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Gelatin accelerates healing of the blood brain barrier in acute brain injury

Microglia and the enzymes that the cells use in the cleaning process change in the presence of gelatin

Researchers already know that gelatin-covered electrode implants cause less damage to brain tissue than electrodes with no gelatin coating. Researchers at the Neuronano Research Centre (NRC) at Lund University in Sweden have now shown that microglia, the brain's cleansing cells, and the enzymes that the cells use in the cleaning process, change in the presence of gelatin.

"Knowledge about the beneficial effects of gelatin could be significant for brain surgery, but also in the development of brain implants", say the researchers behind the study.

Our brains are surrounded by a blood brain barrier which protects the brain from harmful substances that could enter it via the bloodstream. When the barrier is penetrated, as in the case of biopsy or brain surgery for example, leaks can occur and cause serious inflammation.

Researchers at the NRC have previously shown that gelatin accelerates brain tissue healing and reduces damage to nerve cells in the case of electrode implants, but only now are they starting to understand how.

The researchers used sedated rats to investigate how the brain is repaired after being subjected to an injury. Gelatin-coated needles were used in one group, and needles without gelatin in the other.

"The use of gelatin-coated needles reduced or eliminated the leakage of molecules (which normally don't get through) through the blood brain barrier within twenty-four hours. Without gelatin, the leakage continued for up to three days", says Lucas Kumosa, one of the researchers behind the study, which was recently published in the research journal Acta Biomaterialia.

Fewer Inflammatory Cleaning Cells

When there is an injury to the brain, microglial cells - the brain's cleaning cells - gather at the site. They clean up, but can also damage the nerve cell tissue through enzymes they release. In their study, the researchers observed a change in which cleaning cells moved towards the injury site. "When we used gelatin, we saw only a small number of the inflammatory microglial cells. Instead, we observed cells of a different kind, that are anti-inflammatory, which we believe could be significant in accelerating healing", explains Lucas Kumosa.

The hypothesis is that the potentially damaging enzymes are occupied with the gelatin instead. "Gelatin is a protein and its decomposition releases amino-acids that we believe could promote the reconstruction of blood vessels and tissue", explains Jens Schouenborg, professor of neurophysiology at Lund University.

Surgical Significance

Research is currently underway on how electrodes implanted in the brain could be used in the treatment of various diseases, such as epilepsy or Parkinson's. A major challenge has been to find ways of reducing damage to the area when using such implants. "Although the research field of brain electrodes is promising, it has been a challenge to find solutions that don't damage the brain tissue. Knowledge of how injuries heal faster with gelatin could therefore be significant for the development of surgical treatment as well," says Jens Schouenborg.

The research is funded by the Knut and Alice Wallenberg Foundation, the Swedish Research Council, Lund University and the Sven-Olof Jansons livsverk Foundation.

http://bit.ly/2zNHVPW

Mammals switched to daytime activity after dinosaur extinction

Mammals only started being active in the daytime after non-avian dinosaurs were wiped out

Mammals only started being active in the daytime after non-avian dinosaurs were wiped out about 66 million years ago (mya), finds a new study led by UCL and Tel Aviv University's Steinhardt Museum of Natural History.

A long-standing theory holds that the common ancestor to all mammals was nocturnal, but the new discovery reveals when mammals started living in the daytime for the first time. It also provides insight into which species changed behaviour first.

The study, published today in Nature Ecology & Evolution, analysed data of 2415 species of mammals alive today using computer algorithms to reconstruct the likely activity patterns of their ancient ancestors who lived millions of years ago.

Two different mammalian family trees portraying alternative timelines for the evolution of mammals were used in the analysis. The results from both show that mammals switched to daytime activity shortly after the dinosaurs had disappeared. This change did not happen in an instant - it involved an intermediate stage of mixed day and night activity over millions of years, which coincided with the events that decimated the dinosaurs.

"We were very surprised to find such close correlation between the disappearance of dinosaurs and the beginning of daytime activity in mammals, but we found the same result unanimously using several alternative analyses," explained lead author, PhD student Roi Maor (Tel Aviv University and UCL).

The team found that the ancestors of simian primates - such as gorillas, gibbons and tamarins - were among the first to give up nocturnal activity altogether. However, the two evolutionary timelines varied, giving a window between 52-33 mya for this to have occurred.

This discovery fits well with the fact that simian primates are the only mammals that have evolved adaptations to seeing well in daylight. The visual acuity and colour perception of simians is comparable to those of diurnal reptiles and birds - groups that never left the daytime niche.

"It's very difficult to relate behaviour changes in mammals that lived so long ago to ecological conditions at the time, so we can't say that the dinosaurs dying out caused mammals to start being active in the daytime. However, we see a clear correlation in our findings," added co-author Professor Kate Jones (UCL Genetics, Evolution & Environment).

"We analysed a lot of data on the behaviour and ancestry of living animals for two reasons - firstly, because the fossil record from that era is very limited and secondly, behaviour as a trait is very hard to infer from fossils," explained co-author, Professor Tamar Dayan (Chair of The Steinhardt Museum of Natural History, Tel Aviv University).

"You have to observe a living mammal to see if it is active at night or in the day. Fossil evidence from mammals often suggest that they were nocturnal even if they were not. Many subsequent adaptations that allow us to live in daylight are in our soft tissues."

The team say further research is needed to better populate the mammalian family tree to give more accurate information on when the behaviour of species changes from night time to day time activity.

