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New study tracks the evolution of stone tools

Over 2.6 million years, humans got more efficient at making stone tools.

Kiona N. Smith

For at least 2.6 million years, humans and our ancestors have been making stone tools by chipping off flakes of material to produce sharp edges. We think of stone tools as very rudimentary technology, but producing a usable tool without wasting a lot of stone takes skill and knowledge. That's why archaeologists tend to use the complexity of stone tools as a way to measure the cognitive skills of early humans and the complexity of their cultures and social interactions.

Enlarge / Some of the Middle Stone Age stone tools from Jebel Irhoud. Pointed forms such as a-i are common in this period. Also characteristic are the so-called Levallois prepared core flakes. **Mohammed Kamal**

But because the same tool-making techniques didn't show up everywhere early humans lived, it's hard to really compare how stone tool technology developed across the whole 2.6 million-year history of stone tool-making or across the broad geographic spread of early humans. To do that, you've got to find a common factor.

So a team led by anthropologist Željko Režek of the Max Planck Institute for Evolutionary Anthropology decided to study whether the length of the sharp, working edge of stone flakes changed over time relative to the size of the flakes. A longer, sharp edge is more efficient and takes more control and skill to create, so Režek and his colleagues reasoned that it would be a good proxy for how well early humans understood the process of working stone and how well they shared that knowledge with each other.

A quick lesson in stone knapping

When you're trying to knock a sharp flake off a chunk of stone, the size of the flake and the length of its edge depend on how and where you strike the stone core.

"Stone artifacts vary greatly in complexity, but the physics of stone knapping mean that the most fundamental part of the process of their creation—flake detachment—is similar whether one is producing a single large sharp flake to help butcher an animal or putting the finishing touches to a microlithic weapon component," wrote University of Bordeaux archaeologist Natasha Reynolds in a comment on Režek's study.

One of the most important factors is the thickness of the flake at the spot where it starts (called the platform depth). Another is the angle between the surface being hit to create the flake and the surface of the stone core that the flake breaks off from (called the exterior platform angle). A larger exterior platform angle will create a flake with a long edge relative to its size. But getting it right takes planning, skill, and knowledge.

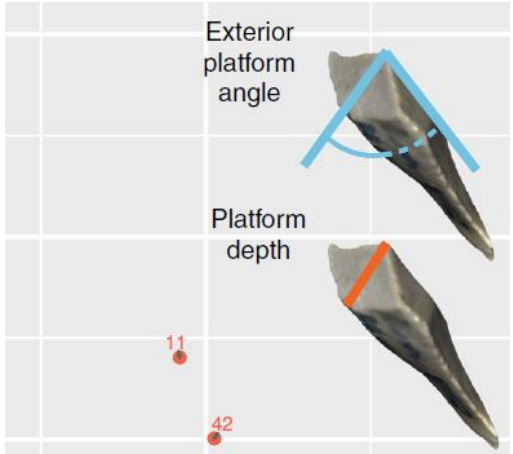


Diagram of exterior platform angle and platform depth. **Željko Režek**

"Controlling these two variables when making a flake requires an ability to direct force at a precise location for a given platform angle," wrote Režek and his team. "This is a skill that is uniquely human." And that, they say, means that the length of a flake's working edge can reveal something about the skill of its makers. That, in turn, can offer clues about how hominin cultures advanced and passed along new skills over the last 2.5 million years.

So Režek and his colleagues measured the edges of more than 19,000 stone flakes from 81 groups of artifacts from sites in Africa, southwest Asia, and Western Europe, spanning a stretch of human history from *Homo habilis* 2.6 million years ago to modern humans 12,000 years ago. Those sites contain artifacts from at least five hominin species: *H. habilis*, *H. erectus*, *H. heidelbergensis*, Neanderthals, and modern humans.

Edges get longer, but also more diverse

Throughout the Pleistocene, the average length of working edges increased relative to flake size. Early Pleistocene stone flakes, made by *H. habilis* and *H. erectus* before about 1 million years ago, had the shortest working edges in the study. After about 1 million years ago, though, flake edges started getting longer, and it appears that *H. erectus*, followed by *H. heidelbergensis* and Neanderthals, learned how to control platform depth and exterior platform angle in order to get more sharp edges relative to the size of their flakes.

That trend continued with modern humans, but at the same time, edge length also started to vary more from site to site. Modern humans living after about 50,000 years ago produced the flakes with both the longest and the shortest sharp edges for their size. It looked as if humans had learned how to make more efficient flakes, but they didn't always put that knowledge to work.

But that variation may actually be a sign of technological progress for early humans.

Being able to get a longer-edged flake out of a single strike is a really efficient use of stone, which gives you an advantage when you're short on resources or when you have to carry a stone a long distance to work or use it. But there are other ways to make sharp edges—for instance, the small, sharp bladelets from the Upper Paleolithic at Abri Pataud cave shelter in France have very short edges but clearly demonstrate sophisticated, efficient craftsmanship.

Meanwhile, the same precision and skill that allowed production of longer edges also allowed toolmakers to vary their edge length for techniques like Levallois or for making short bladelets. Comparing the length of sharp flake edges still offers a good window into the development of the control and skill necessary to do it.

And sometimes a sharper edge wasn't the answer. "The production and use of projectile tools was critical in some contexts, while in others, simple thick flakes may have represented a selective advantage," Režek and his colleagues wrote.

***Enlarge* / This stone biface from the Abri Pataud rock shelter was first shaped by Neanderthals around 100,000 years ago, but modern humans found it and re-shaped it for their own use about 20,000 years ago.** **Sémhur via Wikimedia Commons**

The ability to adapt technique to context is actually pretty sophisticated, and that may be what's behind the increase in variation among flake edges over time. Looking broadly at all these sites, it appears that human culture got better at producing sharp stone flakes over time, even as hominins apparently learned to vary the results as needed.

More questions to answer

Režek's findings generally support what archaeologists have understood for years about the general trend toward skill and complexity in early human technology, but it's one of the first studies comparing large numbers of artifacts across so much time and distance. Edge length gives archaeologists a standardized, concrete way to look at the big picture of human cultural evolution, which has been one of the biggest challenges for Paleolithic archaeologists so far.

If archaeologists can find ways to apply that method to other aspects of stone tool making or in other geographic areas, that could help them tackle some big-picture questions about the development of human culture and cognition.

"It would be interesting to know how these trends hold up when more data are included, for example from early Neanderthals with systematic blade production or more of the varied assemblages associated with anatomically modern humans in North Africa," wrote Reynolds. "It would also be interesting to consider Holocene knapped lithic assemblages, including those from Australia and the Americas."

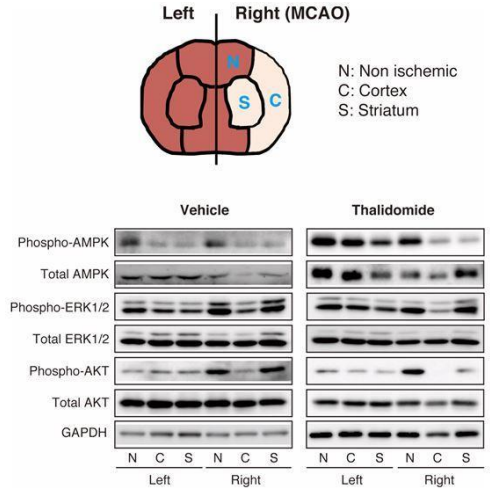
Nature, *2017*. DOI: 10.1038/s41559-018-0488-4 (About DOIs).

http://bit.ly/2FzzLda

How thalidomide is effective against cerebral infarction

Scientists reveal that this dangerous drug could suppress nerve cell death

Notoriously remembered as a major pharmaceutical scandal approximately 60 years ago, thalidomide caused severe birth defects since many pregnant women took the drug as a remedy for their morning sickness. In recent years, however, thalidomide and its derivatives have been widely used to treat hematologic malignancies such as multiple myeloma.



The effect of thalidomide on neuroprotective signalling molecules in the MCAO/R model. **(Scientific Reports 8, Article number: 2459, Figure No. 3ab, Feb, 6, 2018. © Macmillan Publishers Limited.)**

Further, evidence suggests that it also has a neuroprotective effect, reducing both oxidative stress and inflammatory response, but the exact molecular mechanisms of thalidomide on the brain were unknown.

To investigate, scientists at Waseda University and Tokyo University of Pharmacy and Life Sciences studied thalidomide's target protein, cereblon (CRBN), and its binding protein, AMP-activated protein kinase (AMPK), which plays an important role in maintaining intracellular energy homeostasis in the brain. Through their study, they revealed that thalidomide inhibits the activity of AMPK via CRBN under oxidative stress and suppresses nerve cell death.

"We hope that our findings will help with the development of new and safer thalidomide derivatives," says Naoya Sawamura, associate professor of neuropharmacology at Waseda University and leading author of this study, "to better treat diseases such as cerebral infarction, a type of stroke which is a major cause of death worldwide." Their study was published online in *Scientific Reports* on February 6, 2018.

Specifically, Sawamura's research group used cerebral ischemia model rats of the cerebral artery occlusion/reperfusion (MCAO/R) to examine the effect of thalidomide on infarct lesions caused by cerebral ischemia and related intracellular signals. After performing qualitative analysis and assessments on the rats' physical movements, they found that thalidomide treatment significantly decreased the infarct volume and neurological deficits in MCAO/R model rats, and that AMPK was the key signaling protein in the mechanism through additional experiments. Moreover, to determine the molecular mechanisms of the effect of thalidomide on neuronal death, they used oxidative stress-induced neuronal cells, which were induced by administration of H_2O_2, as cerebral ischemia model cells. "In these cells, we found that the AMPK-CRBN interaction weakened and phosphorylation of AMPK enhanced, but thalidomide treatment restored the AMPK-CRBN interaction and suppressed phosphorylation of AMPK," explains Sawamura. "What this implies is that thalidomide regulates AMPK-CRBN interactions in cells under ischemic conditions, meaning, it can suppress nerve cell death."

Further study is needed to identify effective thalidomide derivatives with fewer side effects, as well as more stability because they undergo hydrolysis spontaneously and rapidly in aqueous solutions. Nevertheless, Sawamura is excited about the future possibilities of this study. "Our attention is now on the functions of CRBN as a stress response molecule. The suppression of nerve cell death by thalidomide perhaps occurs because CRBN's function as a stress molecule is

somehow enhanced. We want to elucidate the response of cereblons in aging and stress models to see if decline in the CRBN function could be a biomarker for aging and stress."

About the article

The Neuroprotective Effect of Thalidomide against Ischemia through the Cereblon-mediated Repression of AMPK Activity
Published in Scientific Reports *on February 6, 2018*
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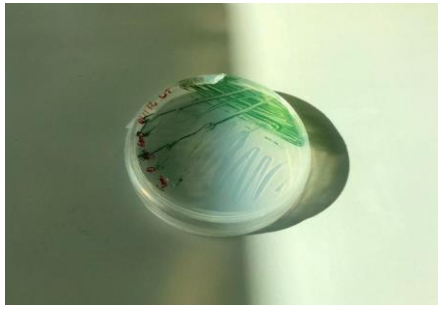
Photosynthesis originated a billion years earlier than we thought, study shows

The earliest oxygen-producing microbes may not have been cyanobacteria

London - Ancient microbes may have been producing oxygen through photosynthesis a billion years earlier than we thought, which means oxygen was available for living organisms very close to the origin of life on earth. In a new article in Heliyon, a researcher from Imperial College London studied the molecular machines responsible for photosynthesis and found the process may have evolved as long as 3.6 billion years ago.

The author of the study, Dr. Tanai Cardona, says the research can help to solve the controversy around when organisms started producing oxygen - something that was vital to the evolution of life on earth. It also suggests that the microorganisms we previously believed to be the first to produce oxygen - cyanobacteria - evolved later, and that simpler bacteria produced oxygen first.



This plate is a culture of Synechocystis sp. PCC 6803, a type of unicellular Cyanobacteria. **Elsevier**

"My results mean that the process that sustains almost all life on earth today may have been doing so for a lot longer than we think," said Dr. Cardona. "It may have been that the early availability of oxygen was what allowed microbes to diversify and dominate the world for billions of years. What allowed microbes to escape the cradle where life arose and conquer every corner of this world, more than 3 billion years ago."

Photosynthesis is the process that sustains complex life on earth - all of the oxygen on our planet comes from photosynthesis. There are two types of photosynthesis: oxygenic and anoxygenic. Oxygenic photosynthesis uses light energy to split water molecules, releasing oxygen, electrons and protons. Anoxygenic photosynthesis use compounds like hydrogen sulfide or minerals like iron or arsenic instead of water, and it does not produce oxygen.

