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Instant liver, just add water'? Not quite, but a better way to grow multiple organs

Improved method to grow an organoid model of the liver, bile duct and pancreas

Tokyo, Japan - Pluripotent stem cells are specialized cells that can become almost any type of cell or tissue in the body. Because of this potential, they are often used in research to study disease. One way this is done is by coaxing stem cells to form organoids, which resemble organs but can be more easily studied in a laboratory. Researchers centered at Cincinnati Children's Hospital Medical Center (CCHMC) and Tokyo Medical and Dental University(TMDU) have devised a better way to make one particular organoid to aid in studies of the liver, bile duct and pancreas.

"Our focus was on generating a hepato-biliary-pancreatic organoid, which would allow us to better understand how the liver, bile duct, pancreas, and associated tissues form during embryonic development and how they normally function together," explains Takanori Takebe, senior author of the study. "The current technical approaches are fairly limited, though, and the resulting models lack the complexity of true organs."

In the technique pioneered by the research team, human stem cells are used to make small "spheres" of cells that each represent different parts of a developing embryo. The spheres are fused together to create an immature organoid, which is then allowed to mature and grow while suspended in a specially engineered three-dimensional gel. With the new technique, the resulting organoid bears a striking resemblance to a liver, pancreas, and the connecting bile ducts.

"What we are most excited about is the sophistication of the organoid," says Hiroyuki Koike, one of the researchers involved in developing the technique. "We could see branches that directly connected the bile duct to the pancreas. Amazingly, the pancreatic tissue that emerged was able to secrete digestive enzymes through the ducts, similar to how the true organ would function. The complexity of the organoid is really quite remarkable."

The researchers also showed that, by making specific genetic mutations, they can stop the stems cells from becoming a working organoid--demonstrating the potential usefulness of the system to study diseases that arise in these organs.

"There are still a number of challenges in the field with respect to creating a robust multi-organ model system that can be easily manipulated in a research setting," Takebe adds. "The work here shows that it is possible to create such a system using human pluripotent stem cells. This is quite exciting, as it lends credibility to the idea that stem cells might be used to make personalized models to study how organs form and how genetic mutations lead to organ malfunction."

The article, "Modeling human hepato-biliary-pancreatic organogenesis from the foregut-midgut boundary" was published in Nature at DOI: 10.1038/s41586-019-1598-0.

https://go.nature.com/2BwDc49

Super-precise new CRISPR tool could tackle a plethora of genetic diseases

The system allows researchers more control over DNA changes, potentially opening up conditions that have challenged gene-editors.

Heidi Ledford

For all the ease with which the wildly popular CRISPR–Cas9 gene-editing tool alters genomes, it’s still somewhat clunky and prone to errors and unintended effects. Now, a recently developed alternative offers greater control over genome edits — an advance that could be particularly important for developing gene therapies.

The alternative method, called prime editing, improves the chances that researchers will end up with only the edits they want, instead of a mix of changes that they can't predict. The tool, described in a study published on 21 October in *Nature*[1], also reduces the 'off-target' effects that are a key challenge for some applications of the standard CRISPR–Cas9 system. That could make prime-editing-based gene therapies safer for use in people.

The tool also seems capable of making a wider variety of edits, which might one day allow it to be used to treat the many genetic diseases that have so far stymied gene-editors. David Liu, a chemical biologist at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts and lead study author, estimates that prime editing might help researchers tackle nearly 90% of the more than 75,000 disease-associated DNA variants listed in ClinVar, a public database developed by the US National Institutes of Health.

The specificity of the changes that this latest tool is capable of could also make it easier for researchers to develop models of disease in the laboratory, or to study the function of specific genes, says Liu.

"It's early days, but the initial results look fantastic," says Brittany Adamson, who studies DNA repair and gene editing at Princeton University in New Jersey. "You're going to see a lot of people using it."

Prime editing may not be able to make the very big DNA insertions or deletions that CRISPR–Cas9 is capable of — so it's unlikely to completely replace the well-established editing tool, says molecular biologist Erik Sontheimer at the University of Massachusetts Medical School in Worcester. That's because for prime editing, the change that a researcher wants to make is encoded on a strand of RNA. The longer that strand gets, the more likely it is to be damaged by enzymes in the cell.

"Different flavours of genome-editing platforms are still going to be needed for different types of edits," says Sontheimer.

But prime editing appears to be more precise and versatile than other CRISPR alternatives developed thus far. Those include modified versions of CRISPR–Cas9 that enable researchers to swap out one DNA letter for another, and older tools such as zinc-finger nucleases, which are difficult to tailor to each desired edit.

Freedom through control

CRISPR–Cas9 and prime editing both work by cutting DNA at a specific point in the genome. CRISPR–Cas9 breaks both strands of the DNA double helix and then relies on the cell's own repair system to patch the damage and make the edits. But that repair system is unreliable and can insert or delete DNA letters at the points where the genome was cut. This can lead to an uncontrollable mixture of edits that vary between cells.

In addition, even when researchers include a template to guide how the genome is edited, the DNA repair system in most cells is far more likely to make those small, random insertions or deletions than to add a specific DNA sequence to the genome. That makes it difficult — and in some cases, nearly impossible — for researchers to use CRISPR–Cas9 to overwrite one piece of DNA with a sequence of their choosing.

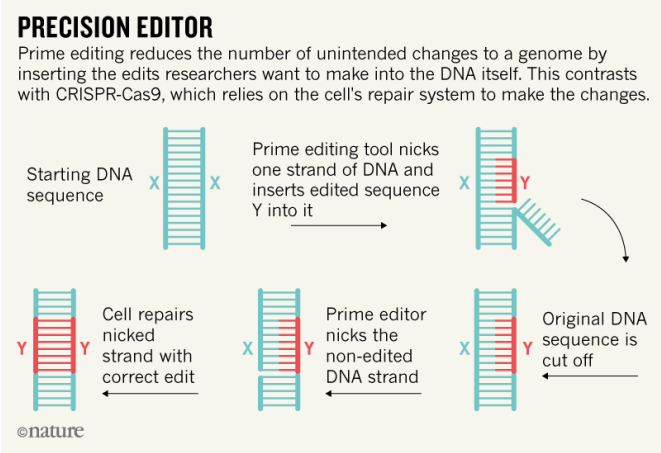
Prime editing bypasses these problems (see 'Precision editor'). Although it also uses Cas9 to recognize specific DNA sequences — just like CRISPR–Cas9 does — the Cas9 enzyme in the prime editing tool is modified to nick only one DNA strand. Then, a second enzyme called reverse transcriptase and guided by a strand of RNA, makes the edits at the site of the cut.

The prime editing enzymes don't have to break both strands of DNA to make changes, freeing researchers from relying on the cell's DNA repair system — which they can't control — to make the edits that they want. This means that prime editing could enable

the development of treatments for genetic diseases caused by mutations that aren't easily addressed by existing gene-editing tools.

A multipurpose tool

Previously, researchers, including Liu, thought that they would need to develop gene-editing tools specific to each category of change they wanted to make in a genome: insertions, deletions or DNA letter substitutions. And the options were limited when it came to making precise substitutions.



An older technique, called base editing, which is comparable in precision to prime editing, chemically converts one DNA letter directly into another — something CRISPR–Cas9 can't do — such as converting a T to an A or a G to a C, without breaking both DNA strands[2]. Developed by Liu, base-editing could be useful for correcting some genetic diseases caused by single-letter mutations, including the most common form of sickle-cell anaemia.

But base-editing can't help with genetic disorders caused by multi-letter mutations such as Tay–Sachs disease, a usually fatal illness typically caused by the insertion of four DNA letters into the *HEXA* gene.

So Liu and his colleagues set out to create a precise gene-editing tool that gave researchers the flexibility and control to make multiple types of edits without having to create bespoke systems. In 2018, the team hit on prime editing: a combination of enzymes, including a modified Cas9 enzyme, that could change individual DNA letters, delete letters, or insert a series of letters into a genome, with minimal damage to DNA strands.

"It's fantastic," says Sontheimer. "The breadth of the mutations that can be introduced is one of the biggest advances. That's huge."

But Liu's team and others will now need to carefully evaluate how well the system works in a variety of cells and organisms. "This first study is just the beginning — rather than the end — of a long-standing aspiration in the life sciences to be able to make any DNA change at any position in an organism," says Liu.

doi: 10.1038/d41586-019-03164-5

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https://nyti.ms/35UJCIm

The Dinosaur-Killing Asteroid Acidified the Ocean in a Flash

The Chicxulub event was as damaging to life in the oceans as it was to creatures on land, a study shows.

By Lucas Joel

What happened to the dinosaurs when an asteroid about six miles wide struck Earth some 66 million years ago in what is today Mexico is well known: It wiped them out. But the exact fate of our planet's diverse ocean dwellers at the time — shelly ammonites, giant mosasaurs and other sea creatures — has not been as well understood.

New research now makes the case that the same incident that helped bring an end to the reign of the dinosaurs also acidified the planet's oceans, disrupted the food chain that sustained life underwater and resulted in a mass extinction. The study, published Monday in Proceedings of the National Academy of Sciences, aims to shore up the hypothesis that the Chicxulub event's destruction of marine life — the result of sulfur-rich rocks depositing acid rain

into the oceans — was just as severe as the fire and fury it brought to land.

"It's flash acidification, and it transformed ecosystems for millions of years," said Noah Planavsky, a biogeochemist at Yale and one of the study's authors. "We were shocked that we actually found this."

The impact of the Chicxulub asteroid — so named for the crater it carved out around the Gulf of Mexico — sent columns of rock into Earth's atmosphere, incinerated the planet's forests and drove tsunamis far across the oceans. But the connection between the crash and the marine extinction has been less solid.

That gap in understanding was on the mind of Michael Henehan, a geochemist, when he attended a conference in 2016 in the Netherlands that included a group outing to the cave system at Geulhemmerberg, which contains stones from the end of the Cretaceous period. There, he came upon a surprisingly thick rock layer made of gray clay that formed just after the asteroid hit. Lacking proper rock sample bags, he emptied the contents of his lunch into his pockets, collected some rocks and put them into his lunch bags.

Back in the lab at Yale University, Dr. Henehan, who is now a researcher at GFZ Helmholtz Center in Potsdam, Germany, cleaned the rocks and found the fossil shells of thousands of tiny marine plankton called foraminifera, or "forams." Finding so many shells was fortunate, he explained, because they preserve trace amounts of boron, a chemical element that is sparse in such fossils, but offers clues to the ancient acid levels of the oceans when enough of it can be found.

Foram shells, shown at eight times magnification, collected in the Geulhemmerberg caves in the Netherlands. They offered clues to the ocean's acid levels after the asteroid struck. **Michael J. Henehan**

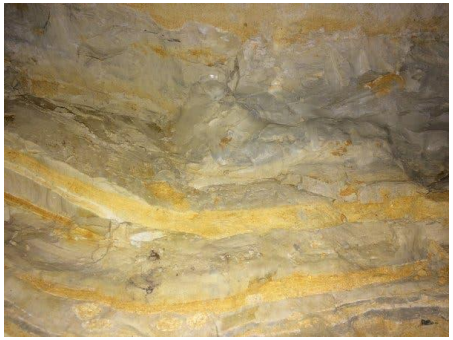
Dr. Henehan and his team measured the boron, and found that the relative proportions of two isotopes of the element changed abruptly right at the time of the impact. In shells like these, Dr. Planavsky explained, proportions of the boron isotopes shift when the acidity of the oceans rises. And because this ancient shift happened in the first 100 to 1,000 years after the impact, it means the oceans became acidic practically overnight.

The flash acidification would have devastated organisms that formed the foundations of ecosystems, leading to problems for other creatures like the ammonites that lived higher up the food chain. "This is a big leap forward," said Chris Lowery, a paleoceanographer at the University of Texas at Austin who was not involved in the new work.

The study offers evidence of what sustained the marine extinction after the asteroid impact got things rolling. That, and it confirms that the asteroid triggered the extinction in the first place.

Around the time that the asteroid struck, there was intense volcanic activity in what is today India, causing over 200,000 cubic miles of lava to be disgorged over the course of about a million years.

For a long time, it was not clear if the marine mass extinction stemmed from changes wrought by the volcanism or by the asteroid. But because the boron shift happened exactly at the boundary, it is now obvious that the asteroid had the bigger effect.



This is the boundary, visible in the rock of the Geulhemmerberg caves, that marks the transition from the Cretaceous period to the Paleogene. **Michael J. Henehan**

"It's very, very strong evidence that the ocean acidification was caused by the impact and not volcanoes," Dr. Lowery said.

The flash acidification and mass extinction, though ancient events, are relevant to our modern world. According to reports from the United Nations Intergovernmental Panel on Climate Change, human emissions of carbon dioxide are not only warming the planet, but also acidifying the oceans. And that modern acidification, Dr. Planavsky says, is happening at a rate and scale comparable to the asteroid-triggered acidification. A similar result, he said, “is on the extreme end of what we could get in the next 100 years.”

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'Missing' virus detected in dozens of children paralyzed by polio-like illness

Study is first to find clear signs of enterovirus in nervous system of AFM patients, strongest evidence to date that disease is viral

A UC San Francisco-led research team has detected the immunological remnants of a common seasonal virus in spinal fluid from dozens of patients diagnosed with acute flaccid myelitis (AFM) -- a polio-like illness that causes permanent, sometimes life-threatening paralysis in young children. The findings provide the clearest evidence to date that AFM is caused by an enterovirus (EV) that invades and impairs the central nervous system.

The study was published October 21, 2019 in *Nature Medicine*.