The work involved collaboration between UCL, Tel Aviv University, The Steinhardt Museum of Natural History at Tel Aviv University and ZSL. It was kindly funded by ISF, Tel Aviv University, the Naomi Kadar Foundation and the UK's Natural Environment Research Council (NERC).

http://bit.ly/2zsfab6

Is anticoagulant warfarin associated with lower risk of cancer incidence?

Bottom Line: ***Use of the blood thinner warfarin was associated with a lower risk of new cancers in people over 50.***

Why The Research Is Interesting: Warfarin is a widely used anticoagulant prescribed to as many as 10 percent of adults in Western countries. Studies disagree on whether warfarin is associated with cancer. Any association between warfarin and cancer would be important to identify given the availability of newer non-warfarin anticoagulants.

Who: About 1.25 million people born in Norway between 1924 and 1954 divided into those taking (92,942) and not taking warfarin (more than 1.1 million). Individuals taking warfarin for atrial fibrillation or atrial flutter were studied as a subgroup.

What and When: Prescriptions for warfarin between 2004 and 2012 (exposure); any new cancer and most common cancers (prostate, lung, breast, colon) between 2006 and 2012 (outcome).

How (Study Design): This is an observational study using Norwegian national registry data. In observational studies, researchers observe exposures and outcomes for patients as they occur naturally in clinical care or real life. Because researchers are not intervening for purposes of the study they cannot control natural differences that could explain study findings so they cannot prove a cause-and-effect relationship.

Authors: James B. Lorens, Ph.D., of the University of Bergen, Norway, and coauthors

Results: Warfarin use was associated with lower risk of any cancer and of three of the most common cancers (prostate, lung, female breast) compared to warfarin non-use. In the subgroup of people using warfarin for atrial fibrillation or atrial flutter, cancer risk was lower at any site and in all four common sites (lung, prostate, breast, and colon).

Study Limitations: Researchers did not collect information on other medications or risk factors that could influence cancer development. New cancers may actually have been cancer recurrences. Prescription of warfarin may be a marker for other health care factors that lead to cancer prevention.

Study Conclusions: Warfarin appeared to be associated with reduced cancer risk in a national European population. The finding could have implications for choosing medications for patients who need anticoagulation but further studies to understand the mechanisms underlying any protective association are warranted.

Incidence rate ratio (IRR) is a measure of cancer risk. An IRR less than 1.0 suggests protection from cancer. All but one of the squares in the figure fall to the left of the central 1.0 line, suggesting an association between warfarin use and reduced risk of any cancer and common cancers for all warfarin users and the subgroup taking warfarin for atrial fibrillation or atrial flutter (AF).

For more details and to read the full study, please visit the For The Media website. (doi:10.1001/jamainternmed.2017.5512)

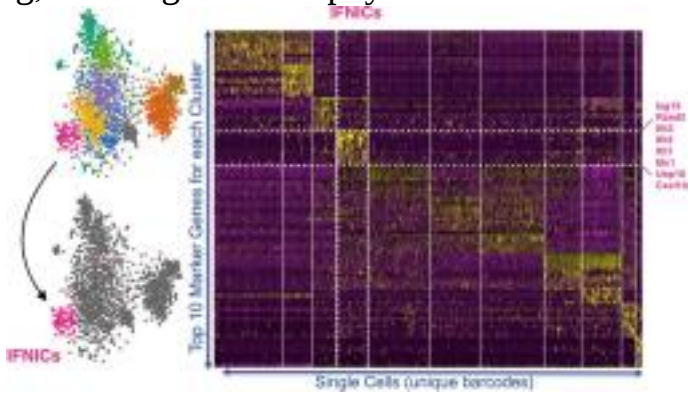
***Editor's Note:** Dr. Lorens reported ownership interest in BerGenBio ASA, which is developing AXL inhibitors. Please see the article for additional information.*

http://bit.ly/2zLJvlB

Immune cells mistake heart attacks for viral infections

Study finds the immune system plays a surprising role in the aftermath of heart attacks

A study led by Kevin King, a bioengineer and physician at the University of California San Diego, has found that the immune system plays a surprising role in the aftermath of heart attacks. The research could lead to new therapeutic strategies for heart disease.



By using single cell RNA Seq, an emerging technique that combines microfluidic nanoliter droplet reactors with single cell barcoding and next generation sequencing, the researchers were able to examine expression of every gene in over 4,000 cardiac immune cells and found the specialized IFNIC population of responsible cells. **University of California San Diego**

The team, which also includes researchers from the Center for Systems Biology at Massachusetts General Hospital (MGH), Brigham and Women's Hospital, Harvard Medical School, and the University of Massachusetts, presents the findings in the Nov. 6 issue of Nature Medicine. Ischemic heart disease is the most common cause of death in the world and it begins with a heart attack. During this process, heart cells die, prompting immune cells to enter the dead tissue, clear debris and orchestrate stabilization of the heart wall.

But what is it about dying cells in the heart that stimulates the immune system? To answer this, researchers looked deep inside thousands of individual cardiac immune cells and mapped their individual transcriptomes using a method called single cell RNA-Seq. This led to

the discovery that after a heart attack, DNA from dying cells masquerades as a virus and activates an ancient antiviral program called the type I interferon response in specialized immune cells. ¬¬ The researchers named these "interferon inducible cells (IFNICs)."