Previously, scientists believed that anoxygenic evolved long before oxygenic photosynthesis, and that the earth's atmosphere contained no oxygen until about 2.4 to 3 billion years ago. However, the new study suggests that the origin of oxygenic photosynthesis may have been as much as a billion years earlier, which means complex life would have been able to evolve earlier too.

Dr. Cardona wanted to find out when oxygenic photosynthesis originated. Instead of trying to detect oxygen in ancient rocks, which is what had been done previously, he looked deep inside the molecular machines that carry out photosynthesis - these are complex enzymes called photosystems. Oxygenic and anoxygenic photosynthesis both use an enzyme called Photosystem I. The core of the enzyme looks different in the two types of photosynthesis, and by studying how long ago the genes evolved to be different, Dr. Cardona could work out when oxidative photosynthesis first occurred.

He found that the differences in the genes may have occurred more than 3.4 billion years ago - long before oxygen was thought to have first been produced on earth. This is also long before cyanobacteria - microbes that were thought to be the first organisms to produce oxygen - existed.

This means there must have been predecessors, such as early bacteria, that have since evolved to carry out anoxygenic photosynthesis instead.
"This is the first time that anyone has tried to time the evolution of the photosystems," said Dr. Cardona. "The result hints towards the possibility that oxygenic photosynthesis, the process that have produced all oxygen on earth, actually started at a very early stage in the evolutionary history of life - it helps solve one of the big controversies in biology today."
One surprising finding was that the evolution of the photosystem was not linear. Photosystems are known to evolve very slowly - they have done so since cyanobacteria appeared at least 2.4 billion years ago. But when Dr. Cardona used that slow rate of evolution to calculate the origin of photosynthesis, he came up with a date that was older than the earth itself. This means the photosystem must have evolved much faster at the beginning - something recent research suggests was due to the planet being hotter.
"There is still a lot we don't know about why life is the way it is and how most biological process originated," said Dr. Cardona. "Sometimes our best educated guesses don't even come close to representing what really happened so long ago." Dr. Cardona hopes his findings may also help scientists who are looking for life on other planets answer some of their biggest questions.
The article is "Early Archean origin of heterodimeric Photosystem I" by Tanai Cardona (DOI: 10.1016/j.heliyon.2018.e00548). The article appears in Heliyon *(March 2018), published by Elsevier.*

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Archaeologists Closer to Finding Lost Viking Settlement

A prominent archaeologist says the lost settlement likely resides in northeastern New Brunswick

By Owen Jarus, Live Science Contributor | March 6, 2018 06:17am ET

A lost Viking settlement known as "Hóp," which has been mentioned in sagas passed down over hundreds of years, is said to have supported wild grapes, abundant salmon and inhabitants who made canoes out of animal hides. Now, a prominent archaeologist says the settlement likely resides in northeastern New Brunswick.
If Hóp is found it would be the second Viking settlement to be discovered in North America. The other is at L'Anse aux Meadows on the northern tip of Newfoundland.

The only known Viking site in North America is located at L'anse aux Meadows, Newfoundland. It was declared a World Heritage site.
WendyCotie/Shutterstock

Over the decades, scholars have suggested possible locations where the remains of Hóp might be found, including Newfoundland, Prince Edward Island, New Brunswick (on the east coast of Canada), Nova Scotia, Maine, New England and New York. However, using the description of the settlement from sagas of Viking voyages, along with archaeological work carried out at L'Anse aux Meadows and at Native American sites along the east coast of North America, an archaeologist has narrowed down the likely location of Hóp to northeastern New Brunswick. The likeliest location there? The Miramichi-Chaleur bay area.
Based on the research, "I am placing Hóp in the Miramichi-Chaleur bay area," Birgitta Wallace, a senior archaeologist emerita with Parks Canada who has done extensive research on the Vikings in North America, told Live Science. Hóp, she said, may not be the name of just one settlement, but rather an area where the Vikings may have created multiple short-term settlements whose precise locations varied from year to year. Tales of the Viking voyages were passed down orally before being written down, and "Hóp" may have been misunderstood as being just one site when it could have referred to several seasonal settlements, Wallace said.

Narrowing the search

Wallace found that northeastern New Brunswick is the only place that meets all the criteria in the sagas for Hóp: It contains wild grapes and salmon, barrier sandbars and a native population that used animal-hide canoes. "New Brunswick is the northern limit of grapes, which are not native either to Prince Edward Island or Nova Scotia," said Wallace, noting that grapes were not found in Maine, either.

Additionally, "barrier sandbars occur along the coasts of [Prince Edward Island], Massachusetts and Long Island, but they are particularly dominant along the New Brunswick east coast," Wallace said. Wild salmon was abundant in eastern New Brunswick at the time, but research conducted by archaeologist Catherine Carlson shows that they were not found at pre-Columbian Native American sites in Maine or New England, Wallace said.

Hide canoes were used by the Mi'kmaq people in the Miramichi-Chaleur bay area, and that region was so abundant in wild salmon (before overfishing in the past century caused the population to fall) that the Mi'kmaq used the salmon as a totem (a creature of spiritual significance), Wallace said. "The only area on the Atlantic seaboard that accommodates all the saga criteria [for Hóp] is northeastern New Brunswick," Wallace told Live Science.

Additionally, excavations at the Viking settlement at L'Anse aux Meadows revealed the remains of three butternuts and wood from a butternut tree — species that are native to New Brunswick, Wallace said. They also reveal the presence of white ash, beech, eastern hemlock and white elm - all of which can be found in New Brunswick.

This wood fragment may be a boat patch. It was found at L'Anse aux Meadows, the only confirmed Viking settlement in North America. Viking ships likely sailed from L'Anse aux Meadows to Hop. **Owen Jarus**

Finding Hóp

While Wallace can narrow down the location of Hóp, finding the actual site(s) will be difficult and perhaps impossible, Wallace said.

Hóp was likely used as a summer camp, and any tents or buildings constructed there would have been used only for a few months at most, making them difficult for archaeologists to find, Wallace said. At the end of the summer, the Vikings likely brought the remains of anyone who died back to Greenland (the home base for the Vikings in the region). Any tools they used would likely have been brought back to Greenland or L'Anse aux Meadows. Additionally, the sagas indicate that the Vikings at Hóp would have focused on gathering wood and food, an activity that wouldn't leave a large trace in the archaeological record, as organic materials don't preserve well. Furthermore, the landscape in the Miramichi-Chaleur bay area has changed, and any Viking site (or sites) could be paved over.

Even so, "I hope that all archaeologists working in this area keep their eyes open just in case they should run across something not fitting the cultural patterns they set out to explore," Wallace told Live Science.

An essay containing some of Wallace's research was published recently in Canada's History magazine.

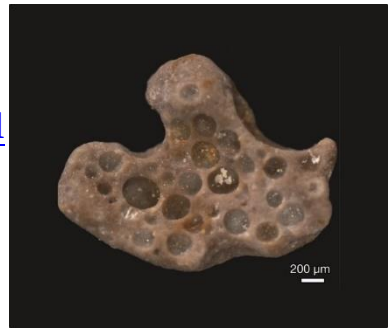
http://bit.ly/2FpxMwc

1.6-Billion-Year-Old Breath of Life Frozen in Stone

A nondescript series of pockmarks in rock is actually the captured breath of microbes from 1.6 billion years ago.

By Stephanie Pappas, Live Science Contributor

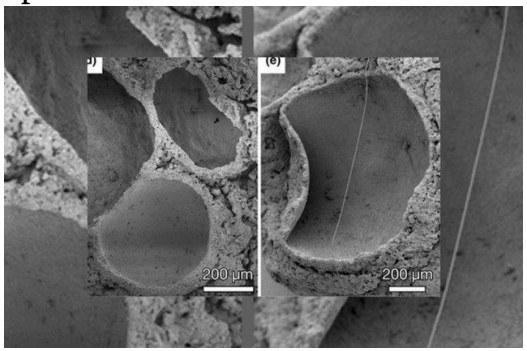
The fossils come from fossilized mats of microbes found in central India. Most of the microbes are cyanobacteria, according to new research published Jan. 30 in the journal Geobiology. These ancient microbes, among the oldest life on Earth, were photosynthesizers — like modern plants, cyanobacteria turned sunlight into energy, exhaling oxygen as a byproduct.



Fossilized bubbles formed by cyanobacteria some 1.6 billion years ago were found in the so-caled Vindhyan supergroup in central India. **Stefan Bengtson**

Their ancient exhalations oxygenated Earth's atmosphere beginning around 2.4 billion years ago, paving the way for life as we know it today. Cyanobacteria also excreted minerals that hardened into layered mats called stromatolites. Stromatolites are found in a few places today, notably Shark Bay in Western Australia and in a remote patch of freshwater in Tasmania, but they once dominated Earth's shallow seas. Swedish Museum of Natural History biogeologist Therese Sallstedt and her colleagues studied some of these mats from a thick sedimentary layer called the Vindhyan Supergroup, which may contain fossils of some of the oldest animal life on the planet.

Amid the rock layers, the researchers found tiny spherical voids. Bubbles like this have been found before, the researchers wrote in their new paper, both in fossil microbial mats and in microbial mats that thrive today in hydrothermal water.



Some of the ancient oxygen bubbles had been partly compressed, suggesting they were once flexible. **Stefan Bengtson**

The bubbles are tiny, just 50 to 500 microns in size (for comparison, a human hair is about 50 microns in diameter). Some of the spheres are compressed, as if the once-flexible mats were squished before they became locked in stone. The mats also contain filament structures that are probably the remains of cyanobacteria, the researchers reported.

The bubbles indicate that the mats were filled with oxygen produced by the microbes inside, the researchers wrote. These particular stromatolites contain high levels of calcium phosphate, putting them in a category known as "phosphorites." The discovery of oxygen bubbles within these phosphorites suggests that cyanobacteria and other oxygen-producing microbes may have played a larger role than researchers realized in constructing this type of microbial mat in ancient shallow oceans, Sallstedt and her colleagues wrote.

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The brain's immune system may be key to new Alzheimer's treatments

TREM2 mediates anti-amyloid toxicity and can limit Alzheimer's disease pathology and behavioral symptoms

La Jolla, Calif. - Sanford Burnham Prebys Medical Research Institute (SBP) researchers have published two new studies in Neuron that describe how TREM2, a receptor found on immune cells in the brain, interacts with toxic amyloid beta proteins to restore neurological function. The research, performed on mouse models of Alzheimer's disease, suggests boosting TREM2 levels in the brain may prevent or reduce the severity of neurodegenerative disorders including Alzheimer's disease.

"Our first paper identifies how amyloid beta binds to TREM2, which activates neural immune cells called microglia to degrade amyloid beta, possibly slowing Alzheimer's disease pathogenesis," says Huaxi Xu, Ph.D., professor and director of SBP's Neuroscience Initiative, Jeanne and Gary Herberger Leadership Chair in Neuroscience Research and senior author of the study. "The second study shows that increasing TREM2 levels renders microglia more responsive and reduces Alzheimer's disease symptoms."

Alzheimer's disease affects more than 47 million people worldwide, a number expected to grow as the population ages. One of the hallmarks of the disease is the accumulation of amyloid plaques that form between neurons and interfere with brain function. Many drug companies have been working for years to reduce amyloid beta production to thwart Alzheimer's--but with minimal success.

"TREM2 offers a potential new strategy," says Xu. "Researchers have known that mutations in TREM2 significantly increase Alzheimer's risk, indicating a fundamental role for this particular receptor in protecting the brain. This new research reveals specific details about how TREM2 works, and supports future therapeutic strategies to strengthen the link between amyloid beta and TREM2, as well as increasing TREM2 levels in the brain to protect against pathological features of the disease.

Xu led the first study *(TREM2 is a receptor for β-amyloid which mediates microglial function)*, showing that TREM2 binds quite specifically to amyloid beta. In particular, it connects with amyloid beta oligomers (proteins that bind together to form a polymer), which are the protein's most toxic configuration. Without TREM2, microglia were much less successful at binding to, and clearing out, amyloid beta.

Further investigation showed that removing TREM2 downregulated microglial potassium ion channels, impairing the electrical currents associated with the activation of these immune cells. In addition, TREM2 turned on a number of mechanisms associated with the amyloid beta response in microglia.

The second study *(TREM2 Gene Dosage Increase Reprograms Microglia Responsivity and Ameliorates Pathological Phenotypes in Alzheimer's Disease Models)*, a collaboration led by with X. William Yang, M.D., Ph.D., professor in Jane and Terry Semel Institute for Neuroscience and Human Behavior, and Department of Psychiatry & Biobehavioral Sciences at David Geffen School of Medicine at UCLA, added TREM2 to a mouse model with aggressive Alzheimer's disease. They found that the added TREM2 signaling stopped disease progression and even restored cognitive function.

