid, is also a main component of valerian root, an herb used in ancient Greece as an insomnia sleep remedy, and for centuries by the English and also native Americans as an anticonvulsant. Valerian root is still used by as many as 2 million people each week in the United States as an herbal remedy for anxiety and insomnia.

"We are very interested in taking a molecular approach to ethnobotany - the study of plants and their use by local populations - to discover the molecular mechanisms for ancient remedies and to use this knowledge to create safer and more effective drugs. The KCNQ channels we study are typically opened by electrical activity, but we know that they are also incredibly sensitive to the presence of small molecules, including neurotransmitters, but also molecules from outside, such as drugs, and constituents of food and herbal extracts," said Abbott. "Some folk medicines are in danger of being lost, either because traditional practices are being forgotten, or because the plant species used are endangered. Species loss can arise from over-collecting, habitat destruction, or climate change. There is a race against time to prevent this incredible resource being lost forever."

The UCI team found that the herbal extract they studied had different channel subtype preferences than modern drugs that activate the KCNQ2/3 channel, such as the anticonvulsant drug, retigabine. Because of this, by combining the herbal compounds with retigabine, they were able to completely lock open the channel, a feat not previously achieved.

"Locking open the channel is a neat trick, but it could also have clinical implications. Retigabine was removed from the market last year because of a surprising side effect: it turns the skin and whites of the eyes blue. However, by combining retigabine with the herbal components, we found we could greatly reduce the retigabine dosage required for activity. This type of strategy might one day enable us to use drugs like retigabine at dosages low enough to be safe, whilst retaining or even enhancing their efficacy by combining them with natural booster compounds derived from plants," said Abbott.

In addition to the booster effects of the herbal extract, identification of the ability of specific chemicals within plants to activate influential ion channels such as KCNQ2/3 may lead one day to new

epilepsy, anxiety and pain drugs that exploit the alternative chemical spaces offered by the molecular constituents of ethnobotanicals.

This study was supported by the US National Institutes of Health (GM115189).

http://bit.ly/2P0JHo4

Antiepileptic drugs linked to higher risk of stroke in persons with Alzheimer's disease

Antiepileptic drug use associated with increased risk of stroke in persons with Alzheimer's disease

Antiepileptic drug use is associated with an increased risk of stroke among persons with Alzheimer's disease, according to a new study from the University of Eastern Finland. The risk did not differ between old and new antiepileptic drugs. The results were published in the *Journal of the American Heart Association*. The risk of stroke was particularly elevated for the first three months of antiepileptic drug use, and remained elevated after accounting for several chronic disorders, socioeconomic position and use of concomitant medications.

According to another recent study from the same research group, persons with Alzheimer's disease use antiepileptic drugs more often than persons without Alzheimer's disease. The difference was not explained by epilepsy, and there was a considerable increase in antiepileptic drug use around the time when Alzheimer's disease was diagnosed.

Up to 1% of population needs chronic antiepileptic treatment to control epilepsy. Other indications for antiepileptic drug use include neuropathic pain and dementia-related behavioural symptoms in persons with Alzheimer's disease.

The present findings indicate that as persons with Alzheimer's disease are particularly susceptible to adverse events, the use of antiepileptic drugs for other indications than epilepsy or neuropathic pain should be carefully considered in this vulnerable population.

The studies were based on the nationwide register-based MEDALZ cohort that includes all community-dwelling persons with clinically verified diagnosis of Alzheimer's disease in Finland during 2005-2011 (70,718 people). Data on antiepileptic drug use was extracted from the Finnish Prescription Register. To assess the risk of stroke associated with antiepileptic drug use, each antiepileptic drug user was matched to a non-user. The study was conducted at the University of Eastern Finland and funded by the Academy of Finland.

Reference:

Antiepileptic drug use and the risk of stroke among community-dwelling persons with Alzheimer's disease: a matched cohort study. Tatyana Sarycheva, Piia Lavikainen, Heidi Taipale, Jari Tiihonen, Antti Tanskanen, Sirpa Hartikainen, Anna-Maija Tolppanen. Originally published 15 Sept 2018. Journal of the American Heart Association. *2018;7:e009742. DOI:10.1161/JAHA.118.009742*

https://www.ahajournals.org/doi/10.1161/JAHA.118.009742

Incidence and prevalence of antiepileptic medication use in community-dwelling persons with and without Alzheimer's disease. Tatyana Sarycheva, Heidi Taipale Piia Lavikainen, Jari Tiihonen, Antti Tanskanen, Sirpa Hartikainen, Anna-Maija Tolppanen. Journal of Alzheimer's Disease. Pre-press 26 Sept 2018. DOI: 10.3233/JAD-180594

https://content.iospress.com/articles/journal-of-alzheimers-disease/jad180594

http://bit.ly/2QOzBnE

An elusive molecule that sparks multiple sclerosis may have been found

Points a way toward potential new treatments

By Mitch Leslie

Our immune cells normally pounce on intruding bacteria and viruses. But in multiple sclerosis (MS), immune cells target the nervous system instead. Now, researchers may have pinpointed a long-sought molecule called a self-antigen that provokes these attacks, pointing a way toward potential new treatments.

“The work is monumental, and it’s tantalizing,” says neuroimmunologist Hartmut Wekerle of the Max Planck Institute of Neurobiology in Munich, Germany, who wasn’t connected to the research.

Researchers have long suspected that a self-antigen—a normal molecule in the body that the immune system mistakenly treats as a threat—can trigger MS. The prime suspects have been proteins in myelin, the nerve insulation that erodes in patients with the disease. But after years of searching, scientists haven't been able to pinpoint the molecule.

To uncover other candidates, immunologists Roland Martin and Mireia Sospedra of University Hospital of Zurich in Switzerland and their colleagues analyzed immune cells known as T cells that came from a patient who died from MS. T cells normally switch on when they encounter protein fragments containing just a few amino acids that belong to an invading microbe, but they also turn on in people who have MS.

The researchers wanted to determine which protein shards stimulated the patients' T cells, so they tested 200 fragment mixtures, each containing 300 billion varieties. The two fragments with the strongest effect turned out to be part of a human enzyme called guanosine diphosphate-L-fucose synthase, which helps cells remodel sugars that are involved in everything from laying down memories to determining our blood type. T cells from 12 of 31 patients who had who either had been diagnosed with MS or had shown early symptoms of the disease also reacted to the enzyme, the researchers report online today in *Science Translational Medicine*. What's more, T cells from four of the eight patients tested responded to a bacterial version of the enzyme—lending credence to the recently proposed idea that intestinal bacteria may help spark the disease.