When investigators blocked the interferon response, either genetically or with a neutralizing antibody given after the heart attack, there was less inflammation, less heart dysfunction, and improved survival. Specifically, blocking antiviral responses in mice improved survival from 60 percent to over 95 percent. These findings reveal a new potential therapeutic opportunity to prevent heart attacks from progressing to heart failure in patients.

"We are interested to learn whether interferons contribute to adverse cardiovascular outcomes after heart attacks in humans," said King, who did most of the work on the study while he was a cardiology fellow at Brigham and Women's Hospital and at the Center for Systems Biology at MGH in Boston.

The immune system has evolved innate antiviral programs to defend against a diverse range of invading pathogens. Immune cells do this by detecting molecular fingerprints of pathogens, activating a protein called IRF3, and secreting interferons, which orchestrate a defense program mediated by hundreds of interferon-stimulated genes. Investigators found that surprisingly, the antiviral interferon response is also turned on after a heart attack despite the absence of any infection. Their results point to dying cell DNA as the cause of this confusion because the immune system interprets it as the molecular signature of a virus.

Surprisingly, the immune cells participating in the interferon response were a previously unrecognized subset of cardiac macrophages. These cells could not be identified by conventional flow sorting because unique markers on the cell surface were not known. By using single cell RNA Seq, an emerging technique that combines microfluidic nanoliter droplet reactors with single cell barcoding and next generation sequencing, the researchers were able to examine expression of every gene in over 4,000 cardiac immune cells and found the specialized IFNIC population of responsible cells.

Future studies will aim to better understand the interferon response and the IFNIC cell type and explore their roles in the infarcted and remodeling heart. The team is also working to understand the interferon response in other tissues and diseases where cell death occurs.

IRF3 and type I interferons fuel a fatal response to myocardial infarction
doi:10.1038/nm.4428

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Man's earliest ancestors discovered in southern England

Fossils of the oldest mammals related to mankind have been discovered on the Jurassic Coast of Dorset.

The two teeth are from small, rat-like creatures that lived 145 million years ago in the shadow of the dinosaurs. They are the earliest undisputed fossils of mammals belonging to the line that led to human beings.

They are also the ancestors to most mammals alive today, including creatures as diverse as the Blue Whale and the Pigmy Shrew. The findings are published today in the journal *Acta Palaeontologica Polonica*, in a paper by Dr Steve Sweetman, Research Fellow at the University of Portsmouth, and co-authors from the same university.

A reconstruction of the mammals by palaeo-artist Dr Mark Witton. **University of Portsmouth**

Dr Sweetman, whose primary research interest concerns all the small vertebrates that lived with the dinosaurs, identified the teeth but it was University of Portsmouth undergraduate student Grant Smith who made the discovery.

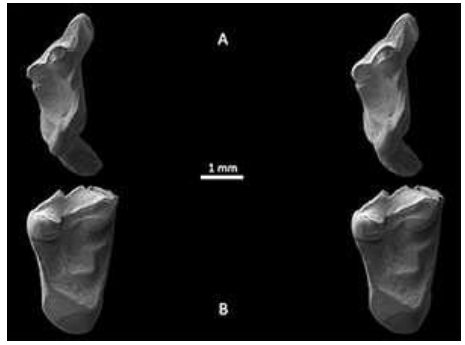
Dr Sweetman said, "Grant was sifting through small samples of earliest Cretaceous rocks collected on the coast of Dorset as part of his undergraduate dissertation project in the hope of finding some interesting remains. Quite unexpectedly he found not one but two quite remarkable teeth of a type never before seen from rocks of this age. I was asked to look at them and give an opinion and even at first glance my jaw dropped."

"The teeth are of a type so highly evolved that I realised straight away I was looking at remains of Early Cretaceous mammals that more closely resembled those that lived during the latest Cretaceous – some 60 million years later in geological history. In the world of palaeontology there has been a lot of debate around a specimen found in China, which is approximately 160 million years old. This was originally said to be of the same type as ours but recent studies have ruled this out. That being the case, our 145 million year old teeth are undoubtedly the earliest yet known from the line of mammals that lead to our own species."

Dr Sweetman believes the mammals were small, furry creatures and most likely nocturnal. One, a possible burrower, probably ate insects and the larger may have eaten plants as well. He said: "The teeth are of a highly advanced type that can pierce, cut and crush food. They are also very worn which suggests the animals to which they belonged lived to a good age for their species. No mean feat when you're sharing your habitat with predatory dinosaurs."

The teeth were recovered from rocks exposed in cliffs near Swanage which has given up thousands of iconic fossils. Grant, now reading for his Master's degree at The University of Portsmouth, said that he knew he was looking at something mammalian but didn't realise he had discovered something quite so special. His supervisor, Dave Martill, Professor of Palaeobiology, confirmed that they were mammalian, but suggested Dr Sweetman, a mammal expert should see them.

Professor Martill said: "We looked at them with a microscope but despite over 30 years experience, these teeth looked very different, and we decided we needed to bring in a third pair of eyes and more expertise in the field in the form of our colleague, Dr Sweetman.



The teeth under an electron microscope. **University of Portsmouth**

"Steve made the connection immediately, but what I'm most pleased about is that a student who is a complete beginner was able to make a remarkable scientific discovery in palaeontology and see his discovery and his name published in a scientific paper. The Jurassic Coast is

always unveiling fresh secrets and I'd like to think that similar discoveries will continue to be made right on our doorstep."