"These studies are important because they show that in addition to rescuing the pathology associated with Alzheimer's disease, we are able to reduce the behavioral deficits with TREM2," says Xu. "To our knowledge this provides convincing evidence that minimizing amyloid beta levels alleviates Alzheimer's disease symptoms." As they learn more about how TREM2 modulates the amyloid signals that put microglia to work, the Xu lab and other researchers have their work cut out for them.

"It could be beneficial in early stages to activate microglia to eat up amyloid beta," says Xu, "but if you over-activate them, they may release an overabundance of cytokines (causing extensive inflammation) damaging healthy synaptic junctions as a side-effect from overactivation."

Still, the ability to use the brain's existing immune mechanisms to clear amyloid offers intriguing possibilities.

"Going after microglia, rather than amyloid beta generation, may be a new research avenue for Alzheimer's disease," says Xu. "We could use brain immune cells to solve what's becoming a public health crisis."

Co-authors of study one (doi.org/10.1016/j.neuron.2018.01.031) include: Yingjun Zhao, Xiaoguang Li, Lu-Lin Jiang, Yu Sun, Bing Zhu, Juan C. Piña-Crespo, and Timothy Y. Huang, SBP; Xilin Wu, SBP and Fujian Medical University (China); Xun Gui, Ningyan Zhang, and Zhiquiang An, University of Texas Health Center; Yan Liu, SBP and Xiamen University (China); Muxian Zhang, Xiamen University; Xiaochun Chen, Fujian Medical University; Goujun Bu, Xiamen University and the Mayo Clinic.

Funding for study one came, in part, from NIH (R21 AG048519, R01 AG021173, R01 AG038710, R01 NS046673, RF1 AG056114, RF1 AG056130), grants from the National Natural Science Foundation to China, the Tanz Family Fund, the Cure Alzheimer's Fund, and the Welch Foundation.

Co-authors of study two (doi.org/10.1016/j.neuron.2018.02.002) include: C.Y. Daniel Lee, Anthony Daggett, Xiaofeng Gu, Peter Langfelder, Nan Wang, Chang Sin Park, Yonatan Cooper, Isabella Ferando, Istvan Mody and Giovanni Coppola, UCLA; Lu-Lin Jiang, Xiaoguang Li and Yingjun Zhao, SBP.

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http://wb.md/2Ifr4qt

Listen Carefully During the Medical Interview

Inquiring whether the clinical history, as we know it, is relevant any more

Charles P. Vega, MD; Fabrizia Faustinella, MD, PhD

Charles P. Vega, MD: In an era with advanced technological means to address patient concerns but real limits on the amount of time that each provider can spend with patients, it's reasonable to ask whether the clinical history, as we know it, is relevant any more. We are going to discuss this today for this month's Critical Issues in Primary Care.

I'm Chuck Vega, and I'm a clinical professor of family medicine at the University of California at Irvine, where I am also Associate Dean for Diversity and Inclusion.

Today, I'm really delighted to be joined by Dr Fabrizia Faustinella, associate professor of internal medicine at the Baylor College of

Medicine. She has led efforts to teach and evaluate the physical exam and history taking for medical students at Baylor, as well as the University of Texas. Fabrizia, it's great to have you on board.

Fabrizia Faustinella, MD, PhD: Thank you very much, Chuck. It's a pleasure.

Dr Vega: I feel like not only is talking to patients the most important key to making a diagnosis, but it also establishes a trust that enlists patients on a plan of care. Better yet, careful listening during a medical interview can help the clinician understand patient beliefs as well as their resources, which are often just as critical to a successful plan of care as the right diagnostic test or treatment plan. Still, we can get so busy in clinical care and perhaps so rooted in going through seemingly the same patient histories again and again, that we become insensitive to small or even large and critical details that affect patient care.

Fabrizia, you have some examples. Can you describe them a little bit?

Case 1: A 72-Year-Old Male

Dr Faustinella: Yes, absolutely. A resident presented to me the case of a 72-year-old Hispanic man who came to the clinic complaining of bilateral knee pain and left-leg weakness. The patient volunteered that his balance was really off and that he had started to trip and fall at home. On physical exam, the resident found crepitus in both knees and decided that the most likely diagnosis was arthritis. Therefore, he suggested ordering a cane and prescribing tramadol.

On further questioning when I entered the room, the patient reported a history of weight loss, decreased appetite, increasing fatigue, and cough for about 3 months. Also, he reported a 50–pack-year smoking history. On physical exam, I found worrisome findings of objective left-leg weakness with obvious motor deficits. At that point, I became very concerned.

On the basis of many red flags—smoking, weight loss, cough, fatigue—I ordered a chest radiograph, which unfortunately showed a very large lung mass. Eventually, further workup revealed the presence of brain lesions consistent with metastasis from small-cell lung cancer, which was later confirmed by the biopsy and workup.

This is a quite interesting case where important elements of the history of the present illness and social history were basically not properly evaluated in the context of the patient's clinical presentation.

Dr Vega: That is a great example and, clearly, a really tragic case. Osteoarthritis should not promote that degree of falling. A lot of times you start with one thing that sets off an alarm, and that opens up a Pandora's box of other symptoms and problems. Sometimes, that can lead you to exactly the right diagnosis instead of a significant delay in diagnosis and management of a serious condition, such as lung cancer.

Case 2: A 55-Year-Old Woman

Dr Faustinella: My next case is in some ways similar. A 55-year-old woman came to our clinic complaining of dizziness, severe headache, nausea, and vomiting. She had been seen in our clinic 1 week earlier with the same symptoms and had received prescriptions for meclizine and antiemetics.

A family member brought the patient back to our clinic by because she was getting worse. On history, she reported that the headache was very severe and very unusual for her—it would keep her up at night. She noticed some twitching in her left leg and left arm that had been going on for 2 or 3 weeks. That concerned me, and I started digging a little bit more into her history.

Unfortunately, she had a history of breast cancer, apparently in remission, but no recent workup was available. Of course, the history of nausea, vomiting, worsening headache, dizziness, in view of the previous past medical history of breast cancer, made me very concerned. I ordered a CT scan, which unfortunately showed a lot of brain lesions. Eventually, we found out it was consistent with recurrent disease.

Dr Vega: One of the things I like to do is ask the patient directly what they think they have. I'm really encouraged by how often they actually know their diagnosis—it's just leading them around to it. When they self-diagnose to some degree, I think their empowerment and adherence

to the plan of care is a lot greater because they discovered this for themselves rather than being told.

In cases where you have a patient who has a really big fear of something like cancer, even though the symptoms do not point to that, at least you are going to address that big fear. It's good for patient communication. This does not take a lot of time in clinical practice.

I am also respectful of the fact we have limited time and resources with patients. Your cases were excellent because they demonstrated these windows of opportunity. Paying attention when there is a red flag or something that does not feel right about a case and taking the time to explore it further can be absolutely critical in treating the patient correctly.

Dr Faustinella: I would like to comment on what you said earlier, that sometimes the patients will tell us what is wrong with them. These are really some of the most critical questions that we can ask: What's going on with you? What are you worried about?

By the same token, patients often have concerns that are really excessive and we can provide reassurance. For example, if patients come to my office with left-sided neck pain and seem overly concerned, I ask what they are worried about. "I'm worried this could be a sign of a stroke," they may say. By asking, not only can we be given critical information to proceed in the right direction, but also we have the opportunity to reassure the patient that maybe what they are concerned about is not really what they should be worried about.

Dr Vega: Great point. That gives us all something to work with constructively. I'm definitely going to use some of these techniques in my clinical practice.

Thank you very much, Fabrizia, for your contributions.

Dr Faustinella: Thank you for having me.

Dr Vega: Thank you very much for attending this session of Critical Issues.

http://bit.ly/2GqFNk6

How Swallowing a Slug Left a Teen Paralyzed

A simple dare had devastating consequences for one teenager in Australia

By Mindy Weisberger, Senior Writer

Accepting a simple dare — eat a garden slug — had devastating consequences for one teenage rugby player in Australia, according to news reports: When the teen swallowed the slug, it led to a parasitic infection that caused a serious brain disease, leaving the teen paralyzed from the neck down.

Slugs and snails can carry a parasite that commonly attacks rats but can also cause life-threatening infections in people. **Shutterstock**

Sam Ballard was 19 years old in 2010 when he swallowed the slug, which was carrying the roundworm parasite *Angiostrongylus cantonensis*, commonly known as the rat lungworm, according to Australian news site News.com.au. As adults, these parasites typically infect rats, but during the earlier stages of their life cycle, they may be carried by slugs and snails that eat rat feces — and they can infect people who consume infected snails or slugs that are undercooked.

In Ballard's case, the parasite caused a serious brain infection. He fell into a coma for 420 days and was paralyzed from the neck down when he was released from the hospital three years later, News.com.au recently reported. Ballard, who is still paralyzed and requires round-the-clock care, was in the news this month after his insurance benefits package from Australia's National Disability Insurance Scheme was recently slashed from 492,000 Australian dollars ($383,700) to about AU$135,000 ($105,000), according to News.com.au.

In addition to snails and slugs, rat lungworm can parasitize frogs, land crabs and freshwater shrimp, which may also pass the infection to

people if these animals are consumed raw or undercooked, according to the Centers for Disease Control and Prevention (CDC).

People with rat lungworm infections often don't develop any symptoms, or they may exhibit mild, short-term symptoms such as fever, headache, stiff neck, or nausea and vomiting. In fact, the parasite generally dies on its own, even if the infected person receives no treatment, the CDC says.

However, the infection can sometimes lead to a rare form of meningitis known as eosinophilic meningoencephalitis, in which a type of white blood cell known as an eosinophil increases in number in the brain and spinal fluid. (Meningitis refers to inflammation of the meninges, the lining of the brain and spinal cord.) In some cases — such as Ballard's — this can lead to severe disruption of the nervous system, causing paralysis or even death, according to the CDC.

Though most of the known cases of rat lungworm infection have been documented in the Pacific islands and parts of Asia, a study published in May 2017 in the journal PLOS ONE indicated that the parasite is now established throughout Florida. What's more, cases of the parasitic infection on Maui in Hawaii are also on the rise, with four people infected and four suspected infections reported in April of last year.

Researchers warned that as the world continues to warm, the worm's range will likely continue to expand, potentially introducing it across the continental United States, Live Science previously reported.

http://theatln.tc/2Gf3Csz

The Fish That Makes Other Fish Smarter

By removing bloodsucking parasites, the cleaner wrasse improves the intellectual abilities of its clients.

- **Ed Yong**

It’s not easy for fish to clean themselves, without limbs or digits to scrub those hard-to-reach places. Fortunately for them, coral reefs come with cleaning stations.

At particular sites, an itchy individual can attract the attention of the bluestreak cleaner wrasse—a slender fish, with blue and yellow markings and a prominent black stripe. On seeing these colors, the itchy “client” strikes a specific pose, allowing the wrasse to snake across its body, mouth, and gills, picking off parasites and dead skin along the way. The wrasse gets a meal. The client gets exfoliated. A single wrasse works for around four hours a day, and in that time, it can inspect more than 2,000 clients.

A cleaner wrasse cleans out the mouth of a cod. **Rand McMeins / Getty Images**

The wrasse are remarkably savvy about how they perform their services. Redouan Bshary, from the University of Neuchâtel, has shown that they sometimes cheat their clients by taking illicit bites of the protective mucus covering their skin. If the clients are watching, the wrasse restrain themselves from such shenanigans, in an effort to maintain their reputation. If disgruntled clients chase them, they try to make amends by offering a complementary fin massage. If high-status clients pop by—large, visiting predators like sharks or groupers—the cleaners prioritize them over smaller fish that live in the area. They’re surprisingly intelligent for fish. And it seems that, by removing parasites, they also make *other fish* more intelligent.

We know this because, in 2000, Alexandra Grutter, from the University of Queensland, started removing cleaner wrasse from patches of reef around Australia’s Lizard Island. Every three months, she and her team would net every cleaner in these areas and move them elsewhere. The other small fish in these patches won’t cross the large tracts of open sand between them. So, for entire generations, Grutter deprived them of the cleaners’ attentions.

On the de-wrassed reefs, the total number of fish species halved, and their numbers fell by three-quarters. Some damselfish remained, but they were smaller than usual—a clear sign that their physical health depends on regular cleaning.

Sandra Binning, who's also from the University of Neuchâtel, has shown that the damsels' mental prowess is also influenced by the cleaners. Working with Grutter and Bshary, she captured damselfish from various reefs and put them through a series of challenges. First, she put square plates on either side of their tank. One of these hid a chunk of food that the fish could smell but not reach, while the other hid a more accessible morsel. The damselfish had to learn which plate to swim up to—a simple spatial-memory test, and one that every individual passed. Next, Binning swapped the location of the correct plate; again, all the fish learned to change their behavior.