AFM, which begins with cold-like symptoms and progresses to limb weakness and paralysis in a matter of days, was first documented in 2012. Since then, AFM outbreaks have occurred every other year, with more than 500 confirmed cases recorded so far. But because scientists have had trouble pinpointing a cause, AFM has been the subject of contentious debate within the medical community.

Mounting evidence implicated EVs as the likely culprit -- specifically the so-called D68 and A71 strains of the virus. EV outbreaks are common and normally cause nothing more severe than cold-like symptoms or the rash-producing hand, foot and mouth disease.

Scientists started to notice, however, that EV outbreaks coincided with spikes in AFM. They also found that respiratory samples from children diagnosed with AFM often tested positive for EVs. Plus, laboratory studies found that these strains caused paralysis in mice.

But many experts remained skeptical of the enterovirus hypothesis, instead proposing that AFM is an autoimmune disorder or is caused by some other, as-yet-undiscovered virus. These EV skeptics argued that that the evidence linking the virus to AFM was circumstantial, because the virus could not be found in 98 percent of AFM patients who had their spinal fluid tested. They maintained that until there was ample evidence of the virus invading the human nervous system, the link between EVs and AFM remained unproven.

"People were hung up on the fact that enteroviruses were rarely detected in the cerebrospinal fluid of AFM patients. They wanted to know how someone could get neurologic symptoms with no virus detectable in their central nervous system," said Michael Wilson, MD, associate professor of neurology, member of the UCSF Weill Institute for Neurosciences, and senior author of the new study. "If we could detect something specific to a virus in in the spinal fluid of AFM patients, we would feel more secure claiming that the neurologic symptoms of the disease are virally mediated."

The group first searched for the virus directly in spinal fluid using advanced deep sequencing technologies, but this sort of direct detection of the virus failed, as it had previously. Therefore, to find evidence of the missing virus, Wilson and his collaborators -- researchers at the Chan Zuckerberg Biohub, the Centers for Disease Control and Prevention, the California Department of Public Health, the University of Colorado, Boston Children's Hospital and the University of Ottawa -- used an enhanced version of a virus-hunting

tool called VirScan, first developed at Harvard Medical School in the laboratory of Stephen J. Elledge, PhD.

VirScan, which is a customized version of a Nobel Prize-winning technique called phage (rhymes with "beige") display, allowed Wilson's team to probe the spinal fluid of AFM patients for signs of an immune response against enterovirus and thousands of other viruses simultaneously.

"When there's an infection in the spinal cord, antibody-making immune cells travel there and make more antibodies. We think finding antibodies against enterovirus in the spinal fluid of AFM patients means the virus really does go to the spinal cord. This helps us lay the blame on these viruses," said Ryan Schubert, MD, a clinical fellow in UCSF's Department of Neurology, a member of Wilson's Lab, and lead author of the new study.

The researchers created molecular libraries consisting of nearly 500,000 small chunks of every protein found in the over 3,000 viruses known to infect vertebrates (including humans), as well as those that infect mosquitoes and ticks (an effort to rule out disease transmission through their bites). They then exposed these molecular libraries to spinal fluid obtained from 42 children with AFM and, as a control, 58 who were diagnosed with other neurological diseases. Any chunks of viral protein cross-reacting with any antibodies present in the spinal fluid would provide evidence for a viral infection in the central nervous system.

Antibodies against enterovirus were found in the spinal fluid of nearly 70 percent of AFM patients; less than 7 percent of non-AFM patients tested positive for these antibodies. Furthermore, because spinal fluid from AFM patients did not contain antibodies against any other virus, every other known virus could be eliminated as a possible culprit. These results were confirmed using more conventional lab techniques.

"The strength of this study is not just what was found, but also what was not found," said Joe DeRisi, PhD, professor of biochemistry and biophysics at UCSF, co-president of the Chan Zuckerberg Biohub, and co-author of the new study. "Enterovirus antibodies were the only ones enriched in AFM patients. No other viral family showed elevated antibody levels."

Though the study provides the most robust evidence so far that enteroviruses cause AFM, many questions around AFM and these viruses remain unanswered. For example, though the AFM-causing enterovirus strains -- EV-D68 and EV-A71 -- were identified decades ago, they only recently seemed to have gained the ability to cause paralysis, with the D68 strain in particular responsible for the most severe cases of AFM.

"Presumably there are changes that are causing the virus to be more neurovirulent, but no one knows for sure what they are," Schubert said. "Because the virus is found in such low amounts, if at all, it's hard to zero in on the differences between an A71 virus that causes routine hand, foot, and mouth disease and one that causes AFM."

Also, because enteroviruses are extremely common, scientists are still trying to figure out why fewer than 1 percent of infected children get AFM, and they're also trying to understand why children are the only ones affected. "We don't know for sure why children get paralysis and adults don't," Schubert said. "The thinking is that young children have low immunity to the virus that increases as they get older, so we see the most severe effects in children around the age of two. But more work needs to be done to understand AFM."

For study co-author Riley Bove, MD, answering these unresolved questions is a deeply personal mission. Bove, an assistant professor of neurology and member of the UCSF Weill Institute for Neurosciences, is the mother of a child who was diagnosed with AFM.

In the summer of 2014, Bove's entire family came down with what seemed to be a severe cold. Everyone recovered except Bove's then four-year-old son. Just days after the onset of the cold-like symptoms, he started experiencing difficulty breathing. Soon, he was paralyzed from head to toe and had trouble breathing on his own.

Today, Bove's son is a thriving nine-year-old, but she says the physical and emotional effects of AFM will be with him the rest of his life. "For every family with a child diagnosed with AFM, the long-term consequences of the disease remain the top issue," she said.

Bove hopes that the new study will lead to a scientific consensus around enterovirus as the cause of AFM, since this a key step on the road to improved diagnostics and the development of a vaccine for the illness.

"Public health education is important, but it's not enough to prevent AFM," Bove said. "The virus is too common to avoid. A vaccine is the only way to meaningfully prevent the disease."

For now, there's no way to prevent or treat AFM. But if it follows the biennial pattern first established after the 2012 outbreak, AFM cases may spike again next year.

"We're all holding our breath for 2020," Schubert said.

Authors: Additional authors on the study come from UCSF, the Chan Zuckerberg Biohub, Massachusetts General Hospital, the University of Ottawa, Kaiser Permanente, the California Department of Public Health, the University of Colorado, the Centers for Disease Control and Prevention, the National Institutes of Health, and Boston Children's Hospital. The full list of contributors can be found in the published study.

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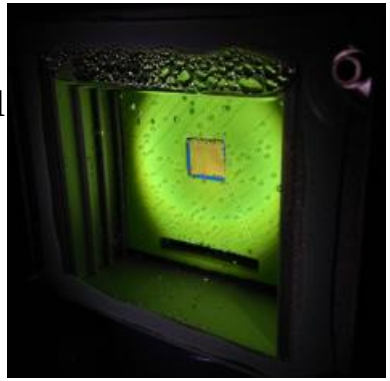
Disclosures: The authors declare no competing interests.

http://bit.ly/2N3HSny

'Artificial leaf' successfully produces clean gas

Could eventually be used to develop a sustainable liquid fuel alternative to petrol

A widely-used gas that is currently produced from fossil fuels can instead be made by an 'artificial leaf' that uses only sunlight, carbon dioxide and water, and which could eventually be used to develop a sustainable liquid fuel alternative to petrol.



The carbon-neutral device sets a new benchmark in the field of solar fuels, after researchers at the University of Cambridge demonstrated that it can directly produce the gas - called syngas - in a sustainable and simple way.

This 'artificial leaf' uses water, sunlight and carbon dioxide to produce a widely-used gas, inspired by the natural process by which plants use the energy from sunlight to turn carbon dioxide into food. **Virgil Andrei**

Rather than running on fossil fuels, the artificial leaf is powered by sunlight, although it still works efficiently on cloudy and overcast days. And unlike the current industrial processes for producing syngas, the leaf does not release any additional carbon dioxide into the atmosphere. The results are reported in the journal *Nature Materials*.

Syngas is currently made from a mixture of hydrogen and carbon monoxide, and is used to produce a range of commodities, such as fuels, pharmaceuticals, plastics and fertilisers.

"You may not have heard of syngas itself but every day, you consume products that were created using it. Being able to produce it sustainably would be a critical step in closing the global carbon cycle and establishing a sustainable chemical and fuel industry," said senior author Professor Erwin Reisner from Cambridge's

Department of Chemistry, who has spent seven years working towards this goal.

The device Reisner and his colleagues produced is inspired by photosynthesis - the natural process by which plants use the energy from sunlight to turn carbon dioxide into food.

On the artificial leaf, two light absorbers, similar to the molecules in plants that harvest sunlight, are combined with a catalyst made from the naturally abundant element cobalt.

When the device is immersed in water, one light absorber uses the catalyst to produce oxygen. The other carries out the chemical reaction that reduces carbon dioxide and water into carbon monoxide and hydrogen, forming the syngas mixture.

As an added bonus, the researchers discovered that their light absorbers work even under the low levels of sunlight on a rainy or overcast day.

"This means you are not limited to using this technology just in warm countries, or only operating the process during the summer months," said PhD student Virgil Andrei, first author of the paper. "You could use it from dawn until dusk, anywhere in the world."

The research was carried out in the Christian Doppler Laboratory for Sustainable SynGas Chemistry in the University's Department of Chemistry. It was co-funded by the Austrian government and the Austrian petrochemical company OMV, which is looking for ways to make its business more sustainable.

"OMV has been an avid supporter of the Christian Doppler Laboratory for the past seven years. The team's fundamental research to produce syngas as the basis for liquid fuel in a carbon neutral way is ground-breaking," said Michael-Dieter Ulbrich, Senior Advisor at OMV.

Other 'artificial leaf' devices have also been developed, but these usually only produce hydrogen. The Cambridge researchers say the reason they have been able to make theirs produce syngas sustainably is thanks the combination of materials and catalysts they used.

These include state-of-the-art perovskite light absorbers, which provide a high photovoltage and electrical current to power the chemical reaction by which carbon dioxide is reduced to carbon monoxide, in comparison to light absorbers made from silicon or dye-sensitised materials. The researchers also used cobalt as their molecular catalyst, instead of platinum or silver. Cobalt is not only lower-cost, but it is better at producing carbon monoxide than other catalysts.

The team is now looking at ways to use their technology to produce a sustainable liquid fuel alternative to petrol.

Syngas is already used as a building block in the production of liquid fuels. "What we'd like to do next, instead of first making syngas and then converting it into liquid fuel, is to make the liquid fuel in one step from carbon dioxide and water," said Reisner, who is also a Fellow of St John's College.

Although great advances are being made in generating electricity from renewable energy sources such as wind power and photovoltaics, Reisner says the development of synthetic petrol is vital, as electricity can currently only satisfy about 25% of our total global energy demand. "There is a major demand for liquid fuels to power heavy transport, shipping and aviation sustainably," he said.

"We are aiming at sustainably creating products such as ethanol, which can readily be used as a fuel," said Andrei. "It's challenging to produce it in one step from sunlight using the carbon dioxide reduction reaction. But we are confident that we are going in the right direction, and that we have the right catalysts, so we believe we will be able to produce a device that can demonstrate this process in the near future."

The research was also funded by the Winton Programme for the Physics of Sustainability, the Biotechnology and Biological Sciences Research Council, and the Engineering and Physical Sciences Research Council.

http://bit.ly/2PjWuC7

50,000-year-old, tar-smeared tool shows Neanderthal smarts

Neanderthals could accomplish complex, multistep tasks that took planning ahead over several days.

By Andrew Curry

Old-school scholars considered Neanderthals brutish and simple, but recent research shows they made jewelry, had a precision grip, and may have even painted cave art. Now, a tar-caked tool found on a Dutch beach supports the idea that Neanderthals could accomplish complex, multistep tasks that took planning ahead over several days.

***Archaeologists reconstructed how Neanderthals manufactured sticky tar from birch bark 50,000 years ago. Neanderthals may have used the tar to attach stone points to wooden spears, as shown.* © Paul Kozowyk**

In 2016, an amateur collector named Willy van Wingerden found a flint flake partly covered in thick black tar on the Zandmotor, an artificial beach in the Netherlands. The beach, made from sand dredged from the bottom of the North Sea, is a treasure trove of prehistoric artifacts. That's because the sand used to be part of a wide expanse of dry, cold steppe, connecting the United Kingdom and the Netherlands during the last ice age, when sea levels were much lower than they are today.

At first glance, the tool doesn't look like much—a small, sharp-edged flint flake with a gob of tar on the end. Once it hardened, the tar provided enough of a handhold for someone to use the flake's sharp edge as a scraper or blade. "It looks quite simple, but it's quite a complex tool," says lead author Marcel Niekus, an independent archaeologist in the Netherlands who analyzed the find. "It took a lot of steps to make and haft the piece."

When Niekus and his colleagues used radiocarbon dating to analyze the tar on the flake, they found it was 50,000 years old, dating back to a time before modern humans arrived, they write today in the *Proceedings of the National Academy of Sciences*.

The tar, preserved by the cold, oxygen-free conditions in sediments several meters beneath the sea floor, might have been an essential element of Stone Age tool kits, says co-author Geeske Langejans, an archaeologist at the Delft University of Technology in the Netherlands. She and her colleagues tried to recreate tool's manufacture, collecting strips of birch bark, mounding clay over them, and building a fire on top to heat the bark inside to 300°C–400°C for hours. The procedure was hot enough to produce thick tar, as the resinous bark disintegrated.