But, immunologist Ashutosh Mangalam of The University of Iowa in Iowa City says, "The gut microbiome angle is a bit of a stretch." Some of the bacteria that produce the enzyme are less abundant in MS patients than in healthy people, he says.

Overall, however, "It's a very well done study" that uses a "very sophisticated technique," says neuroimmunologist Howard Weiner of Brigham and Women's Hospital in Boston.

Although guanosine diphosphate-L-fucose synthase is prevalent in the brain, "it has never been a candidate in the past," says neuroimmunologist Reinhard Hohlfeld of Ludwig Maximilians University in Munich. The discovery, he says, is "a first step in an interesting new direction."

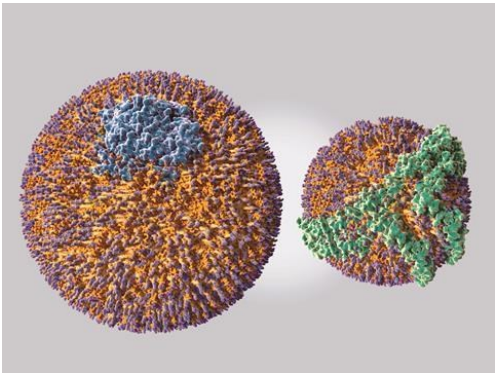
If guanosine diphosphate-L-fucose synthase turns out to be one of the elusive MS self-antigens, dosing patients with it might tame symptoms such as numbness and muscle weakness in much the same way that allergy shots prevent people from reacting to substances like ragweed pollen, Sospedra says. She and her colleagues plan to start to test this strategy with MS patients next year.

http://bit.ly/2pUaPqB

Facing pharma's failures

What are the projects that drug companies wish they'd never started?

Derek Lowe



So far, every effort to harness CETP to rebalance cholesterol from low-density (left) to high-density lipoprotein (right) has failed **© Shutterstock**

Drug discovery has some real success stories, and you can find many accounts of these in the literature. There are papers, speeches at award ceremonies, career retrospectives when longtime researchers retire and so on.

But what doesn't get recounted in anything like this level of detail are the projects – or even the whole therapeutic areas – that the scientists involved wished they'd never heard of or thought to work

on. That's a real gap in the corpus of knowledge, because examining these programmes provides a perspective that's missing from the Greatest Hits repertoire. After all, most clinical trials end in failure, and many projects don't even make it to the clinic at all.

Cholesteryl ester transport protein (CETP) is a classic example of a drug target that would have saved everyone a great deal of time and money to avoid. At one time, there was reason to believe that an inhibitor of its activity would be a great thing for cardiovascular disease. After all, CETP catalyses movement of cholesterol from high density lipoprotein (HDL – the so-called good cholesterol particles) to low- and very low density lipoprotein ((V)LDL, or bad cholesterol). Why not stop it from doing that and give everyone a better, healthier lipid profile?

The first problem was that, although most of the major drug companies piled into discovery efforts, every inhibitor that really worked was shockingly greasy and hydrophobic. They often came decorated with an unusual number of fluorine atoms, making them look like something you might use to produce a new type of non-stick cookware. The CETP protein wouldn't have it any other way: its binding pocket, naturally enough, recognised only greasy blobs. These properties made clinical development a real challenge, but a bigger challenge loomed: once tested on prospective heart patients, none of the drugs seemed to work.

Pfizer's torcetrapib was the leader in the clinic thanks to a huge (and hugely expensive) development programme, until it all imploded in a famous large-trial disaster very late in the game. Most disconcertingly, the drug treatment group turned out to be dying from heart attacks at a slightly higher rate than the control group. One after another, every other CETP program was eventually dropped: later compounds at least didn't look as grim as torcetrapib, but while they did no harm they also did no good. Merck & Co was the last big company in the hunt – anacetrapib actually managed to show a slight benefit. So slight that Merck gave up on the whole idea, as did everyone else.

It would be a more sensible world if all such drug failures had immediate lessons about what to avoid. But it can be hard to distinguish the failures from programmes that worked

Antagonists of the CB1 cannabinoid receptor were another wipeout. The idea was that they would have the opposite effect to the agonist compounds famously found in cannabis: making people crave food less, and thus be a completely new therapy for obesity. But obesity drugs have been a series of disasters, since it's very difficult to alter a behaviour with as much evolutionary backup behind it as eating. Several companies tried this idea out, with Sanofi-Aventis actually getting rimonabant (Acomplia) to approval in Europe – although not in the US, where the Food and Drug Administration (FDA) wasn't convinced of its risk–benefit profile. The agency seems to have had a point: two years later, the drug was withdrawn owing to psychiatric side effects, including intrusive thoughts of suicide. As far as I know, no one has quite figured that one out to this day, and CB receptor mechanisms are still being eyed warily.

It would be a more sensible world if all such drug failures had immediate lessons about what to avoid – too rapid, too slow, too risky, too much caution, or too much pride. But while these are all certainly drug development sins, it can be hard to distinguish these failures from programmes that worked and paid off wonderfully for patients and companies alike. Indeed, if any of the above examples had worked, people would even now be writing about the lessons about determination and courage that could be drawn from their success. The Roman historian Tacitus was right: victory is claimed by everyone, but no one wants to take responsibility for failures. As an industry, we'd much rather talk about the victories ourselves. But we have more failures to deal with, and working out what they have

to teach us isn't easy – made harder when we decide we'd rather not think about them at all.

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

Healthy mice from same-sex parents have their own pups

Advance reveals genetic factors that require mammals to reproduce using two sexes.

Jeremy Rehm

For the first time, researchers have used the DNA from two mouse mothers to create healthy pups, some of which matured and had their own offspring. The scientists also produced baby mice using the combined genetic material from two fathers, although those pups only lived for a couple of days.

A female mouse, born to two mothers, tends to her own pups. **Leyun Wang**

The method the team used to create the pups, described in a study[1] published on 11 October in *Cell Stem Cell*, reveals important genetic factors necessary for the development of healthy embryos. But scientists are sceptical that the technique could ever be applied to people.

Some animals, such as certain species of birds, fish and lizards, can reproduce using only one sex or an individual. Mammals, however, need members of the opposite sex to create the next generation.

Scientists think this is because of genetic imprints, small chemical tags that attach to DNA and turn off a gene. They've found roughly 100 such tags, many of which are found on genes affecting an embryo's growth.