Things changed when she gave them a more difficult task. This time, they had to approach the correct plate based not on its location, but on its appearance. This skill—visual discrimination—is vitally important to a damselfish. "They have to learn very quickly, on the basis of color and pattern, which fish are safe to be around, and what competitors or friends look like," says Binning. "They're very good at that."

But not all of them. The fish that had been serviced by cleaners solved the task faster, and in greater numbers, than those without a history of such services, even when the two groups were matched for size.

"It's easy to imagine how that would work," says Isabelle Côté, a researcher from Simon Fraser University who wasn't involved in the study. "Imagine having an itch that you just can't scratch, no matter what you do. Ultimately, it drives you to distraction. That might well be similar to what these fish that can't visit cleaners are feeling. It means that these cleaning interactions are even more important than we had anticipated."

Without the cleaners, the damselfish might also not have enough energy to fully fuel their demanding brains. They're targeted by parasitic, bloodsucking crustaceans, which makes them "anemic, sluggish, and weak," Binning says. When cleaners remove these parasites, the distressed damsels can divert their energies toward other matters—like thinking. Binning confirmed this idea by collecting fish that *had* grown up in the presence of cleaners, and deliberately infecting them with the bloodsucking parasites. Sure enough, they performed badly in the visual test, just like their peers from cleaner-free reefs.

It's too easy to see the parasites as the villains of this story, however. In many way, they're the glue that cements the relationship between the cleaners and their clients, says the disease ecologist Carrie Cizauskas. "Take them away, and it's debatable whether the cleaner wrasses would be able to survive on client skin detritus alone," she says.

And the cleaners, through their ministrations, could shape the intellectual development of an entire ecosystem. After all, "there are many other species of clients, like parrotfish and groupers, that are *way* more parasitized and get much higher priority," Binning says. "The hierarchy of service is so complex, and our damselfish get cleaned when there's no one else around."

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New insights into why patients have a higher risk of heart attack in the morning

Lower levels of SPM in the blood in the morning could increase risk of blood clots and heart attacks

Heart disease patients have lower levels of an important family of protective molecules in their blood in the morning, which could be increasing risk of blood clots and heart attacks at those times, says early research by Queen Mary University of London

Queen Mary University of London

Cardiovascular disease patients have lower levels of an important family of protective molecules in their blood in the morning, which could be increasing their risk of blood clots and heart attacks at those times, according to early research led by Queen Mary University of London.

The discovery of the importance of this compound in the blood could lead to new ways to diagnose, treat and prevent cardiovascular disease.

The body's clock is set in part by environmental cues including the light-dark cycle and controls many aspects of our body's daily functions, including sleep, heart rhythm and feeding.

Recent studies have shown that the body's defence system also responds to this clock and influences our body's ability to repair itself and respond to injury at different times of the day. And in patients with heart disease, the activation of blood cells in the early hours of the morning is associated with an increased incidence of blood clots, heart attacks and strokes at those times.

Lead researcher Dr Jesmond Dalli from Queen Mary's William Harvey Research Institute said: "For people with heart disease, in the morning just before getting out of bed, an increase in heart rate together with other changes in the blood stream, results in an activation of cells in the blood stream. This leads to the formation of small clots which may lead to blockage of the blood vessels resulting in heart attack or stroke.

"We were surprised to discover that a small group of molecules from an essential fatty acid, previously thought not to have any clinical importance, actually appears to control this vital cell activation process. This helps us to understand how cardiovascular disease may occur, and uncover potential new ways to identify, treat and prevent it."

The study, published in the journal *Circulation Research*, looks at a group of recently discovered molecules, known as specialised pro-resolving mediators (SPMs), which are produced from omega-3 fatty acids, the same fatty acids found in fish oils. SPMs are involved in controlling both white blood cell and platelet behaviour during inflammation, allowing the body to heal itself.

The team collected blood from 7 healthy volunteers and 16 patients with cardiovascular disease. This was collected at different times of the day to measure the SPM levels, and note the behaviour of the blood cells.

In healthy people, they found that the SPM level increased during the early morning hours and helped keep in check the behaviour of both white blood cells and platelets in the blood vessels.

In patients with cardiovascular disease, however, the production of these SPMs was significantly impaired, and associated with a marked increase in blood cell activation and the formation of clusters of white blood cells and platelets which can contribute to clot formation and blood vessel inflammation.

When the researchers replenished the levels of SPM molecules in the blood from patients with blood vessel disease, and also in experiments in mice, they found they could improve the behaviour of cells in the blood stream and reduce blood vessel inflammation.

The work was conducted in collaboration with colleagues at Trinity College Dublin and the Royal College of Surgeons in Ireland, and funded by European Research Council, Wellcome Trust, Barts Charity, Medical Research Council and Science Foundation Ireland.

Research paper: 'Impaired Production and Diurnal Regulation of Vascular RvDn-3 DPA Increases Systemic Inflammation and Cardiovascular Disease'. Romain A Colas, Patricia R Souza, Mary E Walker, Maudrian Burton, Raquel M Marques, Zbigniew Zas?ona, Annie M Curtis, Jesmond Dalli. Circulation Research. *doi 10.1161/CIRCRESAHA.117.312472*

http://circres.ahajournals.org/content/early/2018/02/02/CIRCRESAHA.117.312472.long

http://bit.ly/2Gh2Zij

Saffron may help tense kids

Research suggests the cooking spice might do more than make food taste good.

Andrew Masterson reports.

It sounds at first blush like a bit of dubious homespun hippy wisdom, but a small university-conducted trial has found that taking saffron may reduce anxiety in adolescents.

Saffron: great in a curry, and not bad in a troubled brain, either, it seems. **R. Tsubin / Getty Images**

The study, published in the *Journal of Affective Disorders*, involved 68 young people, aged between 12 and 16, who had been diagnosed as suffering from mild to moderate anxiety.

Over eight weeks, the cohort was given either a daily 14-milligram dose of a commercially prepared saffron extract, or a placebo. During the trial, those receiving the extract reported significant reductions in separation anxiety, social phobia and depression.

Based on self-reported data, overall anxiety was reduced by 33%. Participants on the placebo reported an overall decrease of 17%.

The results, however, were not cut-and-dried. Parents of the participants were also asked to estimate symptom severity in their children, and returned a mix of results inconsistent with the self-reports.

The research was led by psychologists Peter Drummond and Adrian Lopresti of Murdoch University in Perth, Western Australia.

"Saffron was particularly effective in reducing symptoms associated with separation anxiety, depression and social phobia, and participants reported a reduction in headaches over the eight weeks as well," says Lopresti.

"Although cooking with large quantities of saffron may be prohibitively expensive, supplements are a far more cost-effective way to ingest the spice. We are now working to identify the optimal dose needed to lift moods and how long the treatment can be used for."

And while saffron, or a commercial extract thereof, might promise a moderate reduction in anxiety symptoms, Lopresti is quick to say "it is better to identify and treat the cause of stress in the first instance".

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When the doctor's away

Survival benefit seen for some patients when cardiologists are away at academic conferences

AT A GLANCE

- ***Heart-attack sufferers who receive treatment during periods when interventional cardiologists are away at academic conferences are more likely to survive in the month after their heart attack than patients receiving treatment during nonmeeting days.***
- ***Survival differences are seen only in a subgroup of patients who did not receive invasive stenting treatment.***
- ***Patients who received stenting--a procedure that props open blocked arteries in the heart--fared equally well on meeting and nonmeeting dates.***
- ***Benefit may stem from the better holistic care skills of physicians who skip interventional cardiology meetings.***

Heart attacks don't happen on a schedule. So how do patients fare if they suffer a heart attack while many cardiologists are away at academic meetings or research conferences?

The answer depends on the type of heart attack, according to new research from Harvard Medical School.

According to new research from Harvard Medical School, published March 9 in the *Journal of the American Heart Association*, heart attack sufferers who receive treatment during periods when interventional cardiologists are away at academic conferences are more likely to survive in the month after their heart attack than patients receiving treatment during matched days in the weeks surrounding the conferences.

The overall benefit in survival was substantial enough to get the attention of physician-researcher Anupam Jena, lead author of the study. "Many medical interventions deliver no mortality benefit, and the fact that mortality actually falls for heart attack patients during these conference dates raises important questions about how care might differ during these periods," said Jena, who is the Ruth L. Newhouse Associate Professor of Health Care Policy at Harvard Medical School and a physician at Massachusetts General Hospital.

This is not the first time Jena has tackled this line of scientific inquiry. In 2015 Jena and colleagues set out to answer this question, expecting that they would find either no change if the hospitals had enough skilled doctors to cover for the cardiologists who were away at big national cardiology conferences, or a slight increase in mortality, if staffing challenges caused the quality or quantity of care to dip.

Jena said he was surprised to find in that first study that instead of doing worse, patients fared better for acute cardiovascular conditions such as cardiac arrest and heart failure, on the dates of the American Heart Association and the American College of Cardiology meetings than they did on matched dates surrounding those events. The counterintuitive findings suggested that cardiologists who attend the meetings are more prone to using intensive interventions for their patients, and that patients did better with less intensive treatment.

In his latest study, Jena takes a closer look at a more focused physician population, looking for changes in patient mortality on the dates of

Transcatheter Cardiovascular Therapeutics, the world's largest interventional cardiology meeting. Interventional cardiologists specialize in minimally invasive treatment of heart attacks, which involves accessing the heart through a vessel in the groin or arm rather than through open-heart surgery. This approach uses a tiny wire mesh, or stent, to open up a blocked heart artery, and is the most commonly used therapy for treating patients in the throes of a heart attack caused by a blocked artery.

This study's focus on a specific condition and a specific group of doctors who primarily and routinely treat this condition overcame a limitation of the 2015 study, which included cardiologists of all types.

The new analysis revealed a pattern mirroring the findings of Jena's earlier research: A decided survival benefit for patients treated on meeting dates over those treated on nonmeeting dates. Overall, 15.3 percent of patients who went to the hospital with a heart attack on the dates of the meeting died within 30 days of admission, compared with 16.7 percent of patients admitted on nonmeeting dates.

The improved survival outcomes were driven primarily by a group of patients with a specific type of heart attack that does not require immediate stenting. In these patients, who did not undergo stenting, 16.9 percent of those hospitalized during meeting dates died within 30 days of admission, compared with 19.5 percent of those who received care on nonmeeting dates.

The differences may emanate from different nonprocedural skills of physicians who stay behind on meeting dates. Indeed, patients who had heart attacks during meeting dates were equally likely to receive coronary stenting compared to patients who had heart attacks on nonmeeting dates, and mortality reductions were primarily observed among patients who did not receive stents. For patients who don't undergo stenting, mortality risk likely depends on choosing the right cardiac medicines and also accurately identifying and treating concurrent illnesses that may affect the risk of dying, such as certain types of infectious diseases, Jena said.

The findings suggest that while the doctors who stayed were equally skilled at stenting as doctors who attended the meetings, those who stayed may have been better at nonprocedural care, Jena said.

"If doctors focuse their attention on a particular kind of procedure, they might not develop other clinical skills that are as important to influencing outcomes as is knowledge of a specific procedure," Jena said. "Treating a cardiac patient isn't just about cardiac issues--it's about other factors that the patient brings to the hospital."

The researchers found no age or sex differences between physicians who attended and those who did not attend interventional cardiology meetings. However, they did observe that the doctors who attended these meeting performed more stents, were much more focused on publishing research and more likely to run clinical trials than their peers who stayed behind.

"To be clear, these aren't academics who just run research programs," Jena said. "They also do a lot of clinical care."

So what is it that makes the outcomes for patients treated by these two groups of doctors markedly different? Without detailed data about the clinical profiles of patients seen on meeting and nonmeeting dates, Jena said it would be hard to say for sure what the true differences were between the groups.

"Which doctor treats you does matter. The types of doctors who attend these meetings seem to provide different care, at least for a subgroup of patients," Jena said. "This is an unfortunate paradox given that professional conferences are designed to actually makes us better physicians and improve the care we deliver."

Many open questions remain, however. The most critical among them may be: What do the doctors who stay home during meetings do differently to achieve superior results and what can their meeting-attending colleagues learn from them to boost their performance?

"What we really want to know is how we can close the gap in outcomes and save more lives," Jena said.

Andrew Olenski, graduate student in the Department of Economics at Columbia University, Daniel Blumenthal, HMS instructor of medicine at Mass General, Robert Yeh, director of the

Richard and Susan Smith Center for Outcomes Research in Cardiology at Beth Israel Deaconess Medical Center and associate professor of medicine at Harvard Medical School, John Romley, associate professor in the Price School of Public Policy at the University of Southern California, and Dana Goldman, the Leonard D. Schaeffer Chair and director of the University of Southern California Leonard D. Schaeffer Center for Health Policy and Economics, were co-authors of the study.