One of the new species has been named Durlstotherium newmani, christened after Charlie Newman, the landlord of the Square and Compass pub in Worth Matravers, close to where the fossils were discovered.

More information: *Steven Sweetman et al. Highly derived eutherian mammals from the earliest Cretaceous of southern Britain, Acta Palaeontologica Polonica (2017). DOI: 10.4202/app.00408.2017*

Journal reference: *Acta Palaeontologica Polonica*

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Flu Vaccine "Factories" Create Errors That Reduce Protection

Eggs used to grow viruses for flu shots trigger changes that leave people vulnerable

By Melinda Wenner Moyer on November 6, 2017

Flu vaccines saved an estimated 40,000 American lives between 2005 and 2014, but they are not good enough.The vaccine used during the 2016–17 flu season, for example, was only 43 percent effective against the predominant influenza A H3N2 strain, and protection has been almost as low in other years. Two studies now suggest a new reason for the problem: The vaccine strain mutates during the manufacturing process in ways that cause mismatches with real circulating flu strains.

Researchers already knew the flu shot had a flaw. Because the virus evolves very quickly, an inoculation devised months before flu season often differs from what ends up infecting the public. Now it appears other important mismatches are triggered because vaccines are grown inside chicken eggs. "We've got to get out of chicken eggs," says Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, who was not involved in the research. He concedes, though, "that's not easy to do, and that's expensive—very expensive."

Last year's flu vaccine should have worked well. The strain that the U.S. Food and Drug Administration chose for the seasonal vaccine did indeed closely match the viruses that sickened people. So when its effectiveness proved disappointing, Scott Hensley, a microbiologist at the University of Pennsylvania Perelman School of Medicine, and his colleagues began to investigate. Flu vaccines are killed or highly weakened viruses that, when injected into the body, alert the immune system to fight the real thing. For 70 years most flu vaccine strains have been grown in fertilized chicken eggs because egg growth incites excellent yield. But it has long been known that the viruses also evolve in these egg hosts. They adopt genetic changes that help them grow in the egg environment. What Hensley and his colleagues found was such changes can cause problems for the end product.

In a paper published online today in Proceedings of the National Academy of Sciences, Hensley's team zeroed in on a new molecule that the H3N2 virus started wearing on one of its surface proteins in 2014. This molecule, a type of sugar, has become chemically glued to a location on the virus's surface near where human antibodies—immune system watchdogs—attach to mark the virus as a dangerous invader. The sugar made it hard for antibodies to stick, so it helped the virus avoid immune destruction. When flu researchers learned about this new sugar-adorned H3N2 virus in 2014, they made sure to include that strain in the 2016–17 seasonal flu vaccine so that immunized individuals would mount an immune response against it.

But when Hensley and his colleagues studied the strain that ended up in the U.S. vaccine, they saw that, mysteriously, the sugar molecule had disappeared. The loss was bad for the vaccine: In a series of experiments Hensley and his colleagues showed antibodies from humans and ferrets (a good animal model for influenza A studies) that had been exposed to the egg-grown vaccine did not effectively kill the circulating sugar-adorned viruses. Antibodies incited by a similar vaccine that was not grown in eggs, on the other hand, worked quite well. (Two U.S. influenza vaccines do not use egg-adapted strains.

One, FLUCELVAX, is grown in canine kidney cells, and the second, Flublok, is grown in insect cells.)

The new sugar molecule hinders the virus's ability to grow in eggs—so once the vaccine strains are put into eggs, they ditch it. "The viruses, originally isolated in humans, are simply adapting to the new cells in their environment," says Sarah Cobey, an ecologist and evolutionary biologist at the University of Chicago and one of the paper's co-authors. But by eliminating the sugar molecule, the new mutation also affects "a key region in the virus that is targeted by the immune system," Hensley adds, making the vaccine less effective.

Egg-based production changes the flu virus in other important ways, too. In a separate study published on October 23 in PLOS Pathogens, a team of researchers—including Hensley—showed vaccine virus strains grown in chicken eggs also acquire a mutation that alters the structure of the same region important for human antibody binding. Basically, "in acquiring that mutation, the vaccine looks like a triangle, but the viruses that are circulating look like a circle," Hensley says. "So if you mount responses against the triangle, they're not going to bind very well to the circle." Hensley and his team reported this egg-induced mutation, which was present in the 2016–17 U.S. seasonal flu vaccine, decreases the ability of certain antibodies to attach to and destroy the flu virus—by a whopping three orders of magnitude.

These egg-based changes bode ill for the real world. A 2014 study used epidemiological data to show egg-based mutations are associated with low vaccine effectiveness in human populations. The vaccine used during the 2012–13 flu season in Canada did not work very well, despite the fact that the circulating flu viruses had not seemingly changed much after the vaccine strains had been chosen. Upon investigating further, Danuta Skowronski, the lead epidemiologist for flu and emerging pathogens at the British Columbia Centers for Disease Control, and her colleagues reported in PLOS One that the egg-production process had induced three mutations at immunologically important sites in the vaccine virus strain and that these mutations were linked with low vaccine protection.

Recent data from the U.S. Centers for Disease Control and Prevention suggest this season's vaccine may suffer from similar problems. Since May 21, 2017, the agency has analyzed H3N2 viruses that have circulated in the U.S. and internationally. Only 33 percent of these viruses were neutralized by antibodies from ferrets vaccinated with egg-grown strains, whereas 97 percent of viruses were inhibited by antibodies from ferrets inoculated with a non–egg-grown vaccine. A recent study from Australia, which is just finishing its flu season and used the vaccine strains that the U.S. is now using, suggests the H3N2 component of this season's vaccine is only 10 percent effective. This futility is not surprising since this egg-grown vaccine still contains the two mutations described in the new papers.