Many genes that are tagged in one sex remain untagged in the opposite sex. Combining two of the same tagged genes in an embryo — which would happen with parents of the same sex — leads to its death.

Deleting tags

Attempting to overcome this barrier, study author Qi Zhou, a developmental biologist at the Chinese Academy of Sciences in Beijing, and his team used lab-grown embryonic stem cells from either a sperm or an egg. These cells have only one set of chromosomes and, like most cells, contain genetic regions that can produce the chemical tags.

In a process of trial and error, and on the basis of results from previous studies[2], the researchers deleted these genetic regions in batches, searching for groups that could be removed without stopping the production of a healthy embryo. The team then combined a stem cell from a female mouse with the egg from another female to create pups from two mothers. They also took a stem cell from a male and injected it, along with another male's sperm, into an egg without a nucleus to create offspring from two fathers.

After deleting three genetic regions, the scientists managed to produce 29 living mice from two females, 7 of which went on to have their own pups. The team needed to delete 7 regions to produce 12 pups from two male parents — but those baby mice lasted only 2 days after succumbing to problems including trouble breathing and extra fluid in their tissues.

These results revealed some of the most important genetic regions that prevent mammals from reproducing without two individuals of the opposite sex, says Zhou. It also showed "a new and clear way to produce offspring between same-sex mammals".

Risky business

Scientists are sceptical that this technique could ever be applied to humans, however. "Most, if not all, of the embryos that they developed were still abnormal and could not survive," says Jacob Hanna, a molecular geneticist at the Weizmann Institute of Science

in Rehovot, Israel. The authors only had a 14% success rate with embryos from the two mothers and a 2.5% rate with the two fathers.

“I think it’s almost impossible that this would be allowed for clinical application,” Hanna says.

“When you reproduce, you really want every factor possible to have a good outcome,” says Allan Spradling, a reproductive biologist at the Carnegie Institution for Science in Baltimore, Maryland. But nothing indicates how normal these mice are, such as how susceptible they might be to diseases, he adds.

“I don’t think it’s going to lead to people genetically having two mothers or two fathers as a routine thing,” says Spradling. “We don’t understand it well enough, and it might be too risky to take it that far.”

doi: 10.1038/d41586-018-06999-6

http://bit.ly/2Pyz6xG

Scientists develop novel vaccine for lassa fever and rabies

Novel vaccine designed to protect people from both Lassa fever and rabies shows promise

WHAT:

A novel vaccine designed to protect people from both Lassa fever and rabies showed promise in preclinical testing, according to new research published in *Nature Communications*. The investigational vaccine, called LASSARAB, was developed and tested by scientists at Thomas Jefferson University in Philadelphia; the University of Minho in Braga, Portugal; the University of California, San Diego; and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

The inactivated recombinant vaccine candidate uses a weakened rabies virus vector, or carrier. The research team inserted genetic material from Lassa virus into the rabies virus vector so the vaccine expresses surface proteins from both the Lassa virus and the rabies virus. These surface proteins prompt an immune response against both Lassa and rabies viruses. The recombinant vaccine was then inactivated to "kill" the live rabies virus used to make the carrier.

There are currently no approved Lassa fever vaccines. Although Lassa fever is often a mild illness, some people experience serious symptoms, such as hemorrhage (severe bleeding) and shock. The overall Lassa virus infection case-fatality rate is about one percent, according to the World Health Organization (WHO), but that rate rises to 15 percent for patients hospitalized with severe cases of Lassa fever. People contract Lassa virus through contact with infected Mastomys rats and through exposure to an infected person's bodily fluids. Lassa fever is endemic to West Africa where these rats are common. In 2018, Nigeria experienced its largest-ever Lassa fever outbreak, with 514 confirmed cases and 134 deaths from Jan. 1 through Sept. 30, according to the Nigeria Centre for Disease Control.

Africa is also at high risk for human rabies. The WHO estimates that 95 percent of the estimated 59,000 human rabies deaths per year occur in Africa and Asia. Nearly all human rabies deaths are caused by bites or scratches from infected dogs. Effective rabies vaccines and post-exposure shots are available, but many deaths still occur in resource-limited countries.

The newly published findings show that LASSARAB, when administered with GLA-SE adjuvant (an immune response-stimulating protein), elicits antibodies against Lassa virus and rabies virus in mouse and guinea pig models. The vaccine also protected guinea pigs from Lassa fever after being exposed to the virus 58 days after vaccination.

Prior research indicated that an antibody-mediated immune response is not correlated with protection from Lassa fever, the authors note. However, the new findings show that high levels of non-neutralizing immunoglobulin G (IgG) antibodies that bind to the Lassa virus surface protein correlate with protection against Lassa virus. Levels of this type of antibody could potentially be a Lassa fever correlate

of protection used to determine vaccine efficacy, according to the authors. They note the next step is to evaluate the experimental vaccine in nonhuman primates before advancing to human clinical trials.

ARTICLE:

T Abreu-Mota et al. Non-neutralizing antibodies elicited by recombinant Lassa-Rabies vaccine are critical for protection against Lassa fever. Nature Communications DOI: 10.1038/s41467-018-06741-w (2018).

http://bit.ly/2IUrCmn

Study identifies effective ketamine doses for treatment-resistant depression

Subanesthetic dosage levels of the anesthetic drug ketamine that appear to provide significant symptom relief

A study led by Massachusetts General Hospital (MGH) investigators identifies two subanesthetic dosage levels of the anesthetic drug ketamine that appear to provide significant symptom relief to patients with treatment-resistant depression. In the October 2018 issue of Molecular Psychiatry they describe finding that single intravenous doses of 0.5 mg/kg and 1.0 mg/kg were more effective than an active placebo in reducing depression symptoms over a three-day period. Two lower dosage levels that were tested did not provide significant symptom relief, although some improvement was noted with the lowest 0.1 mg/kg dose.

"Treatment resistance in depression is a major issue, with more than half of patients not responding adequately to standard, appropriate antidepressant treatment," says Maurizio Fava, MD, executive director of the Clinical Trials Network & Institute in the MGH Department of Psychiatry and senior author of the *Molecular Psychiatry* paper. "There are only a few approved therapies that can help some patients with treatment-resistant depression, so we critically need more options to choose from."