The research was supported by grants from Office of the Director, National Institutes of Health (NIH; NIH Early Independence Award, Grant 1DP5OD017897), and the National Institute on Aging (Grant 5P01AG033559).

http://bit.ly/2FrwP6y

A Man with a Life-Threatening Heart Infection Was Saved by a Virus Plucked from a Lake

A virus scooped up from a lake saved an 80-year-old Connecticut man who had a life-threatening bacterial infection in his heart.

By Rachael Rettner, Senior Writer

Doctors had tried to combat the infection using antibiotics, to no avail. So they turned to a virus that was originally found in a nearby lake. The virus, a type called a bacteriophage, appeared to eradicate the patient's infection, according to a new report of the case.

Although larger studies are needed, the new report provides early evidence that bacteriophages could be effective treatments against some antibiotic-resistant infections, said the researchers from the Yale School of Medicine in New Haven, Connecticut.

The patient's troubles began in 2012 after he had heart surgery to replace a damaged section of his aorta — the artery that carries blood away from the heart. Doctors replaced this damaged section with a synthetic tube known as a graft.

But soon after the surgery, the man's graft got infected with a type of bacteria called *Pseudomonas aeruginosa*. This type of bacteria is common in the environment, and it is frequently linked to infections acquired in hospitals, according to the Centers for Disease Control and Prevention. [6 Superbugs to Watch Out For]

The patient was treated with a long-term course of antibiotics, but the infection kept coming back. He was admitted to the hospital numerous times over the next few years for *P. aeruginosa* infections in his blood, the report said.

As the patient was running out of treatment options, his physician was contacted by another researcher at Yale who had been studying bacteriophages and thought he had one that could help.

This bacteriophage, known simply as OMKO1, was found in a sample taken from Dodge Pond, which is about 40 miles (64 kilometers) up the coast from New Haven. (The researchers had been studying natural samples for bacteriophages.)

Experiments in lab dishes had revealed that OMKO1 could kill *P. aeruginosa* bacteria by binding to the proteins on the bacterial surface that allow the bacteria to pump out antibiotic drugs before they cause harm. In doing so, the bacteriophages kill the bacteria. What's more, if the bacteria were to evolve to become resistant to OMKO1, they would have to change that pump, and without it, they become more susceptible to traditional antibiotics, the researchers said. That allows researchers to combat the bacteria with a "one-two punch" of sorts.

"The bacteria are backed into an evolutionary corner," study co-author Paul Turner, a professor of ecology and evolutionary biology at Yale University, said in a statement.

The researchers got approval from the Food and Drug Administration to use OMKO1 on the patient. In January 2016, they performed surgery to inject hundreds of thousands of OMKO1 bacteriophages into the man's chest.

Follow-up with the patient showed that he was free of his bacterial infection, despite taking antibiotics for only a short time after the surgery. So far, he has not had a recurrence of the infection and has remained off of antibiotics for 18 months, the report said.

"We argue that the phage therapy played a significant role in contributing to the eradication of the *P. aeruginosa* infection," the researchers wrote in the March 8 issue of the journal Evolution, Medicine and Public Health. "We hope that exploratory studies such as this one can provide preliminary evidence suggesting that phage

OMKO1 can greatly improve the effects of antibiotics for the removal of *P. aeruginosa*," the study authors said.

The researchers are currently screening other types of bacteriophages to see if these might be effective treatments against other antibiotic-resistant bacteria, such as *E. coli* and *Klebsiella pneumoniae*, said study co-author Benjamin Chan, a research scientist at Yale.

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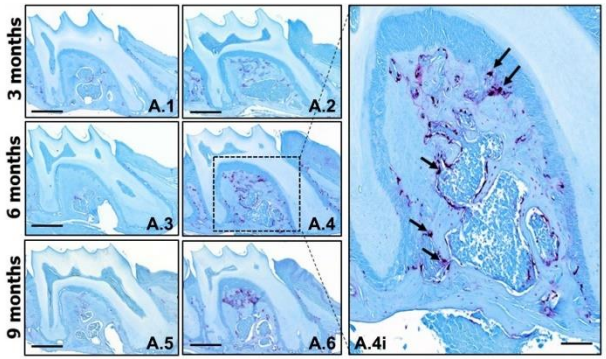
Study: Absence of key protein, TTP, rapidly turns young bones old

Findings could lead to improved care for aging population at higher risk for osteoporosis and periodontitis

BUFFALO, N.Y. - The absence of a protein critical to the control of inflammation may lead to rapid and severe bone loss, according to a new University at Buffalo study. The study found that when the gene needed to produce the protein tristetraprolin (TTP) is removed from healthy mice, the animals developed the bones of much older rodents.



The removal of the gene that produces TTP progressively increases the presence of osteoclasts (red) -- cells that break down and absorb bone -- causing rapid bone loss in mice (middle) compared with healthy mice (left). **Keith Kirkwood**

Within nine months, mice without the gene experienced a nearly 20 percent loss in oral bone. The results also revealed that overexpressing TTP in the animals led to a 13 percent reduction in bone turnover compared to unaffected mice.

Published on March 7 in the *Journal of Dental Research*, the study is the first to test TTP's influence on bone loss in an animal model.

Inflammation is a necessary reaction by the immune system to protect the body from injury or infection, but if not controlled, it can lead to the destruction of bone and the prevention of bone formation.

While TTP is known to play a major role in the regulation of inflammation, its production slows with age. The research results could have a profound impact on the management of bone health in the elderly, a population at higher risk of osteoporosis and periodontitis.

"TTP is the brake on the system. Without it, inflammation and bone loss would go unchecked," says Keith Kirkwood, DDS, PhD, lead author and professor in the Department of Oral Biology in UB's School of Dental Medicine.

"We don't know all of the reasons why TTP expression decreases with age. So, understanding the factors behind its expression and relationship with bone loss is the first step toward designing therapeutic approaches."

The researchers aim to advance their investigation toward similar studies in humans, particularly among the aging.

Osteoporosis, a condition in which bones become weak and brittle, and low bone mass affect nearly 55 percent of people age 50 and older, and it is estimated that by 2020, more than 61 million people will have either condition, the National Osteoporosis Foundation says.

The statistics surrounding periodontitis are equally grim. The infection - which damages the gums, destroys jaw bone and can lead to tooth loss - occurs in 70 percent of adults age 65 and older, according to the Centers for Disease Control and Prevention.

To better understand TTP's role in periodontitis, an inflammatory disease, the researchers studied three groups of healthy mice: a knockout group without the gene to express TTP, a knock-in group whose genes overexpressed TTP, and a control group of unaffected mice.

The rodents were tested for inflammatory conditions, oral bone levels and the presence of osteoclasts - cells that specialize in breaking down bone - in oral tissue at three-, six- and nine-month periods.

The researchers found that bone in the knockout mice aged more rapidly than in the control group. At three months old, the mice had lost 14 percent of their oral bone. By nine months - still a young age for a mouse - bone loss had increased to 19 percent.

In addition to periodontitis, the knockout mice developed arthritis, eczema and other inflammatory conditions. Osteoclast levels were also higher in the knockout group.

Investigators were surprised to find that the absence of TTP vastly altered the oral microbiome, despite all the rodents being housed in the same space. The finding suggests that systematic inflammation can affect the bacteria in the mouth. Further study is needed to determine whether the new bacteria are pathogenic or play a role in bone loss, says Kirkwood.

Overexpression of TTP in the knock-in mice increased protection against inflammation, lowering bone turnover by 13 percent. The increase in the protein had no effect on the number of osteoclasts, however.

A future investigation will study the effect of TTP on bone health over a two-year period. Kirkwood will also partner with Bruce Troen, MD, professor, and Kenneth Seldeen, PhD, research assistant professor, both in the Jacobs School of Medicine and Biomedical Sciences, to examine the differences in the protein's influence on oral bone and overall bone health.

The research was funded by the National Institute of Dental and Craniofacial Research in the National Institutes of Health.

http://nyti.ms/2IiqA9T

How One Child's Sickle Cell Mutation Helped Protect the World From Malaria

The genetic mutation arose 7,300 years ago in just one person in West Africa, scientists reported on Thursday. Its advantage: a shield against rampant malaria.

Carl Zimmer

Thousands of years ago, a special child was born in the Sahara. At the time, this was not a desert; it was a green belt of savannas, woodlands, lakes and rivers. Bands of hunter-gatherers thrived there, catching fish and spearing hippos.

A genetic mutation had altered the child's hemoglobin, the molecule in red blood cells that ferries oxygen through the body. It was not harmful; there are two copies of every gene, and the child's other hemoglobin gene was normal. The child survived, had a family and passed down the mutation to future generations.

A false-color image of healthy red blood cells with some sickle cells, the defective cells that die quickly and cause sickle cell anemia. Sickle cells are the result of a mutation that scientists say arose in a single person in West Africa more than 7,000 years ago. **Eye of Science/Science Source**

As the greenery turned to desert, the descendants of the hunter-gatherers became cattle-herders and farmers, and moved to other parts of Africa. The mutation endured over generations, and for good reason. People who carried one mutated gene were protected against one of the biggest threats to humans in the region: malaria.

There was just one problem with this genetic advantage: From time to time, two descendants of that child would meet and start a family. Some of their children inherited two copies of the mutant hemoglobin gene instead of one.

These children could no longer produce normal hemoglobin. As a result, their red cells became defective and clogged their blood vessels. The condition, now known as sickle cell anemia, leads to extreme pain, difficulty with breathing, kidney failure and even strokes.

In early human societies, most children with sickle cell anemia likely died by age 5. Yet the protection afforded by a single copy of the sickle cell mutation against malaria kept fueling its spread.

Today, over 250 generations later, the sickle cell mutation has been inherited by millions of people. While the majority of carriers live in

Africa, many others live in southern Europe, the Near East and India. Those carriers have about 300,000 children each year with sickle cell anemia.

How humans got the sickle cell mutation is a sprawling saga that emerges from new research carried out at the Center for Research on Genomics and Global Health, part of the National Institutes of Health, by Daniel Shriner, a staff scientist, and Charles N. Rotimi, the center's director. Their study was published on Thursday in the American Journal of Human Genetics.

A colored scanning electron micrograph of a female Anopheles gambiae mosquito, a carrier of malaria. People with the sickle cell mutation are more resistant to malaria. **Dennis Kunkel Microscopy/Science Source**

Dr. Shriner and Dr. Rotimi analyzed the genomes of nearly 3,000 people to reconstruct the genetic history of the disease. They conclude that the mutation arose roughly 7,300 years ago in West Africa.

Later, migrants spread the mutation across much of Africa and then to other parts of the world. Wherever people suffered from malaria, the protective gene thrived — but brought sickle cell anemia with it.

Today, sickle cell anemia remains a heavy burden on public health. In many poor countries, most children with the disease still die young. In the United States, the average life span of sufferers has been extended into the early 40s.

Dr. Rotimi said that an improved understanding of the history of sickle cell anemia could lead to better medical care. It might allow researchers to predict who will suffer severe symptoms and who will only experience mild ones.

"It would definitely help physicians to treat patients at a global level," he said.

Doctors in the United States first noticed sickle cell anemia in the early 1900s. The disease got its name from the way it changed the shape of red blood cells from healthy disks to abnormal curves.

Most cases turned up in African-Americans, doctors found. But 8 percent of African-Americans had at least some sickle-shaped blood cells, even though the vast majority had no symptoms at all.

By 1950, researchers had resolved this paradox, discovering the difference between carrying one mutated copy of the hemoglobin gene and carrying two copies. By then it had also become clear that sickle cell anemia was not unique to the United States.

In Africa, researchers found sickle-shaped red blood cells in people across a broad belt, from Nigeria in West Africa to Tanzania in the east. The cells also turned up at high rates in people in parts of the Near East and India, and in southern European countries such as Greece.

Genetically speaking, this made no sense. Because inheriting two copies of the gene is so deadly, the mutation should have become rarer with passing generations, not more common.

In 1954, a South African-born geneticist named Anthony C. Allison observed that people in Uganda who carried a copy of the sickle cell mutation suffered fewer malaria infections than people with normal hemoglobin.

Later research confirmed Dr. Allison's finding. The sickle cell mutation seemed to defend against malaria by starving the single-celled parasite that causes the disease. The parasite feeds on hemoglobin, and so it's possible that it can't grow on the sickle cell version of the molecule.

"Sickle cell is a rare example of human evolution where we have a good idea of what happened and why," said Bridget Penman, a malaria expert at the University of Warwick in England.

Early genetic studies suggested that five different kinds of DNA, known as haplotypes, surround the mutation. These are named for the places where they were most common: Arabian/Indian, Benin, Cameroon, Central African Republic and Senegal.

These haplotypes became important for diagnosing sickle cell anemia, because some appeared to cause more severe disease than others. But the haplotypes also gave scientists a chance to explore the history of the mutation.