By comparing the chemical composition of the modern tar and its impurities to the ancient tar, Langejans and her team found that the Neanderthals likely used the same procedure.

***This tar-handled tool was made by a Neanderthal 50,000 years ago.* © RMO**

But making enough tar to adorn even an unremarkable tool was undoubtedly difficult without pottery to collect the hot, pooling tar. "It's an ugly little piece, not even retouched or shaped," Langejans says. "That they hafted such a simple flake suggests they used adhesives on a regular basis." Other evidence suggests Neanderthals used pine resin and bitumen as adhesives to stick stone points to wooden spears. This find and two tarred tools from Italy and Germany suggest our extinct cousins used birch bark tar as well. The discovery also adds to previous work showing Neanderthals could engage in complex tasks, including creating finely crafted stone blades and multipart spears.

Paola Villa, an archaeologist at University of Colorado in Boulder who was not involved in the study, says it is "very good work" that

shows the creators of the tools were capable of complex behavior. But, she adds, a literal handful of tools from just three sites is too few to conclude that Neanderthals used birch bark tar routinely.

Niekus hopes more finds dragged up from the bottom of the North Sea could change that: “This is the tip of the iceberg,” he says. “Beneath the sea, there’s a lot of sites, and thanks to beach replenishment we can study them.”

Posted in: Archaeology doi:10.1126/science.aaz9332

http://bit.ly/35Zxlm1

'Cursed' Primate Weirdos Have Extra Thumbs. Scientists Didn't Know About Them Until Now.

There's a little extra thumb-thing on the hand of the aye-aye, a strange-looking nocturnal lemur native to Madagascar.

By Mindy Weisberger - Senior Writer

Tucked near each wrist is a small nub of bone and cartilage that's like a miniature thumb — and until recently, scientists didn't know this pseudothumb existed.

Aye-ayes (*Daubentonia madagascariensis*) are considered by many to be the weirdest of all primates, with their coarse and frazzled bedhead fur, oversize ears, bulging eyes and bony, spindly fingers, one of which is exceptionally long.

***Aye-ayes possess small "pseudothumbs" — complete with their own fingerprints — that may help them grip objects and branches as they move through trees.* (Image: © David Haring/Duke Lemur Center)**

But the discovery of the hidden mini-thumb makes aye-ayes even weirder: They are the only primate to have evolved an extra finger to help with grasping. The formerly unknown digit even has its own fingerprint, scientists reported in a new study.

In local Malagasy folklore, aye-ayes are seen as symbols of death and evil, capable of delivering curses and bringing bad luck, according to the Duke Lemur Center in North Carolina.

However, the aye-ayes' long, flexible fingers are best suited not for cursing humans, but for tapping on tree branches to locate hollow regions where tasty grubs hide, and then to poke inside holes and fish insects out, the Duke Lemur Center said.

"Their fingers have evolved to be extremely specialized — so specialized, in fact, that they aren't much help when it comes to moving through trees," said co-lead study author Adam Hartstone-Rose, an associate professor of biological sciences at North Carolina State University (NCSU).

Aye-aye hands are so strange that when the animals move they appear to be "walking on spiders," Hartstone-Rose said in a statement. It could be this extreme adaptation that drove the evolution of an extra digit to help with grasping, which aye-ayes' long, skinny fingers couldn't manage very well, the researchers wrote in the study.

Strange and unusual

It was during a routine dissection of an aye-aye's forearm when scientists found the extra digit; they were tracing a tendon that unexpectedly divided in two, said co-lead author Edwin Dickinson, a postdoctoral researcher with the NCSU Department of Biological Sciences.

"Rather than attaching to the 'true thumb,' like the muscle does in other primates, it actually split to send half of the tendon to the true thumb and half to an expanded bone in the wrist — a bone which we now know forms part of this novel sixth digit, the pseudothumb," Dickinson told Live Science in an email.

Intrigued, they went looking for this new digit in other lemurs: six adults and one juvenile. Sure enough, they found the mini-thumb in all the individuals, extending from both wrists.

But it isn't that surprising that this miniature thumb went unseen by scientists for so long, Dickinson said. Aye-ayes are rare, found only in Madagascar, and with very few in captivity; they're nocturnal, making their habits difficult to observe; and because their hands are so unusual, most of the attention that they get is focused on the digits that researchers could see, Dickinson explained.

The pseudothumb likely helps the aye-ayes grasp branches and other things, the study authors reported.

"The species has so many features that are unique among primates — ever-growing incisors, their specialized fingers, and huge ears — and their pseudothumb is yet more evidence of this," Dickinson said.

"I think this discovery also really underscores how specializing your anatomy for a specific task — in this case, feeding — can necessitate some really bizarre and unexpected adaptations to compensate," he added. The findings were published online today (Oct. 21) in the American Journal of Physical Anthropology.

http://bit.ly/367JzJ4

Long stretches of Neanderthal and Denisovan DNA helped *Homo sapiens* adapt

Denisovans and Neanderthals passed extra copies of some DNA to modern humans.

Kiona N. Smith

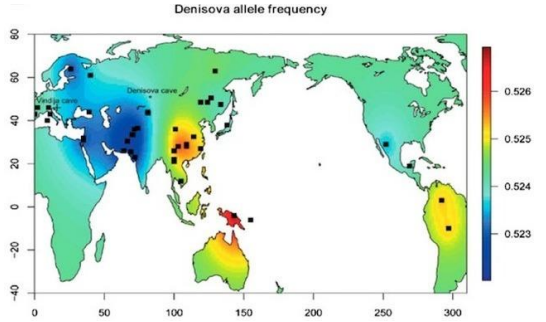
University of Washington geneticist PingHsun Hsieh and his colleagues found Neanderthal and Denisovan versions of some genes in the genomes of people from Melanesia. These versions have several thousand base pairs of DNA that have been duplicated or deleted in the normal human versions. Most of this altered DNA is in or near genes related to metabolism, development, the life cycle of cells, communication among cells, or the immune system. Those gene variants are surprisingly common among Melanesian peoples, and that could mean that their effects were useful enough that natural selection favored passing them along.

DNA from the Denisovans

As *Homo sapiens* first ventured beyond Africa, they encountered other hominins already living in Europe and Asia, and those encounters left their mark on our modern genomes. Most people from outside Africa carry a little Neanderthal DNA (it makes up about one to four percent of the average non-African genome), and some people from East Asian, Melanesian, and indigenous Australian populations also have a bit of DNA inherited from Denisovans (about one to five percent of the average genome; it's highest in Melanesian and indigenous and Australian people). Some of that DNA probably stuck with us for tens of thousands of years because it somehow helped our species adapt to new environments and challenges.

How does this DNA differ from the version found in modern humans? Thanks to the Neanderthal and Denisovan genomes recovered from ancient bones and teeth, scientists can recognize certain alleles that belong to our extinct cousins.

Usually, when scientists talk about Neanderthal or Denisovan genes, they're talking about alleles with small differences from the *Homo sapiens* version—sometimes just a single nucleotide (one "letter" in the genetic code).



Global map of Denisovan gene frequency in modern human genomes Image courtesy of Jacobsson and Skoglund/Proceedings of the National Academy of Sciences

Sometimes those small changes don't make a difference, but other times they're enough to code for a different protein or cause a gene to be active under different conditions.

Hsieh and his colleagues looked for larger differences, in which tens of thousands of base pairs had either disappeared from the chromosome or had been repeated more times than usual. Geneticists call such changes copy-number variations, and they can be bad news; too many or too few copies of most genes can cause health problems or increase the risk of cancer. But some of the copy-number variations that Melanesian peoples inherited from Neanderthals and Denisovans actually seem to have been helpful.

DNA: The gift that keeps on giving

Hsieh and his colleagues studied genomes from modern people, looking for copy-number variants that showed up in the genomes of Neanderthals or Denisovans. They focused on those that appeared in modern people from outside Africa but not in modern people from Africa, whose ancestors wouldn't have run into Neanderthals or Denisovans. They found a total of 51 such chunks of genetic code.

Hsieh and his colleagues were especially curious about Melanesia because the average Melanesian person has a higher percentage of Denisovan DNA in their genome (between three and five percent) than the average member of any other group of people. In a sample of Melanesian people's genomes from research databases, they found 37 copy-number variations that showed up in a larger portion of the population than you'd expect just by random genetic chance.

In other words, it looked like natural selection had acted in favor of those 37 pieces of DNA, making them more common because they somehow helped people live and reproduce more successfully.

Of those 37 apparently helpful sets of duplicated DNA, 19 appeared to have originally come from the Neanderthal or Denisovan genomes. "It is tempting to hypothesize that [DNA] introgression from other hominins may have played a key role in helping humans [who were] migrating out of Africa adapt to new environments by serving as a reservoir of beneficial alleles," wrote Hsieh and his colleagues.

But there's still a large gap between seeing that a genetic variant is likely to have been helpful enough for natural selection to kick in and being able to say exactly what that variant *does*. It is, however, possible to make some general predictions based on which genes are nearby. Based on that, it looks like most of the copy-number variants affect genes—associated with things like metabolism, the immune system, and embryonic development. So far, however, Hsieh and his colleagues can't be sure of the details.

The complex history of chromosome 16

One of the largest and most complex sequences in the study appears to be somehow associated with iron regulation during the development of an embryo. The 383-base-pair sequence (which contains two copied sections of DNA) happens to be located near a spot on chromosome 16 that's already prone to rearrangements. Those rearrangements are associated with the second most common genetic cause of autism that we know of, which affects about one percent of diagnosed people.

Based on what we know about how quickly DNA changes over time, Hsieh and his colleagues say that between 500,000 and 2.5 million years ago, a complex series of changes happened on chromosome 16 in the Denisovans. Some genes got copied, others got deleted, and still others just got rearranged. Eventually, about 60,000 to 170,000 years ago, the resulting alleles got passed to *Homo sapiens*, likely somewhere between southeast Asia and Melanesia. Today, the Denisovan variant shows up in about 80 percent of people in the lowlands of New Guinea.

That section of chromosome 16 already had its own copy-number variant in humans, which originated around 280,000 years ago. As

a result of the extra DNA, that area of the genome was already vulnerable to having its code rearranged. Hsieh and his colleagues suggest that the altered DNA could influence how often the genetic code gets rearranged. But that benefit could also impact the frequency of autism among Melanesians, although it's much, much too early to draw firm conclusions.

What is increasingly clear, however, is that many modern people still carry aspects of our extinct hominin relatives with us. The next step is to unravel exactly how those surviving bits of ancient DNA may still influence the lives and health of modern populations.

Science, *2019. DOI: 10.1126/science.aax2083 (About DOIs).*

http://bit.ly/2MN7C8I

Scientists reveal how the fossil fuel industry misled the public about climate change

For decades, fossil fuel corporations have deceived people about the dangers of their product

An international group of scientists show that fossil fuel corporations have, for decades, denied the public's right to be accurately informed about climate change by funding efforts to deceive people about the dangers of their product. A report illustrating how the industry "polluted the information landscape," and how the damage could be undone is published today [Monday 21 October].

The report entitled, "America misled: how the fossil fuel industry deliberately misled Americans about climate change," by academics from the universities of Bristol, UK; George Mason, U.S. and Harvard, U.S., summarizes more than a decade of peer-reviewed research, and has been published to help inform policymakers, journalists, and the public.

The report includes what the fossil fuel industry knew versus what they did, the arguments they used to seed doubt in the public, the techniques they used to create those arguments, and some strategies for combating them.

The key points in the report are:

1. Internal corporate documents show that the fossil fuel industry has known about human-caused climate change for decades. Its response was to actively arrange and fund denial and disinformation to suppress action and protect its status quo business operations.

2. As the scientific consensus on climate change emerged and strengthened, the industry and its political allies attacked the consensus and exaggerated the uncertainties.

3. The fossil fuel industry offered no consistent alternative explanation for why the climate was changing—the goal was merely to undermine support for action.

4. The strategy, tactics, infrastructure, and rhetorical arguments and techniques used by fossil fuel interests to challenge the scientific evidence of climate change—including cherry picking, fake experts, and conspiracy theories—come straight out of the tobacco industry's playbook for delaying tobacco control.

5. Informing the public about how these arguments are deceptive not only begins to correct the misconceptions, but also will make it harder for future campaigns to use these misleading tactics to confuse the public.

Professor Stephan Lewandowsky, Chair in Cognitive Psychology in the School of Psychological Science and Cabot Institute for the Environment at the University of Bristol, said: "Disinformation about climate change has a straightforward purpose—to block action on climate change. In America, it has largely succeeded, with policies to mitigate climate change blocked or delayed for decades."

Professor John Cook, at the Center for Climate Change Communication at George Mason University, added: "Exposing and explaining the techniques used to mislead are key to inoculating the public from further industry-funded disinformation."

Geoffrey Supran, Research Associate in the Department of the History of Science at Harvard University, explained: "For 60 years, the fossil fuel industry has known about the potential global warming dangers of their products. But instead of warning the public or doing something about it, they turned around and orchestrated a massive campaign of denial and delay designed to protect profits. The evidence is incontrovertible: Exxon misled the public. Like all bad actors, they should be held accountable."

Later this week [Wednesday 23 October], the People of the State of New York will face Exxon Mobil Corporation in court. While the legal proceedings are complicated, the academics state they are underpinned by a simple truth: for decades, ExxonMobil and other fossil fuel corporations funded efforts to deceive the American people about the dangers of their product.