But although abandoning egg-based vaccines is the obvious fix, that move is not going to be easy, Hensley says. "There's a great amount of infrastructure that exists in producing these vaccines in eggs because that's how it's always been done," he points out. It may take years, if not decades, to shift the majority of flu vaccine production out of chicken eggs and into other bio-factories like cells. In the meantime the CDC is working to improve the process. It is using next-generation genetic sequencing to study egg-induced mutations in the hopes of identifying some that improve rather than reduce vaccine effectiveness. Then the agency will select for these viral strains and use them for future vaccines.

Hensley emphasizes that even though the current vaccine does have limitations, people should still get annual flu shots. The vaccine lowers infection risk--it works very well against influenza B--and may also minimize the risk of severe infection. And vaccinated individuals also protect vulnerable people such as those with immune conditions and severe allergies who cannot get vaccinated. The goal of these new studies is not to pooh-pooh the flu vaccine; they are "just trying to

make things better," Hensley says. Scientists have to acknowledge there's room for improvement in order to make progress.

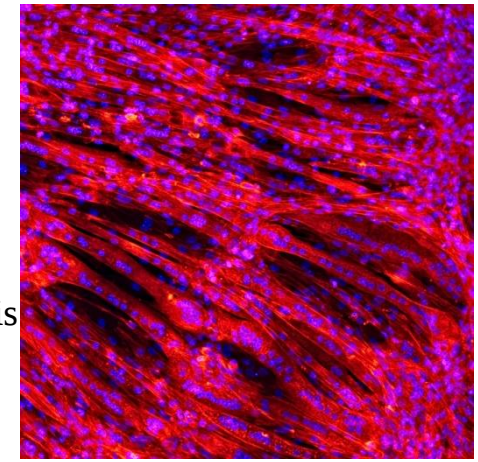
Editor's note: The first paragraph has been clarified on Nov. 6, 2017 to compare low protection rates to a 43 percent figure.

http://bit.ly/2zxEPwP

Muscles out of the spray can

One step ahead towards the artificial heart

Anyone who requires a transplant because of cardiac failure must hope for a suitable donor organ. An artificial heart that does not trigger any rejection reactions in the body after implantation would be an elegant alternative. The Zurich Heart project of the research alliance University Medicine Zurich, of which Empa is a partner, is currently developing such an artificial heart. To ensure that the laboratory-made pump is tolerated by the body, the aim is to envelop and coat it in human tissue, much like a cloak of invisibility.



A network of muscle fibers grows on spun plastic scaffold. Under a confocal laser scanning microscope the muscle fibers appear in red, and the cell nuclei in blue. **Lukas Weidenbacher**

Until now, the culturing of multi-layered functional tissues has been a major challenge in the up-and-coming area of "Tissue Engineering". Empa researchers have now succeeded in letting cells develop into muscle fibers in a three-dimensional synthetic polymer scaffold.

"The human heart is naturally composed of several layers of different tissues," explains Lukas Weidenbacher of Empa's laboratory for Biomimetic Membranes and Textiles in St. Gallen. Muscle fibers in the lining play a decisive role in the structure, for they are responsible for the stability and flexibility of the constantly beating heart. Culturing muscle fibers that grow in multiple layers is challenging, however, because the cells must first be embedded in a three-dimensional scaffold. "To be sure, it is possible to create three-dimensional polymer structures that closely resemble human tissue, by means of so-called electrospinning for example," says Weidenbacher. During this process, gossamer-like threads of liquid polymer are interlaced in the manner of natural tissue. But the harmful solvents that are required for this process are poison for the sensitive cells.

Slobbery protection

The researchers at Empa have therefore packaged the valuable cells in protective capsules. Gelatin sheaths contain one to two cells each. This protects the cells from the solvents. A special spraying process, called electrospraying, makes it possible to inject the capsules into the pores of the spun scaffold. "Cells that are protected in this way survive the spraying very well," explains the materials scientist. And once the cells have settled at the desired location, the gelatinous capsule dissolves within minutes.

Scanning electron microscope images show that the cells feel at home in their synthetic polymer nest: As soon as the capsules have dissolved, the immature precursor cells begin to join up and to mature to form elongated muscle fibers. The aim is to end up with a structure that resembles natural muscle tissue as closely as possible. "As the artificial heart is constantly perfused by the blood circulation, it is important that the surfaces are of a quality that prevents coagulation," says Weidenbacher.

Invisible to the immune system

The researchers have used the immature muscle cells of a mouse cell line for their series of experiments. These precursor cells differentiated in the scaffold and produced proteins that normally occur in muscle. However, in the future the aim is to clad the implantable artificial heart with cells that derive from the patients themselves. In this way, a personal heart could be grown for the patient that remains "invisible" to the body's immune system.

http://bit.ly/2i0q65I

New possibility to prevent and treat Parkinson's disease with licorice extract

Korean researchers verified the new mechanism of inhibition of dopamine neuronal cell death using licorice extract 'liquiritigenin'

DGIST's research team led by Dr. Yun-Il Lee in Well Aging Research Center has identified a new mechanism of inhibition of dopaminergic neuronal apoptosis and suggested the possibility of preventing and treating Parkinson's disease.