Long used as a general anesthetic drug, ketamine has been found in several studies to rapidly relieve depression symptoms when given at low, subanesthetic doses. Most of those studies used a standard 0.5 mg/kg intravenous dose, leaving determination of the optimal dosage unclear. To investigate that question, the study tested four different ketamine dosages - 0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg and 1.0 mg/kg - compared with an "active" placebo, a drug that induces side effects, the lack of which could lead participants to realize they are not receiving the medication being tested, potentially biasing their perception of symptom improvement.

The study enrolled 99 adults with treatment-resistant depression at six research centers - MGH, Baylor College of Medicine/Debakey VA Medical Center, Icahn School of Medicine at Mt. Sinai, Stanford University School of Medicine, University of Texas/Southwestern Medical Center, and Yale University. Participants were randomized into five groups - the four dosage levels and the active control group, with neither they nor the research staff aware of group assignments - and continued taking their previously prescribed antidepressants during the study period.

Participants were assessed with a standard depression rating scale the day they received the infusion and 2, 3, 5, 7, 14 and 30 days later. Additional instruments measured aspects of mood and suicidal thought. Dissociative symptoms such as memory loss and feelings of detachment from reality were assessed during and after ketamine infusion, and vital signs were measured after treatment and at all follow-up visits.

On the standard depression scale, participants receiving ketamine had significantly greater symptom improvement during the three days after infusion than did those in the active control group. Comparison of dosage levels, after adjusting for multiple comparisons, found statistically significant improvement compared to the control group only for participants receiving 0.5 mg/kg and 1.0 mg/kg doses. The low 0.1 mg/kg dose produced significant relief only prior to adjustment, and the 0.2 mg/kg dose did not show any

significant benefits. It is possible that the lack of efficacy at the 0.2 mg/kg level could reflect the small size of treatment groups and the fact that participants in that group tended to be more treatment resistant to begin with, the authors note.

For most participants in the higher-dose groups, the benefits of ketamine treatment began to decrease on the third day after treatment and were no longer detectable after five days. There were no significant differences in the occurrence of adverse events among all study participants.

Co-author Cristina Cusin, MD, who directs the MGH Psychiatry ketamine clinic, says "These results support the clinical observation that one size - in this case the most studied dose of 0.5 mg/kg - does not fit all, as some patients may require a lower-than-average dose; and each patient needs a tailored treatment plan that may include ketamine, together with other medications and talk therapy. We still do not understand which factors play a role in determining lack of response to treatments or which is the best possible strategy for patients suffering from severe depression."

Fava, the Slater Family Professor of Psychiatry at Harvard Medical School, adds, "Along with supporting the efficacy of intravenous ketamine for patients with treatment-resistant depression, our study also suggests that even lower doses may be effective in some patients. Further investigation should examine the efficacy of repeat doses of ketamine, as well as whether higher doses may require less frequent administration."

Additional co-authors of the Molecular Psychiatry *paper are Marlene Freeman, MD, Martina Flynn, Bettina Hoeppner, PhD, Dawn Ionescu, MD, and George Papakostas, MD, MGH Psychiatry; Lee Chang, MD, and Sanjay Matthew, MD, Baylor/Debakey VA Medical Center; Dan Iosifescu, MD, MSc, and James Murrough, MD, Icahn/Mt. Sinai; Charles Debattista, MD, DMH, and Alan Schatzberg, MD, Stanford; Madhukar Trivedi, MD, and Manish Jha, MD, UTexas/Southwestern; and Gerard Sanacora, MD, PhD, and Samuel Wilkinson, MD, Yale. The study was supported by National Institute for Mental Health contract HHSN271201100006I.*

http://bit.ly/2yyHhD0

New techniques can detect Lyme disease weeks before current tests

Rutgers researcher leads team analyzing more exact methods to diagnose the most common tick-borne infection

Newark, N.J. - Researchers have developed techniques to detect Lyme disease bacteria weeks sooner than current tests, allowing patients to start treatment earlier.

The findings appear in the journal *Clinical Infectious Diseases*. The authors include scientists from Rutgers Biomedical and Health Sciences, Harvard University, Yale University, the National Institute of Allergy and Infectious Diseases, FDA, Centers for Disease Control and Prevention, and other institutions.

The new techniques can detect an active infection with the Lyme bacteria faster than the three weeks it takes for the current indirect antibody-based tests, which have been a standard since 1994. Another advantage of the new tests is that a positive result in blood indicates the infection is active and should be treated immediately, allowing quicker treatment to prevent long-term health problems. The techniques detect DNA or protein from the Lyme disease bacteria Borrelia burgdorferi.

"These direct tests are needed because you can get Lyme disease more than once, features are often non-diagnostic and the current standard FDA-approved tests cannot distinguish an active, ongoing infection from a past cured one," said lead author Steven Schutzer, a physician-scientist at Rutgers New Jersey Medical School. "The problem is worsening because Lyme disease has increased in numbers to 300,000 per year in the United States and is spreading across the country and world."

Lyme disease signs frequently, but not always, include a red ring or bull's eye skin rash. When there is no rash, a reliable laboratory test is needed and preferably one that indicates active disease. The only FDA-approved Lyme disease tests rely on detecting antibodies that

the body's immune system makes in response to the disease. Such a single antibody test is not an active disease indicator but rather only an exposure indicator -- past or present.

"The new tests that directly detect the Lyme agent's DNA are more exact and are not susceptible to the same false-positive results and uncertainties associated with current FDA-approved indirect tests," said Schutzer. "It will not be surprising to see direct tests for Lyme disease join the growing list of FDA-approved direct tests for other bacterial, fungal and viral infections that include Staphylococcus, Streptococcus, Candida, influenza, HIV, herpes and hepatitis, among others."

The authors developed the paper after a meeting at Cold Spring Harbor Laboratory's Banbury Conference Center, a nonprofit research institution in New York to discuss current Lyme disease tests and the potential of new scientific advances to increase the accuracy of an early diagnosis.

http://bit.ly/2PBEznL

Antibiotic-free treatment of dairy cows underway

Is antibiotic resistance signalling the end for modern treatments of udder infections in the dairy industry? Not so fast, according to researchers who are developing breakthrough technology that's effective against all tested bacteria.

CORDIS

Antibiotic resistance is increasing dramatically all over the world. As more and more bacteria become resistant to the antibiotics designed to kill them, they render these drugs ineffective, undermining our ability to treat common infectious diseases. Unless urgent action is taken, the World Health Organization foresees us entering a post-antibiotic era where common infections and minor injuries can once again prove fatal.