"It has been an open question as to whether the actual sickle cell mutation itself emerged several times or just once," said Dr. Penman.

Some researchers saw the five haplotypes as evidence that the mutation arose on five separate occasions in five different places. Other researchers thought it unlikely that genetic lightning could strike so many times.

"We said, 'How do we jump into this forty-year debate?'" said Dr. Rotimi.

He and Dr. Shriner examined the genomes of 2,932 people from around the world. They found that 156 of the subjects — mostly from Africa, but also from Barbados, the United States, Colombia and Qatar — carried a copy of the sickle cell mutation.

The researchers scanned the DNA surrounding the mutation in those people. While most of it was identical from person to person, in some spots it differed.

Combining their findings, the researchers concluded that all 156 people inherited the same mutation from a single person who lived roughly 7,300 years ago. "This alone is a big contribution to our understanding," said Dr. Penman.

The new study also offers hints as to how the mutation spread to millions of descendants.

The oldest version of the sickle cell mutation is found in people from western and central Africa. They may have inherited it from an ancestor in the green Sahara.

The mutation might have spread to other parts of Africa with the expansion of a people called the Bantu. Arising about 5,000 years ago around what is now Cameroon and Nigeria, they converted woodlands to farm fields on a massive scale.

As they cleared land for agriculture, they may have promoted the spread of malaria by mosquitoes. The insects thrived by laying eggs in standing water around the farms and feeding on the growing population of farmers. The intensification of malaria in human populations may also have accelerated the spread of the protective sickle cell mutation.

Over the next few thousand years, the Bantu carried the mutation across much of eastern, central and southern Africa, Dr. Shriner and Dr. Rotimi conclude. In places where malaria was prevalent, the mutation offered protection. But malaria is rarer in southern Africa, and there the sickle cell mutation became rarer, too.

Later, the study suggests, Africans carried the mutation to other parts of the world. Waves of migrants made their way to the Near East. As people from different ancestries interbred, the mutation made its way further afield, into Europe and India.

Some West Africans captured in the slave trade brought the sickle cell mutation to the Americas. But in places like the United States, where malaria was uncommon or nonexistent, the mutation offered less of an evolutionary advantage. As a result, African-Americans have a lower rate of sickle cell anemia than Africans today.

Frederick B. Piel, an epidemiologist at Imperial College London, said he looked forward to bigger genome-based studies on the sickle cell mutation. It remains to be seen if these patterns can be found in thousands of carriers, instead of just 156, he said.

Dr. Penman said that scientists also should study the different genetic variations identified in the new research. These may help explain why the sickle cell mutation leads to deadly symptoms in some people and only mild ones in others — something that scientists still can't explain. "This knowledge might inspire treatments in itself," she said.

http://bit.ly/2DjBLVl

A Mysterious Lung Disease Is Striking Virginia Dentists

A mysterious lung disease is striking dentists in Virginia, according to a new report.

By Rachael Rettner, Senior Writer | March 9, 2018 04:45pm ET

So far, health officials have identified nine dentists or dental workers who were diagnosed with the disease, called idiopathic pulmonary fibrosis, all of whom were treated at the same specialty clinic in Virginia, according to the report, from the Centers for Disease Control

and Prevention (CDC). The disease is often fatal: Of the nine cases, seven have died, the report said.

Overall, dentists made up 1 percent of idiopathic pulmonary fibrosis cases seen at the clinic. But that's still a strikingly high rate — it's 23 times higher than what would be expected based on the number of dentists in the U.S. population.

And the cause of the disease still isn't clear.

However, health officials are following some leads: It's possible, for example, that the dentists were exposed to something on the job that might have increased their risk of the disease, the researchers said.

Idiopathic pulmonary fibrosis is a progressive disease that occurs when tissue deep in the lungs becomes thick and stiff, or scarred, according to the National Heart, Lung and Blood Institute. This scarring prevents the lungs from working properly. Doctors don't know the cause of the disease — by definition, "idiopathic" means "arising spontaneously or from an obscure or unknown case," according to Merriam-Webster — and there is no cure. In many cases, people with the disease live only about three to five years after their diagnosis, the CDC said.

Although the disease has been linked with certain jobs that involve exposure to dust, wood dust and metal dust, the new report marks the first time that researchers have found a connection between the disease and being a dental worker.

The cluster of cases first came to light when a Virginia dentist went to get treatment for idiopathic pulmonary fibrosis at a clinic and he realized that other dentists in his area had also been treated at the clinic for the same condition.

The dentist contacted the CDC with his concerns, which led health officials to identify the eight other cases that occurred between 2000 and 2015. All of the patients were men, ages 49 to 81 years old, and eight were dentists; one patient was a dental technician.

Of the two patients who were still alive, only one was able to give an interview to health officials. The man told the CDC that during his dental career, he had polished dental appliances and prepared dental impressions without a wearing a mask. This means he could have been exposed to particles of silica in the air or other compounds that can have potentially toxic effects on the respiratory system, the report said.

Still, the researchers only found an association between dental work and this lung disease, and cannot say for certain whether the work did indeed cause the disease. There may be other factors involved — for instance, the man who gave the interview also said he was a street sweeper for three months before he went to dental school, which would also have exposed him to dust.

The researchers recommend that dental workers wear certified respiratory masks if they perform tasks that could result in respiratory hazards and the work area is not well ventilated.

The report concluded that more work is needed to better understand the risk of this lung disease in dental workers "to develop strategies for prevention of potentially harmful exposures."

http://bit.ly/2p25hdH

Russian Gov't Says Not to Worry About These 54 Severed Human Hands Found in Siberia

A fisherman in Siberia made a grim discovery yesterday (March 8) while walking near the icy Amur River: 27 pairs of human hands, severed at the wrist and stuffed into a bag.

By Brandon Specktor, Senior Writer | March 9, 2018 08:43am ET

Russian authorities said the hands were likely disposed of by a local forensics lab, bucking proper protocol.

According to the Siberian Times, the fisherman found the bag of hands on a small river island near the city of Khabarovsk, Russia, located in the country's far southeast about 18.6 miles (30 kilometers) from the Chinese border. The Amur River is a popular local fishing destination, the Times reported.

Initially, the fisherman saw only one hand sticking up out of the snow there, and discovered the full bag soon after. Photos taken at the scene and shared anonymously to Russian media reveal the discovery in brutal detail. In one image, the 54 hands lie in a haphazard pile in the

snow like leathery catcher's mitts, seemingly upended from the bag; in another photo, the hands have been lined up in neat rows.

While many social media spectators (naturally) suspect foul play, officials from the Investigative Committee of The Russian Federation — a government agency responsible for criminal investigations — have said that the hands appear to have been improperly disposed of by a forensics lab in Khabarovsk.

"The biological objects (hands) found are not of a criminal origin," the Investigative Committee wrote in a post (as translated) on the messaging app Telegram, "but were disposed of in a manner not provided for by law."

Indeed, medical bandages and plastic hospital-style shoes were discovered near the hands. According to the Siberian Times, it's not unheard of for forensics labs in Russia to cut off the hands of unknown corpses in order to retain fingerprint information after the rest of the body has been discarded.

Despite this possible explanation, investigators have been able to lift fingerprints from only one of the 27 pairs of hands. Little is known about the hands' previous owners.

"Based on the [investigation] results, a legal assessment will be made of the actions of officials of the forensic medical institution in the city of Khabarovsk responsible for the disposal of these biological objects," the Investigative Committee wrote.

This investigation is ongoing.

http://wb.md/2tFoWEW

Think Like Cardiologists: What Did They Learn in the Past 12 Months That Primary Care Should Know?

A one-page crib sheet of the five articles subspecialist members found to be most important

Laurie E. Scudder, DNP, NP Editorial Director, Medscape Family Medicine
Joanna M. Pangilinan, PharmD Pharmacist, Ann Arbor, Michigan

Primary care clinicians, by necessity, are jacks of all trades. Keeping up with changes in virtually every specialty and translating that new knowledge into busy primary care practice is a gargantuan task. This likely helps explain why, on average, it takes 17 years for medical advances to be widely implemented.[1]

Our new series aims to bring primary care clinicians a one-page crib sheet of the five articles subspecialist members—across all specialties—found to be most important, as evidenced by what they chose to read in the last 12 months.

First up: cardiology. Here's what cardiologists focused on:

Substudy Provides Clues to Digoxin Threshold for Atrial Fibrillation

A subanalysis of the ARISTOTLE trial[2] provides some clues about safe use of this old drug for atrial fibrillation (AF).

Digoxin is prescribed for almost 30% of AF patients worldwide despite guidelines[3,4] indicating that it should rarely be used. Gaetano M. De Ferrari, MD, one of the study authors, emphasized that for every 0.5-ng/mL increase in digoxin level, there is a 19% or 20% increase in mortality. He stressed using extreme caution with digoxin, particularly in women.

Take-home message. Use digoxin only as a last resort and only after trying all other means to control rate and improve symptoms. If digoxin is prescribed, maintain blood levels at ≤1.1 ng/mL.

DOAC Dos and Don'ts

Drs Robert McBane, Ariela Marshall, and Gayatri Acharya of Mayo Clinic discuss the direct-acting oral anticoagulants (DOACs).

For the first time in 50 years, we have medications for anticoagulation

that do not need to be directly monitored and have very few food or drug interactions. DOACs include two classes:

- Direct thrombin inhibitors: dabigatran (Pradaxa®)
- Direct factor Xa inhibitors: rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Savaysa®), and betrixaban (Bevyxxa®)

There are subtle differences between the drugs with respect to metabolism, efficacy, and rates of bleeding. Yet all are rapid acting and have relatively long half-lives. Bleeding reversal is a concern; idarucizumab has been approved to reverse the effects of dabigatran, and others are in the pipeline.

Several DOACs are recommended for stroke prevention in patients with nonvalvular AF.[5] They are the preferred first-line agents for treatment of deep venous thrombosis or pulmonary embolism.[6] Refer to product labeling for approved indications.

Take-home message. Adherence to DOAC therapy is critical. "[E]nsure that patients are both filling the prescription and taking the medication," instructed Dr McBane.

Vitamin D for Statin-Related Myalgia

Philip J. Gregory, PharmD, answers the question: Do low vitamin D levels increase the risk for myalgia in patients who are taking statins?

About 1%-2% of statin users experience myalgia to a degree that may preclude use of this effective agent. Vitamin D deficiency is also associated with similar myalgia. While the mechanism of statin-associated myalgia is not clearly elucidated, it has been proposed that statins may decrease vitamin D levels. The actual effect of statins on vitamin D levels is unclear; clinical trials and observational studies have produced mixed results. In fact, a recent meta-analysis found *increased* vitamin D levels in statin users.[7]

If statins do not lower vitamin D levels per se, could it be that patients with low levels are predisposed to experience myalgia if prescribed statins? A review of the evidence concludes that the data are conflicting, with not all studies finding an association between low vitamin D and risk for myalgia. However, some uncontrolled studies have suggested that in statin-treated patients with muscle symptoms and low vitamin D levels, supplementation may be effective.

Consider using the American College of Cardiology's Statin Intolerance Tool to help you treat your patients.

Take-home message. Vitamin D supplementation may be worth considering in patients with low vitamin D levels who are experiencing statin-related myalgia.

Statins for Primary Prevention in the Elderly

Results of a secondary analysis of ALLHAT-LLT show no benefit of statins for primary prevention in older adults.

Back in 2002, the ALLHAT-LLT trial, an unblinded, randomized, 6-year trial of pravastatin versus usual care in patients with hypertension and dyslipidemia found no significant reduction in all-cause mortality or coronary heart disease events with the statin.

The recent post hoc analysis of the almost 3000 participants ≥65 years of age suggested that statins for primary prevention do not lower the risk for cardiovascular (CV) or all-cause mortality in older adults with CV risk factors. While not statistically significant, there was a trend towards increased all-cause mortality in patients ≥75 years taking statins. The trial has well-recognized limitations, and experts cautioned that the trial was not originally designed to study statins in older adults and that the analyses are underpowered.

Best bet is to refer to the latest guidelines for primary prevention of cardiovascular disease (CVD).[8]

Take-home message. Statins may have significant benefit in appropriately selected patients; older adults may not be those patients.

The Saturated Fat Wars

In response to a perceived trend in consumer media touting the benefits of some saturated fats (eg, whole milk, butter, coconut oil), the American Heart Association (AHA) released an advisory on dietary fats and CVD, reiterating that individuals should replace saturated fats with poly- and monounsaturated vegetable oil to help prevent heart disease.[9]

The AHA's position was not without its critics, who argued that other epidemiologic studies and expert reviews found weak to nonexistent evidence for the link between saturated fat and heart disease. In a detailed rebuttal on Medscape, Nina Teicholz, author of *The Big Fat Surprise*, and cardiologist Eric Thorn charged that the AHA cherry-picked their data and ignored significant evidence that shows no association between the consumption of saturated fats and coronary heart disease.