Parkinson's disease (PD) is a typical degenerative brain disease caused by the death of dopaminergic neurons in the middle cerebral blood. It is a disease with a higher incidence in the population aged 60 or older, exhibiting symptoms such as tremor, stiffness, slow motion and postural instability.

In particular, as the majority of Parkinson's patients suffer from the progressive neurodegenerative disease, many researchers newly started to focus on cell death, a loss of dopamine-producing neurons, to treat PD. With regard to the cell death process, in vivo cell stress and damages activate PARP-1 (Poly ADP-ribose polymerase-1) and induce excessive accumulation of PAR (Poly ADP-ribose) and those activities activate AIF (Apoptosis-Inducing Factor), a factor that induces cell death, and destroy DNA. This new mechanism of cell death (Parthanatos) has recently been known as the cause of degenerative brain diseases such as Parkinson's disease, stroke, heart attack, diabetes, etc. and the mechanism has been extensively studied as previous research to treat these diseases.

Currently, medications are being used to alleviate symptoms of Parkinson's disease. However, there are no government-approved drugs that can inhibit dopaminergic neuronal cell death. Then, the research teams have found the possibility in licorice, the herb medicine.

Dr. Yun-Il Lee carried out joint research with Professor Joo-Ho Shin and Professor Yunjong Lee from Sungkyunkwan University School of Medicine to study candidate compounds for the treatment of Parkinson's disease. For example, the researchers have identified the mechanism that cortisol, a stress hormone, promotes dopaminergic neuronal activity by inducing parkin protein expression that inhibits dopamine neuronal cell death.

In this study, the research teams found the candidate drugs that induce the expression of RNF146 protein involved in the inhibition of neuronal cell death through high-speed mass screening method using the natural materials library of the Natural Medicine Bank of Korea Foundation.

As a result, the study has confirmed that liquiritigenin, a licorice extract, induces the expression of RNF146 protein and removes excessively accumulated PAR binding and modified substrate proteins using the ubiquitin proteasome system and results in inhibition of dopamine neuronal cell death.

In addition, the research teams have been working on identifying the mechanism which induces liquiritigenin's RNF146 protein expression and demonstrated that it regulates transcription through binding and activity with estrogen receptors in cell and animal models. Consequently, it has been scientifically proved that liquiritigenin, a licorice extract, can be used as a treatment for degenerative Parkinson's disease.

Dr. Yun-Il Lee stated "Neuronal death is involved in a variety of signaling systems in vivo. Therefore, it is essential to identify a new mechanism that is able to control the system comprehensively and we have found additional possibilities in licorice extract." He added "I would like to contribute to the treatment of degenerative brain diseases such as Parkinson's disease by conducting advanced researches, comprehensive research and clinical studies."

This study has been published in the online edition of Oncotarget, international journal of oncology, on October 11.

For more information, please contact:
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Hyojung Kim, Sangwoo Ham, Joon Yeop Lee, et al., "Estrogen receptor activation contributes to RNF146 expression and neuroprotection in Parkinson's disease models," Oncotarget 2017 https://doi.org/10.18632/oncotarget.21828

http://bit.ly/2zQelJQ

Dietary isoflavones linked to increased risk of advanced prostate cancer

Dietary intake of isoflavones linked with elevated risk of advanced prostate cancer

Dietary intake of isoflavones was linked with an elevated risk of advanced prostate cancer in a recent International Journal of Cancer study.

No statistically significant associations were observed between the intake of isoflavones and non-advanced prostate cancer.

Isoflavones are a type of phytoestrogen, a family of estrogen-like compounds found in plants, and are found in soybeans, kudzu root, and American groundnuts.

During a median follow up of 11.5 years, 2598 cases of prostate cancer (including 287 advanced cases) were identified among 27,004 men in the intervention arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Dietary intake was assessed with a food frequency questionnaire.

"Prostate cancer is a major cancer in Western countries and its incidence rate has been remarkably increasing in Asian countries during the last several decades," said senior author Dr. Jianjun Zhang, of the Indiana University Fairbanks School of Public Health.

"Our study offers novel evidence that dietary intake of isoflavones has different effects on advanced and non-advanced prostate cancer. This observation is important for understanding the etiology and prevention of prostate cancer but needs to be confirmed in more epidemiologic studies among populations with diverse dietary habits."

http://bit.ly/2zwdJbN

When you're tired, your brain cells actually slow down

Sleep rhythms can disrupt normal activity in specific regions of the brain, say Tel Aviv University, UCLA and UW researchers

It has been established that sleep deprivation slows down our reaction time, but it has been unclear exactly how the lack of sleep affects brain activity and subsequent behavior.

A new Tel Aviv University study published in Nature Medicine finds that individual neurons themselves slow down when we are sleep deprived, leading to delayed behavioral responses to events taking place around us. The neural lapse, or slowdown, affects the brain's visual perception and memory associations.

The study was an international collaboration led by Dr. Yuval Nir of TAU's Sackler Faculty of Medicine and Sagol School of Neuroscience; Prof. Itzhak Fried of UCLA, TAU and Tel Aviv Medical Center; and sleep experts Profs. Chiara Cirelli and Giulio Tononi at the University of Wisconsin-Madison.

"When a cat jumps into the path of our car at night, the very process of seeing the cat slows us down. We're therefore slow to hit the brakes, even when we're wide awake," says Dr. Nir. "When we're sleep-deprived, a local intrusion of sleep-like waves disrupts normal brain activity while we're performing tasks."