The EU-funded project PanaMast is tackling the problem of antibiotic resistance by focusing on bovine mastitis, a commonly occurring inflammation of the udder affecting dairy cattle worldwide. While mastitis is normally treated using conventional antibiotics, PanaMast is developing the world's first non-antibiotic solution to treat lactating cows.

Health and economic benefits of the innovative technology

Called long-acting reactive species (LARS), the novel non-antibiotic antimicrobial technology has so far been found to be effective against all tested microorganisms, including antibiotic-resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA). More importantly, it doesn't induce resistance. Highly effective against both gram-negative and gram-positive bacteria, LARS has also demonstrated an excellent safety/low toxicity profile in vivo and in vitro. It can be administered in different ways, including in aerosolised or nebulised form, and its low minimum inhibitory concentrations make it appropriate for a wide range of therapeutic applications.

Besides the health advantages it presents, the new treatment also offers significant economic benefits to dairy farmers. With conventional antibiotics, farmers lose milk revenues, since milk from cows undergoing treatment cannot be sold for a period of time during and after treatment. Furthermore, when the antibiotics don't work, infected cows have to be culled. This costs the European and American dairy industries over EUR 3 billion a year. But when infected cows are treated with LARS, milk can potentially be sold both during and after treatment, significantly benefiting farmers and milk producers.

In a press release published by project leader Westway Health, CEO Dr. Ruairi Friel explained the company's innovative approach: "The genesis of the idea was knowing that there are other ways to kill bacteria like MRSA. This is done every day around the world using disinfectants for example, or through steam cleaning. What we have been able to develop is a new method of killing bacteria which does

not harm living tissue. Our solution is based on a combination of compounds inspired by nature, and if we can develop and scale our solution we believe we can help tackle this global challenge of antibiotic-resistance."

By the end of the 24-month project, PanaMast (Progressing a non-antibiotic antimicrobial treatment for Bovine Mastitis towards market – PanaMast) intends to have completed the testing of its novel product and have it ready for market implementation (technology readiness level 8). Subject to regulatory approval by the European Medicines Agency, the aim is to have the product available on the market by 2021 or 2022.

More information: *PanaMast project web page: westwayhealth.com/h2020/*

https://wb.md/2ygSPeU

A Low-Risk, Low-Cost Way to Slow Cognitive Decline

Intervention uses goal setting and action plans to reinforce healthy cognitive, physical, and social activity

Arefa Cassoobhoy, MD, MPH

Hello. I'm Dr Arefa Cassoobhoy, a primary care internist, Medscape advisor, and senior medical director for WebMD. Welcome to Medscape Morning Report, our 1-minute news story for primary care.

In the United States, black patients have twice the rate of dementia as white patients.

A new study focused on this group, working with more than 200 older African Americans with mild cognitive impairment. The researchers tested behavioral activation as a method to slow cognitive decline and prevent dementia. The intervention uses goal setting and action plans to reinforce healthy cognitive, physical, and social activity.

The action plans rely on visual cues, written schedules, and step-by-step sequencing to complete a goal, like meeting a friend for a walk. The control group in the study received standard supportive treatment. The primary outcome for cognition was measured by a decline in recalled words. The secondary outcome was a decline in functional ability.

The results are impressive.

At 24 months, the rate of cognitive decline was 1.2% in the behavioral-activation group compared with 9.3% in the supportive-therapy group. To give context, prior studies suggest that the expected decline would be between 12% and 41%.

Behavioral activation appears to be a low-cost, low-risk intervention that you can consider adding to treatment for your patients with mild cognitive impairment.

https://bbc.in/2Pz5SyP

Doctors can prescribe medical cannabis from November in UK

Doctors will be able to prescribe cannabis products to patients from 1 November, the Home Secretary Sajid Javid says.

The new regulations apply to England, Wales, Scotland and Northern Ireland.

Mr Javid decided to relax the rules on when cannabis products could be given to patients after a review into medicinal cannabis earlier this year.

This followed an outcry over Alfie Dingley and Billy Caldwell being denied access to cannabis oil.

The parents of the two young epilepsy sufferers said the product helped to control their seizures.

Alfie's mother, Hannah Deacon, welcomed the move, saying: "We urge the medical world to get behind these reforms so they can help the tens of thousands of people who are in urgent need of help.

Image caption Billy Caldwell and Alfie Dingley were granted licences to allow them access to cannabis oil

"I have personally seen how my son's life has changed due to the medical cannabis he is now prescribed."

Professor Mike Barnes, the medical cannabis expert who secured the first long-term licence for its use for Alfie, encouraged doctors to embrace the changes to the laws on prescribing medicinal cannabis.

An initial review by chief medical officer Dame Sally Davies concluded there was evidence medicinal cannabis has therapeutic benefits.

The Advisory Council on the Misuse of Drugs (ACMD), which carried out the second part of the review, then said doctors should be able to prescribe medicinal cannabis provided products met safety standards.

It recommended cannabis-derived medicinal products should be placed in schedule two of the Misuse of Drugs Regulations 2001.

Cannabis has previously been classed as a schedule one drug, meaning it is thought to have no therapeutic value but can be used for the purposes of research with a Home Office licence.

http://bit.ly/2CKoclR

Calm the immune system, halt premature birth

University of Connecticut researchers report a potential treatment that could stop many cases of premature labor and birth in their tracks

Premature birth is the leading cause of infant death and disability in the U.S., and costs billions in dollars and heartache every year. Now, University of Connecticut researchers report in Reproductive Sciences a potential treatment that could stop many cases of premature labor and birth in their tracks.

UConn Health's Christopher Nold, an obstetrician who practices maternal-fetal medicine at Hartford Hospital, and Anthony Vella, an immunologist, were curious about the immune system's role in premature birth.

Most pregnancies last about 40 weeks. A baby born before 37 weeks may be too small to regulate body temperature or breathing, and suffer from brain bleeds or other organ troubles, as well as long-term impacts such as developmental delays and cognitive problems.

In this nation alone, about 337,000 babies were born prematurely in 2016. But in other mammals premature birth is quite rare, and usually happens only if there is an infection or inflammation.

The researchers knew that cytokines, small proteins that alert the body to infection and cause inflammation, had been found in the amniotic fluid of many women who gave birth prematurely.

That made them wonder. The fetus is different enough from its mother that the immune system ought to attack it, but something blocks that from happening during pregnancy. What if that protection stopped for some women, causing premature labor?