More information: *'America misled: how the fossil fuel industry deliberately misled Americans about climate change' by John Cook, Geoffrey Supran, Stephan Lewandowsky, Naomi Oreskes, Ed Maibach: www.climatechangecommunication … 0/America_Misled.pdf*

http://bit.ly/3668Qn5

Bans on rebuilding in disaster-prone areas ignore homeowners preferences – raising costs works better

As California's wildfire season intensifies, a growing number of residents in the state want to ban people from building in areas at greatest risk.

Alexander Smith*

That's because taxpayers bear the burden of protecting homes in dangerous areas when fire breaks out – and they often help foot the bill when it's time to rebuild. A recent assessment showed that 1 in 4 Californians live in an area at "high risk" of wildfire. And people tend to want to rebuild in the same spot that was hit by a disaster.

As a behavioral economist who studies the psychology of decision-making, I try to understand people's motivations before taking a position in a policy debate. I believe there's a better way for policymakers to achieve the same goal of getting people to avoid building in disaster-prone areas without forcing people from their homes.

A bird in the hand

In behavioral economics, there's something known as the endowment effect.

The endowment effect is basically the idea that people overvalue things they already own. And it helps explain the common and seemingly irrational desire of many homeowners to rebuild in places at great risk of wildfire, hurricanes or other natural disasters.

Behavioral economists Daniel Kahneman, Jack Knetsch and Richard Thaler were the first to explain this effect in 1990. They conducted an experiment in which half their subjects were given a coffee mug. They asked those subjects to name the lowest price at which they'd be willing to sell their mug. They then asked those without mugs how much they would be willing to pay buy one.

Since the subjects who received a mug were randomly chosen, there should have been little difference between the selling and buying prices, which represent how each group valued the mug.

Instead, the researchers discovered a significant gap between two groups. The median selling price, representing the people who already had mugs, was US$5.79, more than double the $2.25 people were willing to pay. The conclusion is that someone with an item values it a lot more than someone who does not have it regardless of their actual preferences.

Pigouvian taxes

In the context of California wildfires or other natural disasters, the endowment effect says that someone who owns a damaged or destroyed home will have a strong preference for rebuilding over moving somewhere else.

To ignore this preference by putting an outright ban on rebuilding disregards the wishes of these people. It also squanders the

potential impact of increased economic activity as a result of the new construction. Areas recovering from disaster are in great need of this kind of stimulus.

At the same time, I don't think we should stand idly by and watch people continue to build homes in disaster zones. Such an approach creates an unfair burden for the state, which spends a significant amount of money providing disaster relief to affected areas.

Rather, my view – which is common among economists – is that the best policy when an activity imposes costs on society is to create a pricing system that pushes those costs back onto the individuals responsible.

With fuel for gas-guzzling vehicles, for example, the best policy is a tax equal to the cost that the pollution causes for society – this is how carbon pricing works. Such taxes are called Pigouvian taxes after economist Arthur Pigou, who developed the concept of "externalities" – or the unrelated side effects of some economic activity.

In the case of disaster zones, municipal property taxes need to reflect the additional costs of public services like disaster relief that are often provided by state and federal authorities. Governments can then use the extra revenue to finance disaster mitigation efforts or other initiatives in the public interest.

The key thing is that the tax creates a disincentive to engage in the undesirable activity short of an outright ban. And research shows these kinds of taxes are effective.

A softer approach

A challenge with the implementation of such a policy is that it is hard to assess the costs of relief in advance.

However, the insurance industry is very good at risk and cost assessment, and governments can use their methods to achieve the right pricing mechanism. The additional property taxes that would result would make living in disaster-prone areas more costly – and some people would certainly be willing to bear this burden – but this is what society needs in order to reduce the activity.

This softer approach, which could achieve the same ends as a heavy-handed ban, is a much better way to create a financial incentive for people to avoid rebuilding in dangerous parts of the country – saving taxpayer dollars and avoiding the inconvenience of preemptive blackouts like we've seen recently in California.

Associate Professor of Economics, Worcester Polytechnic Institute

Disclosure statement

Alexander Smith does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond their academic appointment.

http://bit.ly/343a2Wx

Science and engineering organisations under fire for arms and fossil fuel industry ties

Professional engineering and science organisations in the UK have been accused of inappropriate financial ties to the fossil fuel and arms industries.

By Anthony King

This charge was made in a report by Scientists for Global Responsibility (SGR).

The report details how some of the most influential organisations prominently, and at times preferentially, promoted the fossil fuel and arms sector. Some of these science and engineering organisations also promoted these industries to school children and other audiences, but didn't discuss any ethical issues with them.

Those receiving most financial support from these industries were the Royal Academy of Engineering, EngineeringUK and the Energy Institute. Nine organisations published teaching resources or ran school education activities that were sponsored by or otherwise directly involved fossil fuel or arms companies.

Over 70% of external funding received by the Royal Academy of Engineering for its school education programmes flowed from the

fossil fuel industry. Almost all its downloadable teaching resources involved arms corporations, mainly BAE Systems. And the sole lead sponsor of EngineeringUK's Big Bang science fair has been BAE for many years.

Opaque funding

The report charges that most of the details of these relationships are not transparent. 'The links with the school education programmes were particularly disturbing,' says Stuart Parkinson, report author at SGR, an organisation that advocates ethical and accountable practices in science and technology. 'Removing all such branding from school material would be a very straightforward thing to do.'

Four organisations had 'very high' levels of investments in the fossil fuel industry – the Energy Institute, EngineeringUK, the Institute of Physics (IoP) and the Royal Statistical Society. The report's authors had difficulty deducing investment in the arms industry by these four organisations. 'Data was either lacking completely or wasn't collected to a high degree of detail,' says Parkinson.

'Professional institutions claim an ethical leadership role, yet on issues such as tackling climate change or the arms industry, they weren't playing a leading role, but supporting the status quo,' Parkinson says.

The two organisations with the largest funds disclosed very little about where their money was invested – the Royal Society, which holds £200 million, and the Institution of Engineering and Technology with £110 million. Only the Geological Society identified where at least 50% of its fund was invested.

A spokesperson for the Royal Society said it 'does not invest in organisations which conflict with the charity's purpose', noting that it has no tobacco industry links. 'The Royal Society has long worked with industry, including energy companies, because of their commitment to research and development in the UK,' the spokesperson explained.

The study looked at 20 UK-based professional organisations, including bodies in engineering and technology, natural sciences, social sciences and maths. No professional chemistry bodies were examined by the SGR. Professional organisations now face the same dilemma that medical research organisations faced in previous decades when the tobacco industry offered them lucrative funding, the report notes.

Making changes

The report makes a number of recommendations for these professional bodies including being much more transparent about financial links to 'controversial sectors', especially in relation to school education programmes, investments and prestige event sponsorship. Educational material for school-age children should also discuss the ethical issues related to fossil fuels and use of military technologies, and financial links to these industry sectors could be curtailed based on ethical criteria. Parkinson says a partial divestment could start by avoiding companies engaged with coal, tar sands or shale sands, or those involved in cluster bombs, landmines or armed drones.

'This report does a good job of trying to uncover "sponsorship bias" in the programmes of these [professional engineering and scientific societies]. This is an increasingly important concern,' comments Jeffrey Kovac, chemist and philosophy of science scholar at the University of Tennessee, Knoxville. 'If the societies become dependent on funding from industries, which would be adversely affected by the results of objective research, there is the possibility that the research will be suppressed or the conclusions altered to soften the blow.'

He cites the influence of tobacco companies on research on smoking and health as a canonical case. Kovac notes that the

Quaker Peace and Social Justice programme helped fund the report, which is written from a pacifist perspective. 'I find this a comfortable position, but many people do not,' he adds.

Asked to comment on the report, the Royal Academy of Engineering said it works with organisations and companies to advance engineering excellence and provide leadership for the profession. 'While funding from corporate partners is only a small proportion of our total income, it provides us with the flexibility to independently design and deliver activities that meet our strategic priorities and deliver benefit to our stakeholders.'

In a statement, the Energy Institute said it exists to meet the needs of the whole world's energy workforce, and is funded by individual and company members for that purpose. 'This includes oil and gas, wind power, battery storage, energy efficiency and other technologies that have a growing role in keeping the lights on and emissions down.'

An EngineeringUK spokesperson said that the majority of its funding 'comes from the registration fees of a quarter of a million individual engineers'. 'We are currently reviewing the findings and recommendations of the SGR report,' the spokesperson said.

The IoP was also asked for comment but had not responded at the time of publication.

http://bit.ly/2pcS19v

Simple test predicts dangerous pregnancy disorder

Researchers have developed a simple, low-cost way to predict preeclampsia, a potentially deadly condition that kills 76,000 mothers and 500,000 babies every year.

Australian researchers have developed a way to predict the onset of a deadly pregnancy condition that kills 76,000 women and half a million babies each year, mostly in developing countries.

Researchers from Edith Cowan University in Perth Western Australia have developed a simple, low-cost way to predict preeclampsia, one of the leading causes of maternal-foetal mortality worldwide. Preeclampsia can cause devastating complications for women and babies, including brain and liver injury in mothers and premature birth.

Survey gives early warning

ECU researchers assessed the health status of 593 pregnant Ghanaian women using the Suboptimal Health Questionnaire.

The Suboptimal Health Questionnaire was developed in 2009 by Professor Wei Wang from ECU's School of Health and Medical Sciences. Combining scores for fatigue, heart health, digestion, immunity and mental health, the questionnaire provides an overall 'suboptimal health score' that can help predict chronic diseases.

Professor Wang's PhD candidate Enoch Anto found that 61 per cent of women who scored high on the questionnaire went on to develop preeclampsia, compared with just 17 per cent of women who scored low. When these results were combined with blood tests that measured women's calcium and magnesium levels, the researchers were able to accurately predict the development of preeclampsia in almost 80 per cent of cases.

Mr Anto said preeclampsia was very treatable once identified, so providing an early warning could save thousands of lives.

"In developing nations, preeclampsia is a leading cause of death for both mothers and babies. In Ghana, it's responsible for 18 per cent of maternal deaths," Mr Anto said. "But it can be treated using medication that lowers blood pressure once diagnosed.

"Both blood tests for magnesium and calcium and the Suboptimal Health Questionnaire are inexpensive, making this ideally suited to the developing world where preeclampsia causes the most suffering."

'Integration of suboptimal health status evaluation as a criterion for prediction of preeclampsia is strongly recommended for healthcare management in pregnancy: a prospective cohort study in a Ghanaian population' was recently published in the *EPMA Journal*.

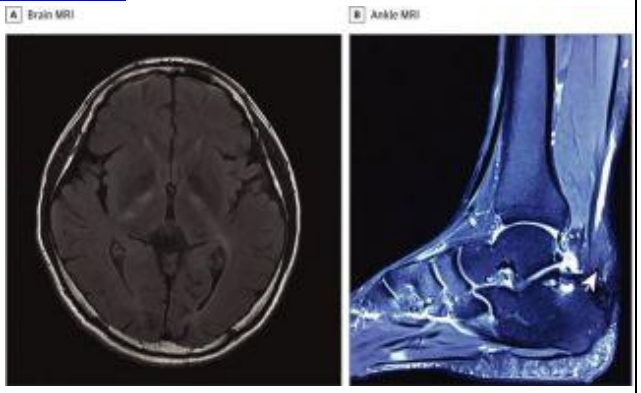
http://bit.ly/2Jml3ua

How Lumps on a Man's Heels Signaled a Rare Disease in His Brain

The man developed lumps on his Achilles tendon a decade before he was hospitalized for neurological problems.

By Rachael Rettner - Senior Writer

Problems with the Achilles tendon, the thick band of tissue that connects the calf muscles to the heel bone, typically don't signal a brain condition. But for one man in China, lumps on the Achilles tendon were an early sign of a serious metabolic disease that affected his brain.



***Lumps on a man's Achilles tendon were an early sign of a serious metabolic disease, called cerebrotendinous xanthomatosis, that also affects the brain. Above, MRIs of the patient's brain (A) and ankle (B). The arrowhead in image B points to an enlargement on the patient's Achilles tendon that tapers at the end. (Image: © Reproduced with permission from JAMA Neurology. 2019. doi:10.1001/jamaneurol.2019.3551.* Copyright©(2019) American Medical Association. All rights reserved.)**

The 27-year-old man was hospitalized after he developed neurological symptoms, including a change in his personality, according to a report of the case, published yesterday (Oct. 21) in the journal JAMA Neurology. He became irritable and hyperactive and had problems with his memory, according to the authors, from The First Affiliated Hospital of Chongqing Medical University in Chongqing, China.

Two years before his hospitalization, the man developed glassy eyes and lethargy, and about a decade ago, he developed painless masses on both his Achilles tendons that were 2 inches (5 centimeters) in diameter, the report said.

At his hospitalization, doctors at Chongqing Medical University noticed that the man still had painless lumps on both his Achilles tendons, but the lumps were now larger, about 3 inches (8 cm) in diameter. He also had trouble maintaining balance while walking in a straight line. Lab tests additionally revealed that the levels of fat in his blood, called triglycerides, were unusually high — more than double the normal level.

An MRI of his ankles showed enlargement of his Achilles tendons, and an MRI of his brain also showed abnormalities, the report said.

A genetic test finally led to the man's diagnosis: He had cerebrotendinous xanthomatosis, a rare genetic condition in which a person's body cannot effectively break down fats such as cholesterol, according to the National Institutes of Health (NIH)'s Genetic and Rare Diseases Information Center (GARD). This leads to the development of fatty growths, called xanthomas, in the body, especially in the brain and tendons.

The condition often causes progressive neurological problems, including dementia and difficulty with movement, as well as behavioral changes, including agitation, aggression and depression. It can also cause cataracts and mental impairment, GARD says.