We've gathered a range of opinions in a special report on saturated fats and CVD.

Take-home message. The weight of medical guidance supports a consensus that a diet rich in whole foods and low in sugar/processed foods is likely best.

Disclosure: Joanna M. Pangilinan, PharmD, has disclosed no relevant financial relationships.

http://bit.ly/2FK09EQ

Deadly superbug just got scarier—it can mysteriously thwart last-resort drug

It's the first time researchers have seen colistin-heteroresistant germs in the US.

Beth Mole - 3/9/2018, 11:51 PM

For the first time, researchers have discovered strains of a deadly, multidrug-resistant bacterium that uses a cryptic method to also evade colistin, an antibiotic used as a last-resort treatment. That's according to a study of US patients published this week by Emory University researchers in the open-access microbiology journal *mBio*.

***Enlarge* / Medical illustration of carbapenem-resistant Enterobacteriaceae.**
CDC

The wily and dangerous bacteria involved are carbapenem-resistant *Klebsiella pneumoniae* or CRKP, which are already known to resist almost all antibiotics available, including other last-line antibiotics called carbapenems. The germs tend to lurk in clinical settings and can invade the urinary tract, bloodstream, and soft tissues. They're members of a notorious family of multidrug-resistant pathogens, called carbapenem-resistant *Enterobacteriaceae* (CRE), which collectively have mortality rates as high as 50 percent and have spread rapidly around the globe in recent years. A 2013 report by the Centers for Disease Control and Prevention estimated that there were more than 9,300 CRE infections in the US each year, leading to 600 deaths. Both the CDC and the World Health Organization have listed CRE as one of the critical drug-resistant threats to public health, in need of "urgent and aggressive action."

That's what we knew about CRKP before this week.

In the new study, the Emory researchers discovered two strains of CRKP—isolated from the urine of patients in Atlanta, Georgia—that can also resist colistin. But they do so in a poorly understood, surreptitious way. At first, they appear vulnerable to the potent antibiotic in standard clinical tests, but with more advanced testing and exposure to the drug, they reveal that they can indeed survive it. In mice, the strains caused infections that couldn't be cured by colistin and the mice died of the infections. Mice infected with typical CRKP were all saved with colistin.

So far, there's no evidence of CRKP infections surprisingly turning up resistant to colistin during treatment in patients. But the authors, led by microbiologist David Weiss, say that may be because the evidence is difficult to gather, and the data so far is cause for concern. The researchers concluded that the findings "serve to sound the alarm about a worrisome and under-appreciated phenomenon in CRKP infections and highlight the need for more sensitive and accurate diagnostics."

Deadly riddle

In an interview with Ars, Weiss emphasized the CRKP's stealth resistance is "obviously most concerning when it's to a last-line drug," such as colistin. "The patients who could be treated don't have many options at this point."

And the dire situation is what makes the problem hard to study in the clinic. For instance, by the time most patients with CRKP infections get to the point of needing colistin, they're usually extremely sick, Weiss adds. In those cases, doctors tend to throw as many antibiotics at patients as they can, which makes it tricky to tell if stealth colistin resistance is a problem. "I'm not saying if it were me I wouldn't want a whole bunch of antibiotic drugs," he said. But to really know if this hidden colistin resistance is a problem, you'd have to be using a single therapy of just colistin.

In the lab, however, the researchers can explore the cryptic resistance, called hetero-resistance. Weiss, director of the Emory Antibiotic Resistance Center, has been studying hetero-resistance for several years, but the phenomenon is still a bit of a mystery.

When microbiologists get bacterial isolates from patients, they grow them up in big batches of nutrient broth. This generally results in a genetically identical population of bacteria that—usually—have uniform set-points of resistance or susceptibility to a certain antibiotic. In other words, if they're susceptible, a relatively low concentration of the drug will kill off the population. If the bacteria can withstand higher doses, they collectively enter resistance territory. Resistance can occur along a spectrum, but there are often standardized thresholds for determining that a bacterial strain is resistant. In other words, if the population on the whole survives "X" concentration of a certain antibiotic, it's then considered resistant.

Hetero-resistant populations don't play by these rules. In standard diagnostic tests, the population may look completely susceptible. But in advanced tests, researchers can detect sub-populations that are resistant. Usually, this might suggest that there were just some contaminating bacteria that had a genetic element that protected them from the drug. But these sub-populations in hetero-resistant bacteria appear genetically identical to their susceptible counterparts. They're clones of each other that for some reason are doing something different to be resistant to the drug.

Underhanded microbes

This was the case for the CRKP clinical isolates that Weiss and his colleagues collected and studied. Standard tests for resistance suggested that colistin concentrations of 0.5 µg/mL or less could kill the populations—they were susceptible. But further experiments found that 1 in 1,000 cells could survive 2µg/mL of colistin. And 1 in 1,000,000 survived 100µg/mL.

When the researchers grew up the population in colistin, the resistant subpopulations took over. But switching the populations to broth without colistin, the population reverted to susceptible again—except for the 1 in every 1,000 cells. The researchers also sequenced the genomes of bacteria resisting colistin and those susceptible to it. They were genetically identical.

Even though they have the same blueprints, they're activating their genes differently, Weiss says. It's unclear how or why this happens. So far, Weiss and his colleagues hypothesize that a specific sensory system may be key to the resistance trick. The system—a type of two-component signal transduction system—involves a protein embedded in the bacteria's membrane that responds to some environmental cue. That protein can then pass the signal to another protein inside the cell that then switches genes on or off accordingly.

This system appeared turned "on" in some of the resistant sub-populations. And when researchers used genetic engineering to break the system in other hetero-resistant bacteria, the populations lost their mysterious antibiotic evasion.

It's unclear what genes the system is controlling, but evidence so far suggests that genetic tinkering allows the cell to make its outer membrane less negatively charged to thwart colistin. The antibiotic is positively charged and seems to kill by breaking down bacterial cells' otherwise negatively charged outer membranes. But the precise mechanism behind this and the bacteria's defenses are still unclear.

"I think we got to a place [with antibiotics] where [we said] 'oh that one stopped working? Who cares? We'll use the next one,'" Weiss said. "So,

there wasn't this urgency to understand all of the details of it because we had back-up options. Now that we're running out of back-up options, people are much more interested."

Overall, "there's a bunch we don't know still," he said, emphasizing the need for more research funding. "But we're working on it."

mBio, *2018. DOI: 10.1128/mBio.02448-17 (About DOIs).*

http://bit.ly/2FstPqy

Man's 'Missing' Brain Was Actually a Large Air Pocket Inside His Head

Falls are a common problem among older adults, but for one 84-year-old man in Northern Ireland, a brain scan revealed a highly uncommon cause for his falls: A part of his brain appeared to be missing.

By Rachael Rettner, Senior Writer | March 9, 2018 11:15am ET

The stunning scan revealed a large, black space behind his forehead, where the front of his brain should have been.

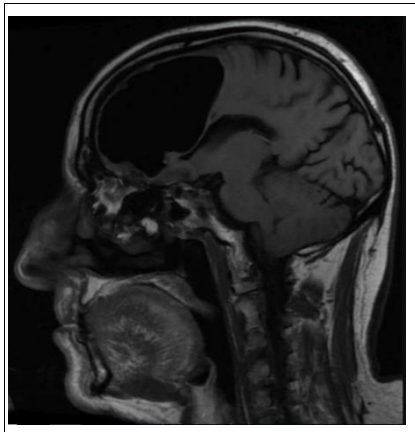
His physician, Dr. Finlay Brown, a general practitioner in Belfast, first reviewed the brain scan while waiting to hear back from radiologists. (Typically, radiologists provide a report that accompanies a scan, detailing what the image shows.)

"Immediately, I could see the abnormality and wondered if the patient had failed to tell us about a previous brain surgery in his younger years" or if the patient was born with a brain abnormality, Brown told Live Science. When doctors were told that neither of these scenarios applied to the patient, they were "left very curious as to the cause of these findings," Brown said.

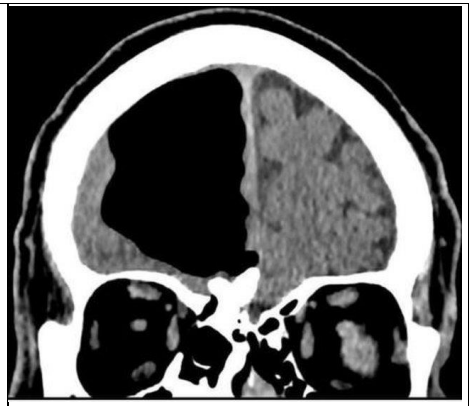
It turned out that the patient had a pocket of air inside his skull, called a pneumatocele, which was compressing his brain tissue. These air pockets are seen more commonly in patients who have facial trauma or infections, or who have had brain surgery, according to a report of the case, published Feb. 27 in the journal BMJ Case Reports.

Brown said he had never seen a case of brain pneumatocele tied to symptoms of falling, and he decided to publish this case to emphasize "the importance of thorough investigation of even the most common of symptoms," Brown said. "Because every now and then, there will be a rare [or] unknown causation of these that could be overlooked," he said.

When the patient first spoke with his doctors, he told them told that, in addition to his frequent falls, he felt weakness in his left arm and leg.



A man in Northern Ireland had a highly uncommon cause for his falls: He had a pocket of air inside his skull, called a pneumatocele. Above, an MRI of the man's brain, showing the 3.5-inch (9 centimeters) air pocket in his right frontal lobe. **BMJ Case Reports**



A CT scan of the patient's brain, showing a large, black space in part of the brain, which is actually an air pocket or pneumatocele. **BMJ Case Reports**

But he was otherwise feeling well, and his initial physical exam was normal.

But when the man was sent for a CT scan, the doctors discovered the 3.5-inch (9 centimeters) air pocket in his right frontal lobe. An MRI scan also revealed an osteoma, or benign bone tumor, in a part of the skull that separates the brain from the nasal cavity, called the ethmoid bone.

The doctors determined that the osteoma wore away part of the ethmoid bone, which allowed air to be pushed, under pressure, into his brain, "creating a 'one-way valve' effect," the report said.

The MRI also revealed that the patient had experienced a small stroke related to the air pocket in his brain.

Doctors told the man that they could perform brain surgery to release the air from the cavity, which would allow his brain to resume its normal shape, as well as a separate surgery to remove the osteoma.

But as with any surgery, there would be some risks for the patient. For example, decompressing the brain area could have led to more problems, and the surgery might not have helped the patient's symptoms, Brown said.

Given the risks and potential benefits, the patient decided not to have the surgery. He was treated with a statin and anti-clotting medication to lower his risk of having another stroke, Brown said.

Twelve weeks after his hospital stay, the patient remained well and no longer felt weakness on his left side, the report said.

http://bit.ly/2HrSEj8

Burn specialists report a dramatic increase in burn injury survival over the past 30 years

Great strides in burn care over the last 30 years have dramatically increased their chances of survival

CHICAGO: For many years, people who sustained severe burn injuries often died. But great strides in burn care over the last 30 years have dramatically increased their chances of survival, according to new study findings published as an "article in press" on the *Journal of the American College of Surgeons* website ahead of print publication.

"Mortality has decreased three to fivefold since the 1980s, ostensibly from the substantial advances in burn care that occurred between 1980 and 1989," said lead study author David N. Herndon, MD, FACS, chief of staff and director of research at the Shriners Hospitals for Children, Galveston, and director of burn services at the University of Texas Medical Branch (UTMB). "Yet, until now, there has never been a definitive study showing the cumulative effect of these advances on survival."

Burns are one of the leading causes of unintentional death and injury in the U.S., according to the American Burn Association.* Very large burns--those that cover 50 percent or more of the body's surface area--put people at high risk of infection and death. In addition to burn size, old age, female gender, and damage to lungs due to the inhalation of smoke put people at greater risk of death.

This is the most definitive report of the role advanced burn treatment has played in reducing risk of death, the authors said. Dr. Herndon and colleagues examined the records of 10,384 adult and pediatric burn patients admitted to Shriners Hospitals for Children®, Galveston, or the Blocker Burn Unit in Galveston from 1989 to 2017. Over this time period, protocols directly derived from these advances were used to guide care of these patients.

The researchers applied multivariate regression analysis to create a statistical profile of their burn patients and to identify the main factors associated with mortality. Factors such age, sex, burn size, whether the patient suffered smoke inhalation injury (damage to the airways), and length of stay were collected at admission.