"There's a lot of anti-inflammatory mechanisms that prevent the fetus from being rejected. So we thought maybe dangerous inflammation, that can break down the tolerance barrier, could mediate the start-up of birth," even - or especially - premature birth, says Vella.

So Nold and Vella took cells from the female reproductive tract and the amniotic fluid that surrounds fetuses in the womb, and exposed them to pieces of bacteria in the lab. As they expected, the cells produced lots of cytokines - the equivalent of shouting "hey, there's an invader!"

But the cytokines weren't primarily the inflammation-causing kind the researchers were expecting.

Instead, they saw much more granulocyte-macrophage colony-stimulating factor (GM-CSF) than they expected. GM-CSF is a kind of cytokine that causes cells to grow up quickly and become bacteria-eating macrophages. The population of macrophages in pregnant women does tend to ramp up right before the women give birth. But it's unclear if that is directly connected to birth, or a side effect of another process.

Nold and Vella's finding that GM-CSF is released in response to perceived bacterial infection is intriguing, because there's already a drug available that blocks GM-CSF.

Treating pregnant mice with this drug sharply reduced preterm birth in mice that had been exposed to pieces of dangerous bacteria. If preventing premature births could be that straightforward, it would be a game changer. Nold and Vella have filed for a provisional patent on the technology.

But first the researchers need to figure out if GM-CSF is really what's causing premature birth in women.

Nold has been collecting samples from women early in pregnancy to see if there's anything detectable early on that could show who is at risk of giving birth prematurely. He and Vella would like to test those samples for GM-CSF, and see if GM-CSF levels early in pregnancy can give clues as to how early the pregnancies end.

"We're hoping to do more immune mechanism studies in mice. And in the not-too-distant future, we hope to start looking at human studies," Nold says. Hartford Hospital has already given them a small grant, and they are looking for more funding to pursue the research further.

http://bit.ly/2NGcV72

An RNA key that unlocks innate immunity

Versatile RNA molecule may be a key player in human cells' frontline defenses against viruses

RNA has long been the neglected middle child of biomolecules, the go-between between DNA, which encodes the cell's instructions, and proteins, which carry them out. Increasingly, though, researchers are recognizing RNA as a versatile molecule with, possibly, as many functions as proteins have. New research from Emory University, published in the *Journal of Biological Chemistry*, shows that one such versatile RNA molecule may be a key player in human cells' frontline defenses against viruses.

Graeme Conn, the biochemistry professor who oversaw the work, studies how RNA is involved in the body's responses to infections. When a human cell senses a virus, it activates a signaling pathway: a protein called OAS gets turned on and produces a signaling molecule, which in turn activates another protein that both directly defends against the virus as well as activating other parts of the cell's innate immune system.

As it turns out, human RNA might play an important role in this pathway, specifically a human RNA molecule called nc886. The "nc" stands for "noncoding," which means this RNA molecule is not carrying instructions for building a protein. It's doing something all on its own.

What it's doing, the new paper shows, is turning on OAS, thus setting off the chain of events that destroys viruses.

"We saw that (nc886) wasn't just an activator of this pathway, but a very potent activator," said Brenda Calderon, who carried out the research as a graduate student in Conn's lab.

The nc886 molecule can adopt two different shapes, and one of them is much better at activating OAS than the other. This is another way in which this RNA molecule acts like a protein: its function depends strongly on its 3-D shape and structure. Although nc886 is present in all human cells, it's unknown whether the relative abundance of the immune-activating and less-active form might change in response to infection.

"We'll be asking these questions about infected and uninfected cells," Conn said. "How does the level of the RNA change? How do the levels of these two (forms) change?"

Getting deep into the molecular details of cells' first responses to viruses opens the door to new kinds of treatments. Calderon speculates that understanding the factors that activate this pathway may enable researchers to someday manipulate it to strengthen antiviral defenses.

"Such approaches have the potential to underpin novel, broad antiviral therapies (that don't rely) on acquired immunity, and therefore are suitable for infants, elderly, and immunocompromised patients," Calderon said.

The study was funded by the National Institutes of Health and Emory University.

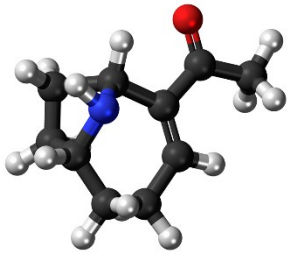
http://bit.ly/2QKxeSK

Anatoxin-a

The compound formerly known by the no-nonsense name 'very fast death factor'

By Gege Li12 October 2018

Ben Valsler



On a hot summer's day, a dip in an open air lake or pond can seem like a great way to cool off. And although we may be wary of the dangers beneath the surface, sometimes, it's the stuff floating on the top that is the biggest risk. Here's Gege Li.

Gege Li

A teenager goes for a seemingly harmless dip in the local pond with his friends in Wisconsin. 48 hours later, he suffers convulsions and a seizure and eventually dies of heart failure. The circumstances of Dane Rogers' death back in 2002 remained mysterious until the coroner found that the 17 year old boy had taken in several mouthfuls of water while wrestling and playing in the apparently 'scummy and dirty' pond. This scum, probably enough to set off alarm bells in itself, was actually an algal bloom, and might have been responsible for killing Rogers and giving his decidedly more fortunate friend diarrhoea and abdominal pain. But what made it potentially lethal?

Blood and stool samples revealed that something sinister could have been lurking in the pond: a potent neurotoxin called anatoxin-a. Produced by several species of blue-green coloured cyanobacteria including *Oscillatoria* (technically not algae at all but photosynthetic prokaryotes), anatoxin-a used to be known by a name that helped cement its reputation as a killer: Very Fast Death Factor, or VFDF. It earned this name after blooms on lakes across North America were held responsible for wiping out the cattle who were drinking from the water in a mere hour – instead of over the course of several hours or days like most other toxins. As well as being found in drinking water, this bicyclic alkaloid – containing a core homotropane moiety with a secondary amine – can also find its way to us through contaminated food and skin contact while swimming. Luckily, it has a short half-life.

But despite numerous and well-documented cases of anatoxin-a toxicity on mice, cows and dogs, in the end medical investigators weren't able to conclusively determine whether it killed the Wisconsin teenager. They had no previous human anatoxin-a related deaths to compare it to, and the lethal dose of anatoxin-a for humans hasn't and still can't be determined, though it ranges from 10 to 40mg per kilo of bodyweight in other animals. The time elapsed between the boy's swim and death could rule out this speedy-acting toxin as the culprit, although this was the only puzzling fact standing in the way of a firm verdict – theoretically the amount of anatoxin-a from the samples was enough to cause a rapid death.