The disorder is caused by mutations in a gene called CYP27A1, which produces an enzyme involved in breaking down cholesterol, according to the NIH. This condition is estimated to affect about 1 in a million people worldwide, the NIH says.

Some symptoms can appear as early as infancy or childhood, but the signs are often missed or patients are given the wrong diagnosis; as a result, the true diagnosis can be delayed up to 25 years, the report said. The condition is often treated with a medication called chenodeoxycholic acid (CDCA), which can reduce cholesterol levels. However, even with treatment, patients'

neurological symptoms often worsen over time, the authors of the case report said.

In the current case, the man experienced some improvement in his glassy eyes after 18 months of treatment and the size of his brain lesions also decreased slightly, the report said. But his symptoms of agitation and hyperactivity remained the same, and he is now bedridden and unable to care for himself, the report's authors said.

They concluded that "early diagnosis and intervention are key factors" in the outlook for patients with cerebrotendinous xanthomatosis.

http://bit.ly/32ME8NR

New organelle discovered inside cells found to prevent cancer

Scientists at the University of Virginia School of Medicine have discovered a strange new organelle inside our cells that helps to prevent cancer by ensuring that genetic material is sorted correctly as cells divide.

by Josh Barney, University of Virginia

The researchers have connected problems with the organelle (a subcellular structure) to a subset of breast cancer tumors that make lots of mistakes when segregating chromosomes. Excitingly, they found their analysis offered a new way for doctors to sort patient tumors as they choose therapies. They hope these insights will allow doctors to better personalize treatments to best benefit patients—sparing up to 40% of breast cancer patients, for example, a taxing treatment that won't be effective.

"Some percentage of women get chemotherapy drugs for breast cancer that are not very effective. They are poisoned, in pain and their hair falls out, so if it isn't curing their disease, then that's tragic," said researcher P. Todd Stukenberg of UVA's Department of Biochemistry and Molecular Genetics and the UVA Cancer Center. "One of our goals is to develop new tests to determine whether a patient will respond to a chemotherapeutic treatment, so they can find an effective treatment right away."

The Disappearing Organelle

The organelle Stukenberg and his team have discovered is essential, but ephemeral. It forms only when needed to ensure chromosomes are sorted correctly and disappears when its work is done. That's one reason scientists haven't discovered it before now.

Another reason is its mind-bending nature: Stukenberg likens it to a droplet of liquid that condenses within other liquid. "That was the big 'wow' moment, when I saw that on the microscope," he said.

These droplets act as mixing bowls, concentrating certain cellular ingredients to allow biochemical reactions to occur in a specific location. "What's exciting is that cells have this new organelle and certain things will be recruited into it and other things will be excluded," Stukenberg said. "The cells enrich things inside the droplet and, all of a sudden, new biochemical reactions appear only in that location. It's amazing."

It's tempting to think of the droplet like oil in water, but it's really the opposite of that. Oil is hydrophobic—it repels water. This new organelle, however, is more sophisticated.

"It's more of a gel, where cellular components can still go in and out, but it contains binding sites that concentrate a small set of the cell's contents," Stukenberg explained. "Our data suggests this concentration of proteins is really important. I can get complex biochemical reactions to occur inside a droplet that I've been failing to reconstitute in a test tube for years. This is the secret sauce I've been missing."

While it's been known for about eight years that cells make such droplets for other processes, it was unknown that they make them on chromosomes during cell division. Stukenberg believes these droplets are very common and more important than previously realized.

"I think this is a general paradigm," he said. "Cells are using these non-membranous organelles to regulate much of their work."

Better Cancer Treatments

In addition to helping us understand mitosis—how cells divide—Stukenberg's new discovery also sheds light on cancer and how it occurs. The organelle's main function is to fix mistakes in tiny "microtubules" that pull apart chromosomes when cells are dividing. That ensures each cell winds up with the correct genetic material. In cancer, though, this repair process is defective, which can drive cancer cells to become more aggressive.

Stukenberg has also developed tests to measure the amount of chromosome mis-segregation in tumors, and he hopes that this might allow doctors to pick the proper treatment to give cancer patients. "We have a way to identify the tumors where the cells are mis-segregating chromosomes at a higher rate," he said. "My hope is to identify the patients where treatments such as [chemotherapy medication] paclitaxel are going to be the most effective."

Having looked at breast cancer already, he next plans to examine the strange organelle's role in colorectal cancer.

Stukenberg and his colleagues described their latest findings in the scientific journal *Nature Cell Biology*.

Prasad Trivedi et al. The inner centromere is a biomolecular condensate scaffolded by the chromosomal passenger complex, Nature Cell Biology (2019). DOI: 10.1038/s41556-019-0376-4

Journal information: Nature Cell Biology

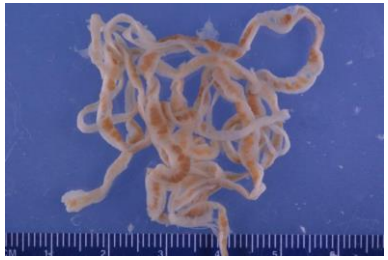
http://bit.ly/31L2jek

Scientists discovered mechanisms that protect tapeworms from being digested by their host

Previously unknown tapeworm proteins suppress the activity of trypsin and efficiently protect the parasites from being digested inside a host's intestinal tract

A team of scientists from Tyumen together with colleagues found and described previously unknown tapeworm proteins that suppress the activity of trypsin and efficiently protect the parasites from being digested inside a host's intestinal tract.

The analogs of these proteins are found in many other living organisms and were described in some other parasite worms. The results of the study were published in the Molecular & Biochemical Parasitology journal.



This is an image of a tapeworm from open sources. **FWC Fish and Wildlife Research Institute**

Tapeworms or cestodes are a class of flat parasite worms that usually have several hosts during their life cycle. The adults live in the intestinal tracts of the vertebrates and may pose a considerable threat to human and animal health.

Due to their parasitic mode of life these worms completely lost their digestive apparatus but have a well-developed reproductive system and special organs that help them attach to the host's tissues. They also needed a mechanism to protect themselves from intestinal substances, specifically from digestive enzymes. One of such enzymes called trypsin breaks down proteins.

"There are lots of studies describing the inhibitors (proteins that block the activity of digestive ferments) of nematode worms and covering numerous species of these parasites, including the well-known ascarides. However, few works address the biochemistry of cestodes, and their molecular diversity is only superficially studied. The researchers of tapeworms traditionally paid attention mainly to tenias and echinococci, as they are the most dangerous for humans and animals.

Other species remained understudied, and neither their inhibitors nor the mechanisms of their work have been known until recently",

said Eugene Rogozhin, PhD (Bioorganic Chemistry), and a senior researcher at Tyumen State University.

The team studied the *Triaenophorus nodulosus* worms. These parasites are the cause of triaenophorosis -- a dangerous disease leading to mass extinction of young fish in certain freshwater species.

The worms were produced from the intestines of a common pike caught in the Rybinsk Reservoir. The proteins obtained from the homogenate of the cestodes were divided into fractions using the liquid chromatography methods. After that the fractions that were the most effective in inhibiting digestive enzymes were selected.

The molecular mass of the inhibitors was determined using polyacrylamide gel electrophoresis (a method based on the differences in the mobility of molecules with different sizes in a gel under the influence of an electric field).

The scientists managed to identify two previously unknown polypeptides (around 14.4 kDa in mass) with different N-terminal amino-acid residues.

After searching for homologous sequences the team concluded that the peptides belonged to their own type of trypsin inhibitors similar to Kunitz-type proteins that are found both in in- and vertebrates.

Besides their inhibition activity, these ferments also play a role in blood clotting and inflammation processes.

Proteins of the same type had been previously obtained from other tapeworm species, in which they also weakened the host's immune resistance.

The members of the team also represented Papanin Institute for the Biology of Inland Waters of the Russian Academy of Sciences, Institute of Bioorganic Chemistry of the Russian Academy of Science, Gause Institute of New Antibiotics, Institute of Systematics and Ecology of Animals of the Siberian Brunch of the Russian Academy of Sciences, and Tomsk State University.

http://bit.ly/2MPqV18

The earliest well-preserved tetrapod may never have left the water

New and surprising light cast on one of the earliest tetrapods

Superbly preserved fossils from Russia, excavated by an international team and reported in the journal *Nature*, casts new and surprising light on one of the earliest tetrapods—the group of animals that made the evolutionary transition from water to land, and ultimately became the ancestors of amphibians, reptiles, birds and mammals.

The first tetrapods evolved from fishes during the Devonian period, which ended about 360 million years ago. For many decades, our idea of what Devonian tetrapods were like has been based on just a few genera, chiefly Ichthyostega and Acanthostega, which are known from near-complete skeletons. Most other Devonian tetrapods are known only from a few scraps of jaws or limb bones—enough to show that they existed, but not really enough to tell researchers anything useful.

The Sosnogorsk lagoon just before a deadly storm. **Credit: Mikhail Shekhanov for the Ukhta Local Museum**

Furthermore, Ichthyostega and Acanthostega lived at the very end of the Devonian. Some of the fragmentary tetrapods are a lot older, up to 373 million years old, and the oldest fossil tetrapod footprints date back a whopping 390 million years. So Devonian tetrapods have a long early history about which researchers have known very little until now. This is a frustrating picture for paleontologists,

considering that this represents one of the most important events in the history of the backboned animals.

The new Russian tetrapod, *Parmastega aelidae*, changes all this. At 372 million years old, its fossils are only marginally younger than the oldest fragmentary tetrapod bones. They come from the Sosnogorsk Formation, a limestone formed in a tropical coastal lagoon, which is now exposed on the banks of the Izhma River near the city of Ukhta in the Komi Republic of European Russia.

When the limestone is dissolved with acetic acid, perfectly preserved bones emerge from the head and shoulder girdle—more than 100 specimens, so far—which can be pieced together into a three-dimensional reconstruction of the animal, by far the earliest for any tetrapod. Large and small individuals are found, the biggest with a head length of about 27 cm. Fish-like characteristics in some bones indicate that this is not only the earliest but also the most primitive of the well-preserved Devonian tetrapods.

The researchers consider the animal to be unusual. Like other Devonian tetrapods, Parmastega is vaguely crocodile-like in shape, but its eyes are raised above the top of the head, and the curve of its snout and lower jaw create a disconcerting "grin" that reveals its formidable teeth. A clue to its lifestyle is provided by the lateral line canals, sensory organs for detecting vibrations in the water, which Parmastega inherited from its fish ancestors. These canals are well-developed on the lower jaw, the snout and the sides of the face, but not on top of the head behind the eyes.

This probably means that it spent a lot of time hanging around at the surface of the water, with the top of the head just awash and the eyes protruding from the water surface. But why? Crocodiles do this today as they watch for land animals to hunt. Researchers don't know very much about the land that surrounded Parmastega's lagoon, but there may have been large arthropods such as millipedes or "sea scorpions" to catch at the water's edge. The slender, elastic lower jaw looks well-suited to scooping prey off the ground, its needle-like teeth contrasting with the robust fangs of the upper jaw that would have been driven into the prey by the body weight of *Parmastega*.

However, the fossil material springs one final surprise: The shoulder girdle was made partly from cartilage, which is softer than bone, and the vertebral column and limbs may have been entirely cartilaginous as they are not preserved. This strongly suggests that *Parmastega*, with its crocodile-like head and protruding eyes, never really left the water. Did it creep up on prey at the water's edge and surge onto the shore to seize it in its jaws, only to then slide back into the supporting mass of the water? We don't know. Far from presenting a natural progression of ever more land-adapted animals, the origin of tetrapods is looking more like a tangle of ecological experimentation.

More information: *Morphology of the earliest reconstructable tetrapod Parmastega aelidae, Nature (2019). DOI: 10.1038/s41586-019-1636-y , https://nature.com/articles/s41586-019-1636-y*

https://bbc.in/2PnYqC2

Blood pressure pills 'work better at bedtime'

To get the best out of your daily blood pressure medication, take it just before you go to bed, say researchers.

By Michelle Roberts Health editor, BBC News online

It's a simple tip that could save lives, they say in the European Heart Journal. The pills offer more protection against heart attacks and strokes when taken at bedtime rather than in the morning, a large new study suggests. Experts believe our body's biological 'clock' or natural 24-hour rhythm alters our response to the medication.

Synchronise pills to your body clock

There is mounting evidence that many different drugs, including heart pills, might work better when taken at specific times of the day. This latest trial is the largest so far to look at the phenomenon

with high blood pressure pills, and included more than 19,000 people on these medications. In the Spanish study:

- ***The patients were put into two groups at random - one group took the pills in the morning and the other group took them at bedtime***
- ***Researchers monitored what happened to the patients over the next five or more years***
- ***Patients who took their medication in the evening had nearly half the risk of dying from - or having - a heart attack, stroke or heart failure***

Blood pressure should naturally dip at night, as we rest and sleep.

If it doesn't, and remains consistently high, that puts you at increased risk of heart attacks and strokes, experts say.

The research suggests taking medication in the evening helps keep night-time blood pressure in check, in patients diagnosed with high blood pressure (which doctors call hypertension).

Patients in the study who took their medication at bedtime had significantly lower average blood pressure both at night and during the day, and their blood pressure dipped more at night, when compared with patients taking their medication each morning.

Lead researcher Prof Ramon Hermida, from the University of Vigo, said doctors might want to consider recommending it to patients: "It's totally cost-free. It might save a lot of lives.

"Current guidelines on the treatment of hypertension do not recommend any preferred treatment time. Morning ingestion has been the most common recommendation by physicians based on the misleading goal of reducing morning blood pressure levels.