Investigators recorded the brain activity of 12 epilepsy patients who had previously shown no or little response to drug interventions at UCLA. The patients were hospitalized for a week and implanted with electrodes to pinpoint the place in the brain where their seizures originated. During their hospitalization, their neuron activity was continuously recorded.

After being kept awake all night to accelerate their medical diagnosis, the patients were presented with images of famous people and places, which they were asked to identify as quickly as possible.

"Performing this task is difficult when we're tired and especially after pulling an all-nighter," says Dr. Nir. "The data gleaned from the

experiment afforded us a unique glimpse into the inner workings of the human brain. It revealed that sleepiness slows down the responses of individual neurons, leading to behavioral lapses."

In over 30 image experiments, the research team recorded the electrical activity of nearly 1,500 neurons, 150 of which clearly responded to the images. The scientists examined how the responses of individual neurons in the temporal lobe -- the region associated with visual perception and memory -- changed when sleep-deprived subjects were slow to respond to a task.

"During such behavioral lapses, the neurons gave way to neuronal lapses -- slow, weak and sluggish responses," says Prof. Fried. "These lapses were occurring when the patients were staring at the images before them, and while neurons in other regions of the brain were functioning as usual."

Investigators then examined the dominant brain rhythms in the same circuits by studying the local electrical fields measured during lapses. "We found that neuronal lapses co-occurred with slow brain waves in the same regions," Dr. Nir says. "As the pressure for sleep mounted, specific regions 'caught some sleep' locally. Most of the brain was up and running, but temporal lobe neurons happened to be in slumber, and lapses subsequently followed. "Since drowsy driving can be as dangerous as drunk driving, we hope to one day translate these results into a practical way of measuring drowsiness in tired individuals before they pose a threat to anyone or anything," Dr. Nir concludes.

The paper's other co-authors were Thomas Andrillon of the Ecole Normale Superieure in Paris, Amit Marmelshtein of Tel Aviv University, and Nanthia Suthana of UCLA.

http://bit.ly/2AxtdJo

Boy is given new skin thanks to gene therapy

First ever successful treatment of extensive skin damage using transplants derived from genetically modified stem cells

A medical team at the Ruhr-Universität Bochum's burn unit and the Center for Regenerative Medicine at the University of Modena (Italy) were the first ever to successfully treat a child suffering from extensive skin damage using transplants derived from genetically modified stem cells. The boy is a so-called butterfly child: he suffers from epidermolysis bullosa, a genetic skin disease that had destroyed approximately 80 percent of his epidermis. After all established therapies had failed, the medical team from Bochum decided to try an experimental approach: they transplanted skin derived from genetically modified stem cells onto the wound surfaces. Thanks to the successful therapy, the boy is now - two years after the treatment - able to participate in his family's life and social life. The scientists published their report in *Nature*.

Life-threatening condition

Epidermolysis bullosa is the scientific name of a congenital skin disease that is currently considered to be incurable. Its underlying mechanism is a defect in protein-forming genes that are essential for skin regeneration. Even minor stress can result in blisters, wounds, and skin loss with scar formation. Depending on disease severity, internal organs may likewise be affected, leading to critical dysfunctions.

The disease significantly reduces the patients' quality of life; often it is also life-threatening, as in the case of Hassan, the seven years old: by the time he was admitted to the paediatric intensive care unit at Katholisches Klinikum Bochum in June 2015, 60 percent of his epidermis was lost. "He suffered from severe sepsis with high fever, and his body weight had dropped to a mere 17 kilogrammes - a life-threatening condition," Dr Tobias Rothoeft, Consultant at the University Children's Hospital at Katholisches Klinikum Bochum, points out. All conservative and surgical therapy approaches failed.

First in the world: New therapy concept for large skin defects

Due to the poor prognosis, the Bochum-based team of paediatricians and plastic surgeons, in collaboration with Prof Dr Michele De Luca from the Center for Regenerative Medicine at the University of Modena, opted for an experimental therapy: the transplantation of genetically modified epidermal stem cells. Obtained from the patient

via skin biopsy, these stem cells were processed in Modena. The researchers transferred the intact gene into acquired stem cells. During this process, so-called retroviral vectors were deployed, i.e. virus particles that had been specifically modified for gene transfer.

The genetically modified stem cells had been cultivated in a clean room laboratory and subsequently turned into transgenic transplants. After obtaining the parents' permission, authorities' approvals and certification of the operating rooms at the Bergmannsheil as genetic engineering facility, the transplantation went ahead.

Eighty percent of the body surface transplanted

At the Department of Plastic Surgery at the Bergmannsheil, the transplants were applied to the boy's arms and legs, entire back, flanks, and partially to the stomach, neck and face as well. "Overall, 0.94 square meters of transgenic epidermis were transplanted onto the young patient in order to cover all defects, accounting for 80 percent of his entire body surface," says Associate Professor Dr Tobias Hirsch, head consultant at the department of plastic surgery.

Following the first transplantation in October 2015, the patient's condition began to improve. The transgenic stem cells formed a new epidermis with intact binding proteins in all transplanted areas. The integration of the intact gene through retroviral gene transfer into the genome of the epidermal stem cells had been successful and was proven to be stable.

Excellent treatment result

In February 2016, the patient was discharged. Today, almost two years after the experimental therapy was initiated, high-quality, stress-resistant skin with intact hydrolipid film, as well as early formation of hair. No scar contractures have appeared in transplanted areas. Hassan is attending school again and is actively taking part in his family's social life.