Whether it's a killer of men or not, one thing that is clear is that we shouldn't let ourselves get too relaxed when it comes to anatoxin-a. Environmentally, it contributes to eutrophication and is highly toxic to fish populations, and its presence in drinking water across the world poses a very real health hazard. Symptoms of poisoning can be pretty unpleasant, with muscle tremors, convulsions and respiratory failure being just a few of the ways it demonstrates its dangerous effects. The common feature here is loss of muscle control, which happens when anatoxin-a binds to receptors in the synaptic cleft between neurons in place of the neurotransmitter acetylcholine.

In the short term, this rogue binding isn't any different to the norm – it causes sodium and calcium channels to open, which triggers an electrical signal leading to muscle movement. But anatoxin-a becomes permanently attached to the receptor, and that is the cause for concern. The enzyme acetylcholinase that usually switches off acetylcholine can't cleave the toxin to stop the response either, leading to a build-up of neurotransmitter and – inevitably – over-stimulated and paralysed muscles.

The green scum shown in this image is the worst algae bloom Lake Erie has experienced in decades. Vibrant green filaments extend out from the northern shore.Image captured by the Landsat-5 satellite. Data provided courtesy of the United States Geological Survey.

As scary as this all sounds, it might not in fact be such a terrible thing (and that's definitely not a suggestion to start advocating anatoxin-a induced deaths). The toxin could actually be a viable candidate for treating Alzheimer's. The key to its success lies in the exact mode of action that can prove so dangerous for the unsuspecting individuals that ingest it. By inhibiting acetylcholinase, anatoxin-a can compensate for the drastic loss in acetylcholine – sometimes up to 90% – that Alzheimer's sufferers experience. If we can reduce its toxicity, this classically-deadly toxin has the exciting prospect of opening up doors for combating neurodegenerative diseases.

And we don't have to look for scummy ponds to find the toxin. Due to their similar stereochemistry, the ideal precursor for biologically synthesising anatoxin-a is cocaine, a feat that was accomplished in 1977.

Algae bloom in Reflecting Pool, Washington, DC. 2007 **Eric Vance / USEPA**

In the meantime, anatoxin-a in the wild continues to endanger wildlife, livestock and pets. Treatments for contaminated water are lacking since conventional chlorine can't oxidise the toxin effectively, though activated carbon is looking promising as an alternative. This isn't to say your next glass of water is going to kill you, but do perhaps refrain from letting your dog (or yourself) drink from a pond that's covered in a suspicious amount of algae…

http://bit.ly/2Or1dT2

Could cheese help prevent type 2 diabetes?

People with higher levels of biomarkers of dairy fat had a lower risk of developing type 2 diabetes

Author Fumiaki Imamura *
Interviewed Nita Forouhi **

Many people believe that low-fat dairy products are healthier than high-fat dairy products. Indeed, many public health guidelines recommend low-fat dairy over high-fat dairy. However, our latest research, published in PLOS Medicine, found that people who had higher levels of biomarkers of dairy fat had a lower risk of developing type 2 diabetes.

Dairy products contain calcium and other nutrients that are important for our health, but they are often high in saturated fat – which is considered to be bad for cardiovascular health. Although food manufacturers have created many low-fat dairy products, such as yogurts and flavoured-milk drinks, they often have lots of added sugar. Sugar, of course, is also bad for our health. So which dairy products should we choose: high-fat or low-fat?

Studies on dairy consumption have reported mixed results. The recent evidence shows no clear differences between high-fat and low-fat dairy in terms of the risk of developing type 2 diabetes or cardiovascular diseases.

However, most studies have relied on self-reports of dietary consumption by study participants. And self-reports are notoriously unreliable as people often misjudge how much they have eaten. With

dairy consumption, for example, participants may fail to report baked goods, such as cakes and savoury pies, that contain dairy.

An objective measure

Some scientists have shown that certain types of fat in our body tissue reflect dairy fat consumption. These biomarkers are more reliable than self-reports of dairy consumption.

Using this method, a couple of studies and one systematic review have found no link between dairy fat consumption and a higher risk of heart disease.

And summary evidence from our group, published in 2014, found an inverse association between dairy fat biomarkers and type 2 diabetes risk. In other words, the more dairy fat biomarkers found in a person's blood, the lower their risk of getting type 2 diabetes.

To produce more definitive evidence, we conducted a global study which included data on nearly 64,000 adults from 16 countries. We evaluated the biomarkers we previously examined, but we also included additional dairy-fat biomarkers.

The results of our study further support the evidence that higher concentrations of the dairy-fat biomarkers are associated with a lower risk of developing type 2 diabetes.

Limitations

As with all studies, there are limitations. Biomarkers do not distinguish different types of dairy products, such as milk, cheese and yogurt. Also, our findings were mostly from white populations in the US and Europe – evidence for other populations remains limited.

Dairy products are one of the main sources of saturated fat, but we can't draw conclusions about other sources of saturated fat, such as meat and oil, and the risk of type 2 diabetes and cardiovascular disease. This complexity should also be discussed in different contexts such as how dairy products are consumed with different foods in different cultures and populations, and how dairy fat consumption is linked to other health outcomes, such as cancer and bone health.

Despite the limitations, our new research highlights how objective assessment using biomarkers can help to increase understanding between dairy consumption and health risks. This research indicates that dairy fat may not be harmful, indeed, it may be beneficial. But more work needs to be done to understand the overall effects of dairy, over and above its fat content.

There isn't enough evidence, yet, to change dietary guidelines, which in the UK recommend that saturated fats should make up less than 11% of all calories consumed from food. We hope that our research will further stimulate clinical and public health research and a dialogue to promote an optimal diet, focusing more on foods than nutrients, including dairy.

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http://bit.ly/2OrwG7K

E-cig co. put Viagra, Cialis in vape liquids—the FDA is throbbing mad

Company also claimed a risky anti-obesity drug and its products were FDA approved.

Beth Mole - 10/12/2018, 11:24 PM

The US Food and Drug Administration made clear on Thursday, October 11 that it has a major bone to pick with an electronic-cigarette vendor that illegally pumped prescription erectile dysfunction drugs into unapproved e-liquid products intended for vaping.