"The results of this study show that patients who routinely take their anti-hypertensive medication at bedtime, as opposed to when they wake up, have better-controlled blood pressure and, most importantly, a significantly decreased risk of death or illness from heart and blood vessel problems."

He said more studies in different populations were needed to check that the findings will apply to all patients on different brands of blood pressure tablets.

Vanessa Smith, from the British Heart Foundation, said: "Although this study supports previous findings in this area, further research amongst other ethnic groups and people who work shift patterns would be needed, to truly prove if taking blood pressure medication at night is more beneficial for cardiovascular health.

"If you're currently taking blood pressure medication, it's important to check with your GP or pharmacist before changing the time you take it. There may be specific reasons why your doctor has prescribed medication in the morning or night."

Lifestyle factors also make a difference to blood pressure, so avoid:

- ***Drinking too much alcohol***
- ***Smoking***
- ***Being overweight***
- ***Not doing enough exercise***
- ***Eating too much salt***

http://bit.ly/32PdEeF

Health in old age is a lifelong affair

Reduced food intake in old mice can no longer improve health

Reduced food intake helps both animals and humans to improve health in old age and can prolong life. But when do you have to change your diet to achieve this benefit in old age? Scientists from the Max Planck Institute for Biology of Ageing, the Excellence Cluster for Ageing Research at the University of Cologne, the Babraham Institute in Cambridge and UCL have now shown that mice only become healthier if they start food reduction early and eat less before entering old age. The scientists conclude that healthy behaviour must be established earlier in life in order to improve health in old age and extend lifespan.

How can we stay fit and healthy in old age for as long as possible? Researchers into ageing have a simple answer: eat less and healthily. But when do you have to start and is it enough if you only manage to do this for a short time? To investigate this, researchers led by Linda Partridge, Director at the Max Planck Institute for Biology of Ageing, in an animal study have put young and old mice on a diet - with varying degrees of success.

Reduced food intake in old age has no beneficial effect

Mice live longer and are healthier in old age if they are given 40 percent less to eat after reaching adulthood than animals who are allowed to eat as much as they want. The dieting mice are fed with food enriched with vitamins and minerals to prevent malnutrition. But if food intake is first reduced in mice first start eating less food when they are already seniors, the researchers observe little or no effect on the life expectancy of the mice. On the other hand, when mice are allowed to eat as much as they like after a period of reduced food intake, they have no long-term protection, so reduced food intake has to be sustained for mice to reap the benefits. Reduced food intake must therefore be implemented early and be sustained until the end of their lives to have positive effects on health in old age.

"One should establish healthy behaviors early in life. It may not be as good for your health to change your diet later in life. Health in old age is a lifelong affair", explains Linda Partridge from the Max Planck Institute for the Biology of Ageing and UCL.

Memory effect in fat tissue

But why do older mice no longer react to the change in diet? Oliver Hahn, first author of the study and doctoral student in the Partridge department, investigated gene activity in different organs. While the gene activity in the liver quickly adapted when mice are transferred to a restricted diet, the scientists observed a 'memory effect' in the fat tissue of older animals. Although the mice lose weight, the activity of the genes in the fat tissue is similar to that of the mice that continue to eat as much as they want. In addition, the fat composition in old mice does not change as much as in young mice. This memory effect mainly affect mitochondria, the cells' power houses, which play an important role in the ageing process. Usually, reduced food intake leads to increased formation of mitochondria in fatty tissue. But the study showed that this is no longer the case when older mice are switched to a lower calorie diet. This inability to change at the genetic and metabolic levels may contribute to the shortened lifespan of these animals.

Michael Wakelam, co-corresponding author and Director of the Babraham Institute commented, "The experimental power of integrating data about lipid metabolism and metabolic pathways with tissue-specific understanding of gene expression in mice of different ages and diets has allowed us to demonstrate clearly the importance of a nutritional memory in contributing to healthy ageing."

Original publication

Oliver Hahn, Lisa F. Drews, An Nguyen, Takashi Tatsuta, Lisonia Gkioni, Oliver Hendrich, Qifeng Zhang, Thomas Langer, Scott Pletcher, Michael J. O. Wakelam, Andreas Beyer, Sebastian Grönke, Linda Partridge: A nutritional memory effect counteracts benefits of dietary restriction in old mice Nature Metabolism, October 21st 2019

http://bit.ly/31KLcJr

Stressing cancer with spice

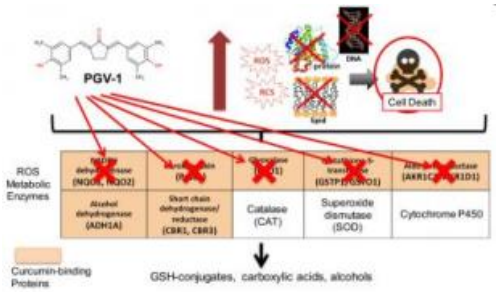
A new study by scientists in Japan and Indonesia reports how an experimental drug agent stops cancer cells from growing.

日本のニュース

A little over a decade ago, Indonesian scientists first reported pentagamavumon-1 (PGV-1), an analogue of a molecule found in turmeric and that has been since discovered to have anti-cancer effects. In the new study, tests on cancer cells and animals reveal that these anti-cancer effects come from PGV-1 inhibiting a series

of enzymes responsible for the metabolism of reactive oxygen species. This finding is expected to clarify how modifications to PGV-1 will lead to its use for cancer treatment.

The popular spice turmeric has for centuries been used not just as a flavoring, but also as medicine, with history having shown it to have a number of anti-inflammatory and even anti-cancer benefits. These medicinal benefits come from the compound curcumin, which is commonly sold as an herbal supplement. Several studies have examined curcumin's anti-cancer properties, but the high doses required and poor understanding of the chemical process through which curcumin acts have limited these efforts.



PGV-1 inhibits metabolic enzymes to increase ROS and kill cancer cells.

Jun-ya Kato

The team of Professor Jun-ya Kato, at Nara Institute of Science and Technology (NAIST), had previously identified that curcumin acts on the same reactive oxygen species enzymes as its analogue, PGV-1. By suppressing the enzyme activity, reactive oxygen species are allowed to cause stress on cells, ultimately leading to cell death. Indeed, many anti-cancer drugs operate similarly, but sometimes with severe side-effects due to stress on healthy cells.

In the new study, Kato's team compared the effects of curcumin and PGV-1 on cancer, finding that they shared many of the same properties, but that PGV-1 did so at higher efficiency and lower dose.

"We found that PGV-1 arrests cells in the cell cycle at M phase" and that "it inhibits many ROS-metabolic enzymes," says Kato. This arrest prevents the cancer cells from dividing, and the enzyme inhibition causes the cancer cells to die.

Intriguingly, PGV-1 was effective on numerous types of cancers. Moreover, when administered to mice injected with human cancer cells, the mice showed no evidence of the cancer and no side-effects. Furthermore, unlike some other anti-cancer drugs, the anti-cancer effects persisted even after the cessation of PGV-1 administration.

"Our results suggest that PGV-1 inhibits the enzyme activity more effectively in cancer cells than in normal cells. This may be the reason why PGV-1 selectively suppresses tumor cell proliferation with few effects on normal cells," notes Kato.

Scientists have long looked at the potential of curcumin to treat cancer. Kato believes PGV-1 could provide a breakthrough.

"Considering the high drug efficacy and low amount of side effects in animals, we propose that PGV-1 should be pharmaceutically developed as an orally administered drug for cancer," he says.

Resource

Title: Pentagamavunon-1 (PGV-1) inhibits ROS metabolic enzymes and suppresses tumor cell growth by inducing M phase (prometaphase) arrest and cell senescence

Authors: Beni Lestari, Ikuko Nakamae, Noriko Yoneda-Kato, Tsumoru Morimoto, Shigehiko Kanaya, Takashi Yokoyama, Masafumi Shionyu, Tsuyoshi Shirai, Edy Meiyanto & Jun-ya Kato Journal: Scientific Reports DOI: 10.1038/s41598-019-51244-3

http://bit.ly/32PVERp

New drug forces flu virus into 'error catastrophe,' overwhelming it with mutations

The flu virus (above) has frustrated scientists with its constant shapeshifting, eluding many vaccines and drugs.

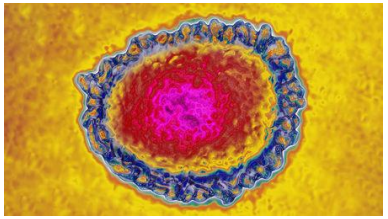
By Kai Kupferschmidt

Scientists often warn about the dangers of pandemic pathogens spreading quickly around the globe. But one virus already sweeps across the world every year, causing tens of millions of infections and hundreds of thousands of deaths: influenza.

Now, a new drug that has shown promise in ferrets may help drive down that toll, researchers report today. The drug appears to be

more effective than the most commonly used treatment, oseltamivir, and there are hints that it won't prompt easy resistance in the virus.

Scientists have long been frustrated by the constant shapeshifting of the flu virus, which necessitates an annual reformulation of flu vaccines to reflect commonly circulating strains. When that match is bad, vaccine protection can be low, especially for elderly people who are most at risk.



The flu virus (above) has frustrated scientists with its constant shapeshifting, eluding many vaccines and drugs. **James Cavallini/Science Source**

Meanwhile, new influenza drugs have been slow to develop, and those that exist are often inadequate. Oseltamivir, for instance, provides a moderate benefit at best, and only when given early in the infection; whether it prevents hospitalizations and deaths is controversial.

What's more, the flu virus has developed resistance to oseltamivir and to an older drug, amantadine. And there are already reports of flu strains resistant to baloxavir, a drug approved by the U.S. Food and Drug Administration just last year.

To come up with an alternative, scientists at Georgia State University and Emory University, both in Atlanta, investigated a compound named N-hydroxycytidine (NHC), which has been known for years to inhibit a broad range of RNA viruses like the flu. Previously, the researchers had shown that NHC is active against influenza; but in tests on macaques, they found the drug is not taken up well by the body, "a potential deal breaker" for human use, says Georgia State molecular virologist Richard Plemper, one of the researchers leading the new work.

The researchers tweaked NHC's structure to create a new compound named EIDD-2801, which converts back into NHC inside the body. They then tested it in ferrets, the most widely used animal model for influenza. If the ferrets received the compound 12 hours after infection, they did not develop disease at all. Those that received it after 24 hours, when fever had started, produced less virus than control animals that received oseltamivir or no treatment at all. The fever also ended faster in treated animals, the researchers write in *Science Translational Medicine*.

"It's important that they showed a reduction in symptoms in ferrets, because it gets much closer to predicting what happens in people," says Andrew Pavia, an infectious disease expert at the University of Utah in Salt Lake City. "It's a major step towards developing a drug for humans."

The scientists also investigated how NHC blocks influenza by sequencing the genomes of flu viruses exposed to the compound. They found that the virus incorporates the drug into its RNA when it replicates, instead of a molecule named cytosine, leading to a cascade of mistakes that virologists call "error catastrophe"—essentially overwhelming the virus with mutations.

To test how easily flu becomes resistant to EIDD-2801, the researchers also grew the virus while keeping it exposed to sublethal doses of NHC or slowly increasing the concentration of NHC—methods that typically don't kill the virus, but give it a chance to evolve resistance. Even though sequencing clearly shows the virus trying to resist the drug, no resistant strains developed. That bodes well, Pavia says, because oseltamivir and other older drugs all eventually fail the test.

Still, it doesn't mean resistance cannot develop, says Albert Osterhaus, a virologist at the University of Veterinary Medicine in Hanover, Germany. Favipiravir, a drug approved in 2014 in Japan for pandemic flu viruses resistant to all other drugs, was thought to have a similarly high barrier to resistance before resistant strains developed.

Plemper says additional toxicity tests in animals have not thrown up any red flags, and the first trials of EIDD-2801 in humans are likely to start next spring. Pavia says the new drug could eventually be used in combination with other drugs to stave off resistance, a strategy already in use for HIV and hepatitis B treatments.

http://bit.ly/2BNFZGk

The World's Oldest Pearl Was Just Discovered on an Island in the Persian Gulf

The pearl dates back 8,000 years to the Neolithic period.

By Yasemin Saplakoglu - Staff Writer

Archeologists have discovered what they claim is the world's oldest natural pearl on Marawah Island, off the coast of Abu Dhabi. The pearl dates back 8,000 years to the Neolithic period — the last stage of the Stone Age.

An 8,000-year-old pearl was discovered on Marawah Island off the coast of Abu Dhabi. **:© Abu Dhabi Department Of Culture And Tourism/EPA-EFE/Shutterstock**

Dubbed the "Abu Dhabi Pearl," this ancient gem is faint pink in color and about 0.3 centimeters (0.13 inches) long. It was found in a layer at a Neolithic site that dates to between 5800 B.C. and 5600 B.C., making it the oldest in the world, according to a statement from Abu Dhabi's Department of Culture and Tourism.

"The presence of pearls at archeological sites is evidence that the pearl trade existed from at least as far back as the Neolithic period," said Abdulla Khalfan Al-Kaabi, the director of the archeological survey unit at Abu Dhabi's Department of Culture and Tourism, in a video posted on the department's official Twitter account.

Indeed, "if we look at historical sources, we find more than one indication that Abu Dhabi was considered one of the major pearl centers," he said. Pearls could have been worn as jewelry or traded for goods from other civilizations, such as ceramics from Mesopotamia, according to the statement.