Of the 10,384 burn admissions, a total of 355 victims died. The researchers looked specifically at the main factors that influenced risk of death in different age groups and then created a risk prediction model. Using mortality data from the medical literature, as well as data from the National Burn Repository, the researchers compared historical predictions of mortality risk with their observed patient data. They found a significant decrease in mortality in their patient population compared with historical predictions from previous studies.

"In this one area of medicine, these new protocols have massively reduced mortality overall," Dr. Herndon said. "Over the last 30 years at our burn center there has been a continuing reduction in the risk of mortality of about 2 percent per year in all age groups, burn sizes, and genders."

The study also identified the most powerful predictors of mortality: the percent of total body surface burned, age, and the presence of inhalation

injury. The probability of death rose as age increased, as burn size increased, and with the presence of inhalation injury.

The data suggest that the continuous improvement in mortality over time is a result of changes in the standard of care, including protocols for management of inhalation injury; nutrition to combat infection and aid in healing; and receiving early burn excision and skin grafts immediately following injury.

"The most dramatic decreases in mortality most recently have been in patients over age 40," Dr. Herndon said. "Remarkably, a patient up to the age of 40 who has sustained a 95 percent body burn now survives half the time, whereas in earlier times a 50 percent body burn killed that same person."

Other factors not assessed in the study that have contributed to better outcomes in burn patients include improvements in the transfer of critically ill patients to hospitals and burn centers.

"We hope our findings will inspire other burn units to try to keep people alive with extensive burns because it's clear that it can be done. Burn specialists also need to focus on implementing the protocols that have allowed this improvement in survival to occur," Dr. Herndon said. "For example, a woman over the age of 40, with very large burns, is a patient who can survive today if these protocols are implemented."

Beyond the effort to reduce mortality rates in burn victims, researchers hope to concentrate on better treatment strategies to improve quality of life. "Our priorities for future advancements need to focus on decreasing scar tissue and morbidity, effective rehabilitation, and returning patients to work," Dr. Herndon said.

The study's coauthors are Karel D. Capek, MD; Linda E. Sousse, PhD; Gabriel Hundeshagen, MD; Charles D. Voigt, MD; Oscar E. Suman, PhD; Celeste C. Finnerty, PhD; and Kristofer Jennings, PhD.

** National Burn Awareness Week. American Burn Association. Available at: http://ameriburn.org/wp-content/uploads/2018/01/aba_infographic_011918.pdf. Accessed March 2, 2018.*

Citation: *Contemporary Burn Survival.* Journal of American College of Surgeons. *Available at: http://www.journalacs.org/article/S1072-7515(18)30026-7/abstract* .

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Complex organic compounds from dying stars could be life precursors

Lab experiments reveal carbon-based molecules are a by-product of red giants.

Richard A. Lovett reports.

Laboratory experiments designed to recreate conditions around carbon-rich red giant stars have revealed that startlingly complex organic compounds can form in the “circumstellar envelopes” created by stellar winds blowing off from them.

The carbon is present because nuclear reactions in these dying stars have progressed to the point that much of their initial complement of hydrogen and helium has been converted into heavier elements such as carbon.

“There is a lot of carbon in these circumstellar envelopes,” says Ralf Kaiser, a physical chemist at the University of Hawaii at Manoa, US.

In research published in the journal *Nature Astronomy*, a team led by Kaiser used a high-temperature chemical reactor to simulate conditions inside these circumstellar envelopes.

The goal, he says, is to demonstrate how complex compounds can be assembled a couple of carbon atoms at a time at temperatures of up to about 1200 degrees Celsius. Previous research found that a host of organic chemicals can indeed be formed, but the new study pushed the process farther, demonstrating that it is possible to create chemicals at least as complex as pyrene, a 16-carbon compound with a structure like four fused benzene rings.

So far, pyrene is the most complex molecule constructed in this manner, but Kaiser thinks that it might be just the beginning. “We hope when we do further experiments that this can be extended,” he says.

What this means, he explains, is that circumstellar envelopes might be able to create molecules with 60 or 70 carbons, or even nanoparticle-sized sheets of graphene, a material composed of a larger array of fused rings.

Such materials, he says, can act as building blocks on which other molecules, such as water, methane, methanol, carbon monoxide, and ammonia can condense as they move away from the star and cool to temperatures as low as minu-263 degrees Celsius. When the resulting chemical stew is exposed to ionising radiation either from nearby sources or galactic cosmic rays, Kaiser says, they can form sugars, amino acids, and dipeptides.

"These are molecules relevant to the origins of life," he adds.

Billions of years ago, such organic-rich particles may have found their way into asteroids that then rained down onto the primordial Earth, endowing us with the precursors for life.

Pyrene is a member of a family of compounds called polycyclic aromatic hydrocarbons (PAHs), the simplest of which is naphthalene, the primary ingredient of mothballs. Simple PAHs have already been detected in space, but the holy grail, Kaiser says, will be if more complex ones, such as pyrene, are found by NASA's OSIRIS-REx mission, now en route to asteroid 101955 Bennu, from which it is expected to send back a sample in 2023.

"We do not know what this mission will find," Kaiser says. But, "if they find carbonaceous materials such as PAHs, then our experiments say how this organic matter can be formed."

Humberto Campins, a planetary scientist from Central Florida University, Orlando, Florida, and member of the OSIRIS REx science team, agrees. Studying the chemical makeup of asteroids, he says, doesn't just tell us about the composition of our own early solar system, but can also reveal information about "pre-solar" compounds.

"One of the beauties of sample return missions is that the latest analytical techniques for chemical, mineralogical, and isotopic composition can be applied to very small components of the sample, such as pre-solar grains or molecules," he says.

"We know that the dust from these kinds of stars gets incorporated into meteorites, so they are absolutely contributing to the compounds that would be present within Bennu," adds Chris Bennett, also of the University of Central Florida (and a former student of Kaiser's, although he was not part of the present study team).

Chris McKay, an astrobiologist at NASA Ames Research Centre in Moffett Field, California, adds that the paper supports the notion that that the universe contains a large amount of carbon in the form of organic molecules. "[That's] not a new result," he says, "but [it is] further support for this key idea in astrobiology."

Kaiser adds that the finding demonstrates the value of interdisciplinary studies. "Most of the scientists dealing with PAHs [in space] are astronomers," he says. "They are excellent spectroscopists, but by nature, astronomy sometimes lacks fundamental knowledge about chemistry." Laboratory studies are necessary to turn theories for how complex chemicals can form in space from "hand-waving" into something more definitive, he says.

But the interdisciplinary impact goes beyond astronomy. Pyrene and other PAHs are common pollutants that can be incorporated into dangerous soot particles created by internal combustion engines and other industrial processes.

Lessons from astrochemistry about how they can be formed, he says, says Kaiser, can therefore have the very practical side effect of helping us develop less-polluting automobile engines.

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Genes influence empathy

Collaboration between researchers and gene-testing company opens window on the basis of caring about others.

Andrew Masterson reports.

At a meeting in February with survivors of a Florida high school mass shooting, US president Donald Trump was photographed holding a list of *aides memoire* which included the prompt, "I hear you".

The need to remind himself to at least appear sympathetic to the feelings of children who had witnessed their school mates being shot by a man with an assault rifle was interpreted by many – if not most – as

indicating that Mr Trump was somewhat deficient in the empathy department.

And perhaps he is – but if so he might not be fully to blame.

A new study based on questionnaire responses matched to genetic samples obtained from 46,000 people suggests that genes are at least partially responsible for a person's ability to feel and express empathy.

Donald Trump's talking points perhaps reflect a lack of empathy, but could his genes be partly to blame? **Chip Somodevilla/Getty Images**

The study, published in the journal *Translational Psychiatry*, was conducted by a team headed by Varun Warrier of the Autism Research Centre at Cambridge University in the UK, in conjunction with US genetics company 23andMe.

Warrier and his colleagues made use of data obtained by the popular business. Each customer completed a questionnaire designed to reflect empathy potential, based on a self-report measure developed by other University of Cambridge researchers 15 years ago. The questionnaire delivers a standardised result on a scale known as the Empathy Quotient (EQ).

Results on the EQ scale were then compared to genetic read-outs generated by sequencing DNA contained in the saliva samples.

The results demonstrated that as much as 10% of variation in EQ scores is the result of genetic differences.

"This new study demonstrates a role for genes in empathy, but we have not yet identified the specific genes that are involved," says co-lead author Thomas Bourgeron.

"Our next step is to gather larger samples to replicate these findings, and to pinpoint the precise biological pathways associated with individual differences in empathy."

The study also found two other significant outcomes. The first was that women were, on average, more empathetic than men, even though these differences were not associated with genetic variations.

The researchers say this result implies that non-genetic factors, such as socialisation, and possibly hormonal influences in the womb, may be important in determining empathy responses.

The other result found that the genetic variants associated with reduced empathy were also linked to higher risk for autism.

"Finding that even a fraction of why we differ in empathy is due to genetic factors helps us understand people such as those with autism who struggle to imagine another person's thoughts and feelings," comments co-author Simon Baron-Cohen.

"This can give rise to disability no less challenging than other kinds of disability, such as dyslexia or visual impairment. We as a society need to support those with disabilities, with novel teaching methods, work-arounds, or reasonable adjustments, to promote inclusion."

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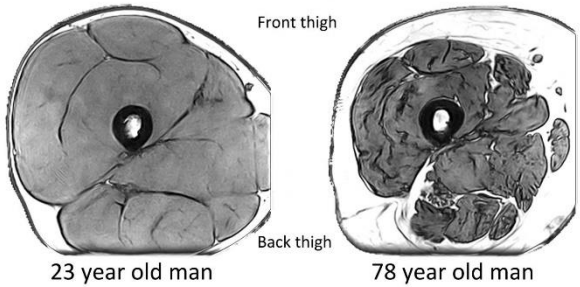
Can we turn back time? Muscles' own protective systems could help reduce frailty

New research published today helps explain why people experience muscle loss in old age, increasing the prospects of reversing the condition in the future.

As people grow older, their leg muscles become progressively smaller and weaker, leading to frailty and disability. While this process inevitably affects everyone living long enough, until now the process has not been understood. This new research, published in the Journal of Physiology, suggests that muscle wasting follows on from changes in the nervous system. By the age of 75, individuals typically have around 30 - 50% fewer nerves controlling their legs. This leaves parts of their muscles disconnected from the nervous system, making them functionally useless and so they waste away.

However, healthy muscles have a form of protection, in that surviving nerves can send out new branches to rescue some, but not all, of the

detached muscle fibres. This protective mechanism is most successful in older adults with large, healthy muscles. When the internal protective mechanism is not successful and nerves are unable to send out new branches, it can result in extensive muscle loss. This can result in a condition called Sarcopenia, which affects an estimated 10-20% of people aged over 65 years.



Magnetic resonance images of the mid-thigh. Femur bone is in the middle creating a black ring, muscles are shaded grey and fat is white.

The femur bone is in the middle creating a black ring, muscles are shaded grey and fat is white. Piasecki et al.

The researchers do not yet understand why the connections between muscles and nerves remain healthy in some people and not in others.

The race is now on to use this new knowledge to delay old-age weakness by either slowing the decline or by increasing the success of nerve branching to rescue detached muscle fibres.

The research carried out by Manchester Metropolitan University in conjunction with University of Waterloo, Ontario, and The University of Manchester, involved using MRI to gain a detailed look at the muscle tissue, followed by enhanced electromyography to record the electrical activity passing through the muscle to estimate the numbers and the size of surviving nerves available to rescue muscle fibres.

The researchers are currently looking at whether regular exercise in middle- and older-age slows the process of muscles becoming disconnected from the nervous system, or improves the success of nerve branching to rescue detached muscle fibres. The goal is to identify the best type of exercise - strength training or endurance - and to understand the physiology of why the nerve-muscle changes occur as we get older.

Professor Jamie McPhee, the senior author on the research, commented on the significance of the findings: "Our challenge now is to find ways to increase the success of nerve branching to rescue detached muscle fibres and thereby reduce the numbers of older people in our neighbourhoods with low muscle mass and muscle weakness. Right now in Europe there are at least 10 million older people with low muscle mass, which is a medical condition known as sarcopenia. They are at higher risk of social isolation, falling, bone fracture, disability and hospital admission. Weakness makes them particularly vulnerable to falls in bad weather, as we've had in recent weeks. Our research helps to explain why muscles decline with advancing age and this new knowledge will help in the search for effective countermeasures."

Dr Mathew Piasecki, the study lead author who has since taken up a position at the University of Nottingham, said: "One of the earliest attempts at research similar to ours showed results from a small group of older people who apparently had just a couple of surviving nerves feeding into a foot muscle. When we started out with our research we were very sceptical of the old data and thought it was an anomaly of out-dated testing procedures. However, now that we have tested a couple of hundred men we think the early observation was probably correct. We have also observed some very old muscles with just a few dozen nerves left, where young and healthy adults have hundreds."