The cocky company, HelloCig Electronic Technology Co. Ltd, even advertised the vape liquids with labels and images using drug brand names. For instance, it sold one of the vaping liquids as "E-Cialis HelloCig E-Liquid" alongside an image of a bottle and tablets of Eli Lilly's erectile dysfunction drug Cialis. It also sold a product with the brand of an anti-obesity drug that had been pulled from the market in Europe for causing psychiatric disorders. The e-liquid really contained the erectile dysfunction drug in Viagra, the FDA found.

In other instances, the company falsely claimed that e-liquid products were "FDA approved product[s] with FDA."

The throbbing mad agency issued a stiff warning and firmly threatened "civil money penalties, criminal prosecution, seizure, and/or injunction" if HelloCig didn't pull its products off the market immediately. The company has 15 days to respond.

FDA Commissioner Scott Gottlieb blasted the company in a statement, saying:

There are no e-liquid products approved to contain prescription drugs or any other medications that require a doctor's supervision. Prescription drugs are carefully evaluated and labeled to reflect the risks of the medications and their potential interactions with other medicines, and vaping active drug ingredients is an ineffective route of delivery and can be dangerous. There are no e-liquids that contain prescription drugs that have been proven safe or effective through this route of administration.

The FDA's warning is part of an ongoing effort to deflate misleading and illegal claims on vaping products. The agency's main goal is to block products that specifically entice youth to try addictive nicotine-containing products. Last month, Gottlieb declared that e-cigarette use among teenagers has "reached nothing short of an epidemic proportion of growth."

"I use the word epidemic with great care," he wrote in a statement at the time. "E-cigs have become an almost ubiquitous—and dangerous—trend among teens. The disturbing and accelerating trajectory of use we're seeing in youth, and the resulting path to addiction, must end. It's simply not tolerable. I'll be clear. The FDA won't tolerate a whole generation of young people becoming addicted to nicotine as a tradeoff for enabling adults to have unfettered access to these same products."

As such, the agency has banged away at e-cigarette companies and any questionable tactics. Most notably, the agency seized more than a thousand sales and marketing documents from popular e-cig maker Juul Labs during an unscheduled inspection a few weeks ago. Juul e-cigarettes resemble USB drive devices and have been wildly popular—particularly with teens. They currently make up the lion's share of the e-cig market. The FDA's primary concern is advertising and e-liquid flavorings, such as candy and fruit flavors, intended at hooking youngsters.

With that focus, FDA conducted lab analysis on HelloCig's e-liquids, finding products that contained tadalafil (Cialis) and/or sildenafil (Viagra). The FDA also scrutinized the company's product called "E-Rimonabant HelloCig E-Liquid," which was marketed alongside an image of a bottle and tablets of Acomplia, an anti-obesity drug developed by Sanofi-Aventis. Acomplia was never approved by the FDA, but it had been previously approved in Europe in 2006. It was withdrawn from the market in 2008, however, after it was found to significantly increase the risk of psychiatric disorders. HelloCig's e-liquid did not contain rimonabant (Acomplia), but it did contain undeclared sildenafil, the FDA found.

http://bit.ly/2RMjQih

Not all people are equally vulnerable to hepatitis C – new study

Molecule that defends against HCV and other pathogens is weaker in humans than in our closest relative, the chimpanzee

Connor Bamford
John McLauchlan

The hepatitis C virus (HCV) infects around 1% of the human population and is a devastating pathogen. In most people, it silently infects the liver for decades, often causing life-threatening inflammation, scarring and even cancer. How the virus achieves this feat has long puzzled scientists.

In our latest study, published in PLOS Pathogens, we found that a molecule that defends against HCV and other pathogens is weaker in humans than in our closest relative, the chimpanzee. This weakened molecule might have made it easier for some viruses, such as HCV, to infect humans and cause disease.

We are not defenceless against HCV. Our liver responds to infection by producing antiviral molecules called interferons. You can think of these molecules as the antiviral alarm system. Interferons are made rapidly once an invader has been spotted inside a cell. They are then released by the infected cell where they float across the nearby cells, warning them that a virus is near and forcing them to defend themselves by making hundreds more antiviral molecules.

In particular, we produce what is known as “lambda” – interferons against HCV that work well in liver cells. Strangely, one interferon lambda, called IFNL4, is associated with a reduced chance of clearing HCV, making it easier for the virus to silently infect the liver for decades. How an antiviral molecule appears to help a virus to sustain infection over such a long time, and how this may have evolved, remains a mystery.

Rare find

The long evolution of humans in Africa and later global spread has resulted in genetically diverse populations of humans, each adapted to suit local environments and diseases.

In our recent study, we searched through all the known genetic diversity of the IFNL4 gene, including that of chimpanzees, to identify whether people who carried versions had different abilities to block viral replication. We hoped this would shine a light on the paradoxical role of IFNL4 during HCV infection.

What we found surprised us. A very rare version of IFNL4, which is only found in pygmies (hunter-gatherers from central Africa), was far better able to inhibit HCV infection in the lab. Even more surprisingly, this version had similar properties to the chimpanzee IFNL4. Nearly all humans, except this group of hunter-gatherers, produce a weaker version of IFNL4.

Protective response

This more antiviral version of IFNL4, found in chimpanzees and a small pocket of Central African hunter-gatherers, was better able to turn on hundreds of antiviral molecules when it was added to cells in the lab. This heightened antiviral response was similar to what was found when we compared the genes produced in the liver in response to HCV in people and in chimpanzees. That is, chimpanzees appeared to mount a greater antiviral response to HCV than humans, turning on anti-HCV molecules and enhancing the immune response.

Chimpanzees are the only animal – other than humans – that can be infected by HCV, which is the reason they were used to study the virus and find effective antiviral drugs and vaccines. However, testing in chimpanzees is now banned.

Correlating with this stronger antiviral response is the fact that HCV infection in chimpanzees is less pronounced than in humans. Chimpanzees don’t develop serious hepatitis C. The virus appears to replicate more slowly, and it might be more difficult for HCV to gain a foothold in chimpanzees. Also, despite searching, scientists have been unable to find natural HCV infection in chimpanzees in the wild.

Our finding that very early in human evolution we evolved an antiviral molecule with a reduced ability to block viral infections,

might help explain the insidious nature of HCV – and possibly other viral infections – in humans.

One remaining mystery is what drove early humans to reduce the antiviral activity of IFNL4 and why do a handful of people retain it? We may not have the answers for a while, but studying the immune responses in our chimpanzee cousins in the wild, or in people who still carry the more antiviral version of IFNL4, may unlock some of the mysteries behind the role of IFNL4 in virus infection.

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Disclosure statement

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