This Neolithic site, composed of collapsed stone structures, was first discovered in 1992 and many artifacts have been found there, including flint arrowheads, beads and ceramics. What's more, because this site sits on an island, many of the artifacts found, such as the bones of fish, turtles, dolphins, dugongs and oysters, relate to the sea. "People in this period were very familiar with the sea and considered it a major part of daily life," Al-Kaabi said. Even centuries later, diving for pearls remained prominent in the area and was an important driver of the United Arab Emirates economy until the 1930s, according to the statement.

The Abu Dhabi Pearl is faint pink in color and about 0.3 centimeters (0.13 inches) long. **: Abu Dhabi Department Of Culture And Tourism/EPA-EFE/Shutterstock**

The Abu Dhabi Pearl will be displayed for the first time in an upcoming exhibition called "10,000 Years of Luxury" at the Louvre Abu Dhabi.

https://nyti.ms/3475Wqg

Two Strains of Polio Are Gone, but the End of the Disease Is Still Far Off

Only polio virus Type 1 persists, and only in Pakistan and Afghanistan. But now mutant vaccine viruses are paralyzing some unvaccinated children.

By Donald G. McNeil Jr.

In another milestone on the long, expensive and sometimes discouraging road to wiping out polio, global health officials announced Wednesday that two of the three strains of wild polio virus have officially been eliminated.

Although that brings the world another step closer to eradication, the effort has taken far longer than was ever anticipated. When the

campaign began in 1988, most public health officials and donors expected the battle to be over by 2000.

But two major obstacles emerged.

First, millions of families around the world have not let their children have the drops because of persistent false rumors that the vaccine is a Western plot to sterilize Muslim girls or do other harm.

Second, in some countries viruses used in the oral vaccine itself have mutated into a form that can be passed on in diapers and sewage, and can paralyze unvaccinated children. That has contributed to fear of the oral vaccine, even though full vaccination is the only protection against such mutant viruses.

Just in the last two months, cases of paralysis caused by mutant vaccine viruses have been reported in the Philippines, Zambia, Togo and Chad. Because paralysis occurs in only about one in every 200 cases of polio, experts assume many more children have been infected.

Stopping such outbreaks typically requires vaccinating hundreds of thousands of children with both the injectable vaccine, which contains killed virus that cannot mutate, and the oral vaccine. The latter contains weakened viruses that normally cannot cause disease but provide better protection than killed viruses.

The strain that the Global Certification Commission for the Eradication of Poliovirus declared eliminated this week is Type 3 wild polio virus, the last case of which was seen in Nigeria in 2012. Type 2 was declared eliminated in 2015; the last case was detected in India in 1999. Type 1, the only wild strain left, circulates only in Pakistan and Afghanistan.

(In the 1950s, the three strains had more evocative names: Brunhilde, Lansing and Leon. The first was named after a lab chimpanzee, the second after the Michigan city where it was isolated, and the third after a Los Angeles boy who died of it. The nicknames later fell out of favor.)

Enormous, multiyear surveillance efforts are required before a viral strain can be declared extinct. Children can be paralyzed by several other viruses, by bacterial brain infections and by neck and spine injuries.

To ensure that polio was not the cause, stool samples must be taken from more than 100,000 paralyzed children every year. Thousands of sewage and water samples are drawn in 70 countries; the virus can be detected at parts-per-million concentrations.

“The certification commission has been very, very careful,” said Dr. Walter A. Orenstein, a polio expert at Emory Vaccine Center in Atlanta and former immunization director at the Centers for Disease Control and Prevention.

In the last decade, a dangerous new front has opened in the war on polio. In countries where vaccination rates are low, the weakened viruses in the oral vaccine can circulate in wastewater and mutate into what are effectively evil twins of themselves.

By piling up random genetic changes, or by swapping genes with other intestinal viruses like Coxsackie virus, viruses can become virulent again and paralyze children who have never been vaccinated.

In the last two years, outbreaks of cVDPV — which stands for “circulating vaccine-derived polio virus” — have struck nearly 20 countries. Although most of those outbreaks have been small and eventually were contained, more children are now paralyzed by cVDPV each year than by Type 1 in Pakistan and Afghanistan.

For example, thus far this year, 88 Pakistani and Afghani children have been paralyzed by the last wild strain, while 95 children in Africa and Asia have been paralyzed by vaccine-derived viruses.

To prevent that, the eradication campaign is taking several steps.

First, health officials are trying to see that every child in the world gets at least one dose of the injected vaccine. It circulates in the

blood, so a child can still get — and spread — a gut infection but won't be paralyzed by it.

Second, a year after Type 2 polio was eliminated worldwide, the campaign rolled out a new "bivalent" vaccine lacking the Type 2 weakened virus.

But there will be no "monovalent" vaccine with only Type 1 weakened virus, said Michel Zaffran, director of polio eradication at the World Health Organization. "The Type 2 was so powerful that it dominated the old vaccine," he said. "Removing Type 3 will not make the current one more immunogenic."

It was a bureaucratic nightmare, he added, to get every country in the world to import and refrigerate hundreds of millions of new vaccine doses and safely destroy their old ones.

"We don't need to create a new problem," Dr. Zaffran said.

Third, the Bill and Melinda Gates Foundation is supporting the creation of new oral vaccines less able to mutate into dangerous forms.

"Tightening the loose ends" by cutting some nucleotides out of the part of the genome that acts as a gatekeeper leaves it less likely to swap genes with other gut viruses, said Dr. Ananda S. Bandyopadhyay, a polio program officer at the foundation.

In addition, rearranging the genes that create the polymerase, which helps the virus copy itself, means fewer "copying errors" that may be dangerous.

Because most recent outbreaks have been caused by mutant versions of Type 2, the foundation has fast-tracked clinical trials on that strain of the new vaccine, Dr. Bandyopadhyay said.

"If all goes well, it could be ready as early as 2020," he said.

Novel versions of Type 1 and Type 3 vaccines should follow in another couple of years, he said.

The new versions are not intended for routine vaccination, he said, but for an emergency stockpile used to fight outbreaks.

http://bit.ly/31L00I4

How life blossomed after the dinosaurs died

Mammals evolved surprisingly quickly after the end-Cretaceous extinction.

By Elizabeth Pennisi

In 2014, when Ian Miller and Tyler Lyson first visited Corral Bluffs, a fossil site 100 kilometers south of the Denver Museum of Nature & Science where they work, Lyson was not impressed by the few vertebrate fossils he saw. But on a return trip later that year, he split open small boulders called concretions—and found dozens of skulls. Now, he, Miller, and their colleagues have combined the site's trove of plant and animal fossils with a detailed chronology of the rock layers to tell a momentous story: how life recovered from the asteroid impact that killed off the dinosaurs 66 million years ago.

***Raccoon-size* Loxolophus *and other mammals evolved surprisingly quickly after the end-Cretaceous extinction.* HHMI Tangled Bank Studios**

Plants and animals came back much faster than thought, with plants spurring mammals to diversify, the team reports today in *Science*. "They get almost the whole picture, which is quite exciting," says functional anatomist Amy Chew of Brown University. "This high-resolution integrated record really tells us what's going on."

When the asteroid slammed into Earth, it wiped out 75% of living species, including any mammal much larger than a rat. Half the plant species died out. With the great dinosaurs gone, mammals expanded, and the new study traces that process in exquisite detail.

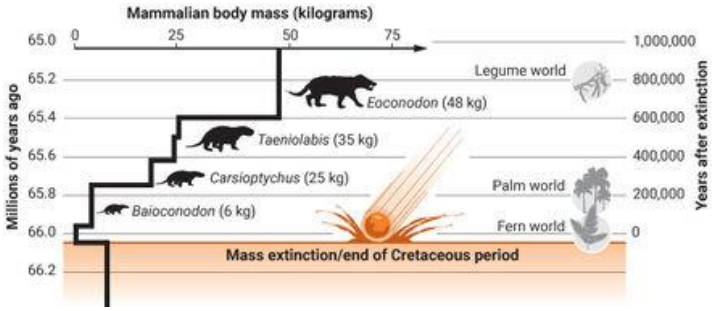
Most fossil sites from after the impact have gaps, but sediment accumulated nearly continuously for 1 million years on the flood plain that is now the Corral Bluffs site. So the site preserves a full record of ancient life and the environment.

Such sites can be hard to date. But Miller, a paleobotanist, and his colleagues collected 37,000 grains of pollen and spores, which revealed a clear marker of the asteroid impact: a surge in the growth of ferns, which thrive in disturbed environments. The site also includes two layers of ash from nearby volcanoes. Volcanic ash includes radioactive minerals whose decay can be used as a precise geochronological clock, providing two time markers. The known flips in Earth's magnetic poles, which some minerals in the layers had recorded, add detail to the chronology. "They have a very strong geochronological framework," says David Fastovsky, a paleontologist at the University of Rhode Island in Kingston.

The record confirms the devastation wrought by the impact. Raccoon-size mammal species had swarmed the site before the catastrophe, but for 1000 years afterward just a few furry creatures no bigger than 600-gram rats roamed a ferny world where flowering plants, with their nutritious seeds and fruits, were scarce.

By 100,000 years later, twice as many mammal species roamed, and they were back to raccoon size. These critters foraged in the palm forests that replaced the ferns. "It's a world that's coming back from complete and utter devastation," Miller says.

Over the next 200,000 years, what he calls the "palm period" gave way to the "pecan pie" period, when walnutlike plants arose. New mammals evolved to take advantage of the nutritious seeds.



Denver Museum Of Nature & Science, Adapted By C. Bickel/*Science*

Mammal diversity increased threefold, and the biggest of the new species reached 25 kilograms—beaver size.

A stepwise recovery

After an asteroid wiped out much of life on Earth, mammals—responding to changes in plants—grew in size and diversity surprisingly quickly.

After about 700,000 years, legumes showed up; their fossil pea pods are North America's oldest discovered to date. Pea and bean species from the "protein bar period" provided protein-rich meals that further boosted mammalian size and diversity, Lyson says. Mammals topped 50 kilograms—a 100-fold increase over those that survived the asteroid. The forests, too, had recovered. "The biggest message is how fast the recovery was … and how closely the vegetation and fauna are tied together," says Vivi Vajda, a paleobiologist at the Swedish Museum of Natural History in Stockholm.

The team also classified 6000 leaves, counting how many species at each time interval had smooth or toothed edges. Smooth-edged species are more common in hot climates. The team concluded that the site underwent three warming periods. They estimate that the first, just after the impact, saw temperatures rise about 5°C, agreeing with earlier work. This period coincides with the massive volcanic eruptions of India's Deccan Traps, which could have warmed Earth by belching carbon dioxide.

"At each warming period you see a change in the plant community and subsequently, changes in the mammals," says Lyson, who thinks temperature drove the stepwise recovery.

Vajda thinks no matter what happened to temperature and plant life, the loss of dinosaurs alone might have opened the door to bigger, more diverse mammals. But Jukka Jernvall, an evolutionary biologist at the University of Helsinki, says the team's analysis of ancient ecosystems shows just how the recovery unfolded. "We are starting to get the time and spatial resolution to reconstruct the

environment and what happened in a way that can be linked to ecological processes."

The record also holds a sobering message about the future, and how quickly ecosystems might recover from ongoing, human-driven extinctions. Even a recovery that geologists call "fast" took hundreds of thousands of years, and the world was never the same. "A very dramatic resetting of the ecosystem could be in our future," Chew says.

http://bit.ly/2NmS2Qq

Heightened risk of adverse financial changes before Alzheimer's diagnosis

A likely consequence of compromised decision making when managing money, in addition to exploitation and fraud by others.

WASHINGTON - Prior to an Alzheimer's diagnosis, a person in the early stages of the disease faces a heightened risk of adverse financial outcomes -- a likely consequence of compromised decision making when managing money, in addition to exploitation and fraud by others. That is the disquieting conclusion of a study published Oct. 25 in the journal *Health Economics*.

Alzheimer's disease isn't usually diagnosed until symptoms are severe, and its progression typically involves a multi-year process of cognitive decline.

"Previous studies show that people in the very early stages of Alzheimer's lose financial capacity; that is, their ability to manage their checkbook, to pay bills on time, to spend in ways that are consistent with the values they had in the past," explains the study's lead author, health economist Carole Roan Gresenz, PhD, interim dean for Georgetown University's School of Nursing & Health Studies.

In the study, Gresenz and her colleagues wanted to know more about that impact. "What happens to financial household outcomes during that period of cognitive decline prior to diagnosis?"

To find the answer, the researchers merged data from two sources: the Health and Retirement Study and Medicare claims.

The Health and Retirement Study is a nationally representative, longitudinal survey of Americans over the age of 50 sponsored by the National Institute on Aging, which includes questions about households' financial assets and liabilities. The Medicare data allow the researchers to identify individuals who have been diagnosed with Alzheimer's disease or related dementia as well as the date of diagnosis.

"These combined data allow us to track backwards from the date of diagnosis to figure out what was happening to households financially prior to diagnosis," Gresenz explains. "What we found was that households in which someone is in the early stage of the disease are vulnerable to large reductions in liquid assets such as savings, money market, and checking accounts," she says.

The team also found evidence that these households are likely to have a reduction in net wealth during that time period.

"The findings are concerning because these adverse financial outcomes are occurring just prior to when substantial resource demands will be placed on these families as they grapple with costs related to caregiving needs," Gresenz says. She says the findings also speak to the potentially important role of financial institutions in reducing the exposure of vulnerable elderly to poor outcomes.

The researchers are now working on matching credit data--which includes more granular financial outcomes measured for more refined time periods--with Medicare data.

"We want to understand more about the specific types of financial decisions and choices that underlie these findings as well as to explore whether financial information offers the potential for early identification of individuals who are in the initial stages of Alzheimer's disease and who should be prioritized for additional clinical screening," she says.

In addition to Gresenz, study authors include Jean M. Mitchell, PhD, of Georgetown's McCourt School of Public Policy, James Marrone, PhD, of RAND, and Howard Federoff, MD, PhD, of University of California, Irvine.

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Gresenz, Mitchell and Marrone report having no personal financial interests related to the studies. Federoff's research includes work to develop blood tests that can be used to predict who will develop Alzheimer's disease; he has filed patents on these blood tests.

https://nyti.ms/2p7NXrf

Scientists Were Hunting for the Next Ebola. Now the U.S. Has Cut Off Their Funding.

Predict, a government research program, sought to identify animal viruses that might infect humans and to head off new pandemics.

By Donald G. McNeil Jr.

In a move that worries many public health experts, the federal government is quietly shutting down a surveillance program for dangerous animal viruses that someday may infect humans.

Arlette Kavugho, 40, mother of six and an Ebola survivor, carries Kambale Eloge, 16 months old, whose mother died of the disease, in Katwa, near Butembo, Democratic Republic of Congo. USAID's Predict project helped identify Ebola's routes of transmission. **Zohra Bensemra/Reuters**

The United Nations Environment Program estimates that a new animal disease that can also infect humans is discovered every four months. Ending the program, experts fear, will leave the world more vulnerable to lethal pathogens like Ebola and MERS that emerge from unexpected places, such as bat-filled trees, gorilla carcasses and camel barns.

The program, known as Predict and run by the United States Agency for International Development, was inspired by the 2005 H5N1 bird flu scare. Launched 10 years ago, the project has cost about $207 million.

The initiative has collected over 140,000 biological samples from animals and found over 1,000 new viruses, including a new strain of Ebola. Predict also trained about 5,000 people in 30 African and Asian countries, and has built or strengthened 60 medical research laboratories, mostly in poor countries.

Dennis Carroll, the former director of USAID's emerging threats division who helped design Predict, oversaw it for a decade and retired when it was shut down. The surveillance project is closing because of "the ascension of risk-averse bureaucrats," he said.

Because USAID's chief mission is economic aid, he added, some federal officials felt uncomfortable funding cutting-edge science like tracking exotic pathogens.

Congress, along with the administrations of George W. Bush and Barack Obama, were "enormously supportive," said Dr. Carroll, who is now a fellow at Texas A&M's Bush School of Government and Public Service.

"But things got complicated in the last two years, and by January, Predict was essentially collapsed into hibernation."

The end of the program "is definitely a loss," said Peter Daszak, president of the EcoHealth Alliance, a nonprofit global health organization that received funding from the program. "Predict was an approach to heading off pandemics, instead of sitting there waiting for them to emerge and then mobilizing. That's expensive."

"The United States spent $5 billion fighting Ebola in West Africa," he added. "This costs far less."

The goal of Predict was to speed up and organize the previously haphazard hunt for zoonotic diseases — those that may jump from

animals to humans. In recent years, scientists have discovered many lethal viruses lurking in wild and domestic animals.

It has long been known, of course, that AIDS originated in chimpanzees and probably was first contracted by bushmeat hunters. Ebola circulates in bats and apes, while SARS was found in captive civet cats in China.

In South Asia, Nipah virus reaches humans through pigs or date palm sap infected by bats carrying the virus. In Saudi Arabia, MERS also is carried by bats; they infect camels, which then infect humans. The virus can jump from human to human, especially in hospitals.

Novel influenza viruses originate in migratory ducks and geese. The viruses spread first to domestic poultry flocks, then to pigs and humans. Mutations picked up along that viral highway can render the viruses far more dangerous.

These discoveries led to new ways of preventing spillovers of infections into human populations: closing markets where wildlife is butchered for food,; putting bamboo skirts on sap-collection jars to keep bats out; or penning pigs and camels in places where they cannot eat fruit that bats have gnawed.

Predict teams have investigated mysterious disease outbreaks in many countries, including a die-off of 3,000 wild birds in a Mongolian lake. One team proved that endangered otters in a Cambodian zoo were killed by their feed — raw chickens infected with bird flu.

A Predict laboratory helped identify bat-borne viruses that a boys' soccer team might have been exposed to while trapped for weeks in a cave in Thailand.

Allowing Predict to end "is really unfortunate, and the opposite of what we'd like to see happening," said Dr. Gro Harlem Brundtland, the former prime minister of Norway and former World Health Organization director-general.

She was co-chair of a panel that in September issued a report detailing the world's failure to prepare for pandemics. "Americans need to understand how much their health security depends on that of other countries, often countries that have no capacity to do this themselves," Dr. Brundtland said.

Even though USAID is "incredibly proud and happy over the work Predict has done," the program is closing because it reached the end of a 10-year funding cycle, said Irene Koek, acting assistant administrator of the agency's global health bureau.

"We typically do programs in five-year cycles, and it had two," she said. Some similar research will be part of future budget requests, "but it's still in the design-and-procurement cycle, so exactly what will continue is a bit of a black box."

In mid-October, the agency said it would spend $85 million over the next five years helping universities in Africa and Asia teach the "one-health" approach that Predict used. ("One health" describes the nexus between animal, human and environmental medicine).

But it will not involve the daring fieldwork that Predict specialized in.

Among the institutions that worked on Predict projects are those staffed by wildlife veterinarians and disease-trackers like the University of California, Davis's One Health Institute; the EcoHealth Alliance; the Wildlife Conservation Society, which runs the Bronx Zoo; the Smithsonian Institution, which manages the National Zoo in Washington; and Columbia University's Center for Infection and Immunity.

Some Predict projects will be taken over by other government agencies, such as the Pentagon's Defense Threat Reduction Agency or the National Institutes of Health. But those agencies have different missions, such as basic research or troop protection. They do not share USAID's goal of training poor countries to do the work themselves.

As an agency that gives money to countries, USAID often has a friendlier, more cooperative relationship with governments in poor nations than, for example, Pentagon-led efforts might.

"I've always been impressed with the way they were able to work with ministries of health," said Dr. James M. Hughes, a former chief of infectious diseases at the Centers for Disease Control and Prevention who was on Predict's advisory board. "They have a high level of trust, and they help countries comply with the International Health Regulations."

(Those regulations, in force since 2007, require countries to report all major disease outbreaks to the World Health Organization and allow the W.H.O. to declare health emergencies.)

USAID still supports some health-related programs like the President's Malaria Initiative and the President's Emergency Plan for AIDS Relief. But Dr. Carroll described those as "cookbook portfolios." How to fight those diseases is well-known, he explained, so the agency just comes up with a budget for drugs, diagnostic kits, insecticides, mosquito nets, condoms or other long-established interventions.

Predict more often placed medical detectives in the field, training local doctors, veterinarians, wildlife rangers and others to collect samples from wild and domestic animals.

It can be highly specialized work. Getting blood samples from pigs or wild rodents is fairly routine, but catching birds, bats or monkeys alive is not. Gorillas are harder. (Scientists usually content themselves with just collecting gorilla feces.)

Predict also experimented with novel ways to catch and release animals unharmed, to transport samples without refrigeration and to use DNA testing that can scan for whole viral families instead of just known viruses, said Dr. Christine Kreuder Johnson, associate director of the One Health Institute at the University of California, Davis.

Predict sponsored epidemiological modeling to predict where outbreaks are likely to erupt. It also sought ways to curb practices, such as hunting for bushmeat or breeding racing camels, that encourage eruptions.

After that West African Ebola outbreak, Predict researchers determined exactly which bat species carried the Ebola Zaire strain that caused it. Another team in Sierra Leone discovered a new strain of the virus, now known as Ebola Bombali.

The Zaire strain was found in a bat that roosts in caves and mines, said Dr. Jonathan Epstein, an EcoHealth Alliance veterinarian, while the Bombali type was in a species that roosts in houses.

Distinctions like that are important for telling people — especially people who eat bats — which species are dangerous.

"We generated an illustrated book on how to keep bats out of houses by putting screens on windows or mesh below the roof thatch," he said. "That's the kind of thing Predict paid for."

Predict served as a proof of concept for a much more ambitious idea that Dr. Carroll proposed several years ago: the Global Virome Project, which envisioned trying to compile a genetic atlas of all the viruses circulating in all animals. By some estimates, there are more than 800,000 such viruses waiting to be discovered.

Many scientists questioned the wisdom of spending as much as would be needed to do that — over $3 billion. But those experts also argued that Predict, which is focused on viruses dangerous to humans, was very much worth the relatively modest amounts of money it cost.

"Predict needed to go on for 20 years, not 10," Dr. Epstein said. "We were getting to the point of having a trained work force that could gather animal samples and labs that could test for unknown viruses, not just known ones."

"Once it stops, it's going to be hard to maintain that level of proficiency."

http://bit.ly/345iRPx

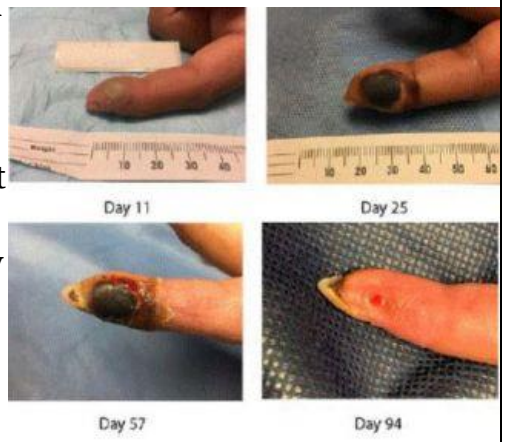
Lab Tech Accidentally Injects Herself with Smallpox-Related Virus

The infection caused the tip of the woman's finger to swell and turn black.

By Rachael Rettner - Senior Writer

A lab worker in San Diego became infected with a smallpox-related virus, known as the vaccinia virus, after she accidentally stuck her finger with a needle, according to a new report.

The infection caused the tip of the woman's finger to swell and turn black. Her case is unique because it marks the first time that doctors have used tecovirimat — a recently approved drug for smallpox — to treat a laboratory-acquired infection with vaccinia virus, the report said.



***A lab worker became infected with a smallpox-related virus, known as the vaccinia virus, after she accidentally stuck her finger with a needle. Above, images of the patient's wound in the days and months after the accident. It eventually healed more than three months later.*: © Whitehouse ER, et al. MMWR 2019/CDC**

Vaccinia virus is similar to the smallpox virus, also called the variola virus. However, vaccinia is less harmful and doesn't cause smallpox. Even so, vaccinia is the virus used to make the smallpox vaccine.

A global vaccination effort involving this vaccine led to the eradication of smallpox from the world in 1980. Though the vaccine isn't used routinely these days, doctors give it to people who are at risk of exposure to smallpox or similar viruses, such as scientists who work with *vaccinia* virus. (In research settings, *vaccinia* virus can be used as a delivery tool for gene or cancer therapies.)

In the case described in the report, the 26-year-old lab worker unintentionally stuck herself with the needle while performing an experiment that required her to inject mice with vaccinia virus, according to the report, which is published today (Oct. 25) in the journal Morbidity and Mortality Weekly Report, put out by the Centers for Disease Control and Prevention (CDC).

The worker immediately rinsed her finger with water for 15 minutes, told her supervisors about the accident and went to the emergency room.

Although the lab worker was offered the smallpox vaccine before she started her work with *vaccinia*, she declined the vaccination.

It's important to note that the smallpox vaccine comes with more side effects than most vaccines people routinely get today. That's because, unlike most vaccines, which use weakened or killed viruses, the smallpox vaccine contains live vaccinia virus, according to the CDC.

Within a few days of getting the vaccine, people are expected to develop a red and itchy lesion at the vaccination site. After that, the lesion turns into a large, pus-filled blister.

While the vaccination site heals, people need to keep the site covered with a bandage that needs changing about every three days. Eventually, a scab forms over the blister and falls off, leaving a small scar, the CDC says. The whole healing process takes about three weeks.

Despite this uncomfortable side effect, the vaccine has a very low risk of serious complications. In contrast, an accidental injection with vaccinia virus during lab work can result in serious wound infections that may require hospitalization, the report said.

About 10 days after the accident, the lab worker developed swelling and a lesion where the needle pricked her finger. Later, she developed a fever, and the swelling worsened. Doctors were concerned that she could develop "compartment syndrome," a serious condition in which there is excessive pressure inside a muscle.

Twelve days after the lab worker's accident, doctors decided to treat her with a 14-day course of tecovirimat, along with a single dose of vaccinia immune globulin, which consists of antibodies derived from people already vaccinated against the disease. The woman also received antibiotics to prevent a bacterial infection of her wound.

Within 48 hours of treatment, her fever went away, and the pain and swelling in her finger decreased, the report said. Still, areas of necrotic (dead) tissue on her finger didn't completely heal for more than three months, and she couldn't go to work during that time.

When asked why she didn't initially get the smallpox vaccine, the lab worker reported that, at the time, she "did not appreciate the extent of infection that could occur" with the vaccinia virus, the report said.

In addition, she thought it would be challenging to manage the lesion at the vaccination site and worried about potential side effects.

The report shows that, in this particular case, tecovirimat was safely used to treat an infection with vaccinia virus, the authors wrote. However, because this was just a single case, it's unclear whether the drug would be warranted for other infections with that virus, they said.

In the United States, the CDC's Advisory Committee on Immunization Practices recommends that people get the smallpox vaccine if they work with vaccinia virus, unless there is a medical reason why they can't get vaccinated.