According to the international medical team, Hassan is the first patient worldwide who has been treated with skin transplants from transgenic epidermal stem cells on a large body surface area. "This approach has enormous potential for research into and development of new therapies for the treatment of epidermolysis bullosa as well as other diseases and trauma causing large skin defects" says Tobias Hirsch.

Because of its large scale, the case is considered unique on a worldwide level. "Transplanting 80 percent of the skin and providing intensive medical care to the patient over a period of eight months was extremely challenging," Tobias Rothoeft and Tobias Hirsch point out. "The close collaboration between the departments in Bochum and the University of Modena's expertise have been the key to success. This makes us very proud."

Bochum-based doctors involved in the therapy

The doctors from Bochum who were involved in the therapy are Associate Professor Dr Tobias Hirsch at the Ruhr-Universität Bochum, Head Consultant of the Department of Plastic Surgery and Burn Unit at the Bergmannsheil (director: Prof Dr Marcus Lehnhardt); as well as Dr Tobias Rothoeft and Dr Norbert Teig, Consultants at the University Children's Hospital at Katholisches Klinikum Bochum (director: Prof Dr Thomas Lücke).

Funding

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http://bit.ly/2iQaJwA

Research reveals the true impact of diabetic foot ulcers

The prognosis for people with an infected diabetic foot ulcer is worse than was previously thought, according to new research.

More than half the patients in the research study did not see their ulcer heal over a year - and one in seven had to have part or all of their foot

amputated. Foot ulcers are open wounds and they affect around a quarter of the 3.3 million people in the UK living with diabetes. The wounds develop because diabetes damages the nerves and blood vessels in the feet.

These wounds are chronic, slow to heal and prone to infection, and it is infection that normally leads to some of the severe consequences such as losing a limb or multiple amputations.

The research, led by Professor Andrea Nelson at the University of Leeds, set out to examine the outcomes for people with infected diabetic foot ulcers and the results underline the need for people at risk of foot ulcers to be closely monitored.

Not only do the ulcers cause disability, there are big financial implications for the NHS. The National Institute for Health and Care Excellence or NICE puts the annual cost for treating diabetic foot wounds at £650 million.

The University of Leeds is at the forefront of research into preventing and treating diabetic foot ulcers as well as skin wounds and pressure sores more generally, a problem that affects people with poor circulation, obesity or limited mobility - and one that is expected to grow as society gets older.

This latest study is published in the journal Diabetic Medicine.

The researchers tracked 299 people who had attended a diabetic clinic with an infected foot ulcer, a big enough sample for it to be representative of the picture across the UK. The patients were followed up a year later.

By then, one in seven people (17.4 percent) had part or all of their foot amputated. Among the others, less than half (45.5 percent) had seen their ulcer heal. The researchers say the outcomes are worse than previously thought - a conclusion based on a more accurate statistical analysis of the scale of the problem.

Professor Nelson from the Faculty of Medicine and Health said: "Foot ulcers are a very nasty condition. They're painful and are debilitating. People with foot ulcers have limited mobility, and that brings with it a whole set of other risk factors - obesity and heart disease, for example. "The key point is that people need to be seen quickly if an ulcer begins to form - that gives health workers the greatest chance of trying to treat the condition." Dr Michael Backhouse, a podiatrist and Senior Research Fellow at the University of Leeds, said: "The results of our study are important and should help clinicians caring for patients with diabetes to identify those most at risk for poor outcomes so that we can look to provide further support."

The full paper can be accessed online: http://dx.doi.org/10.1111/dme.13537

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http://bit.ly/2yw82XH

The Surprising Reason Nighttime Injuries Are Worse Than Daytime Ones

Skin injuries that happen at night heal more slowly

By Tereza Pultarova, Live Science Contributor

Be careful of things that go bump in the night, especially if those bumps lead to skin injuries: A new study from England finds that skin injuries that happen at night heal more slowly than those that take place during the day.

Nighttime skin injuries heal about 60 percent slower than daytime skin injuries, according to the study, published today (Nov. 8) in the journal Science Translational Medicine.

The reason for this may lie in the circadian rhythms of the skin cells, which, like nearly all cells in the body, operate on a 24-hour cycle and go into a bit of a lull at night. But the researchers were even more surprised that not only does the healing process slow down at night, but also that the time of the injury completely determines how fast the injury will heal.

"What we found is that how well you can heal depends on the time when you got injured," said lead study author Ned Hoyle, a molecular biology researcher at Cambridge University in the U.K. "The speed of

the healing depends on how fast certain cells can get to the wounded area in order to repair it, and that depends on their micro-architecture, which is controlled by the biological clock."

To study the timing of wound healing, the researchers first looked at skin cells called fibroblasts that were grown in lab dishes over the course of several days, Hoyle told Live Science. These cells are found in the deepest layer of the skin, called the dermis. When an injury occurs, the fibroblasts travel up to the surface, where they're tasked with synthesizing and building the structural support of the new skin, which includes the so-called extracellular matrix and collagen.

But depending on the time of day, the speed at which the fibroblasts move up to the skin's surface varies, thanks to a protein found in the cells called actin, the researchers found.

Actin is a protein that forms an important part of the cytoskeleton — the supportive structure that gives the cell its shape. When the cells are told by their biological clock to "sleep," the shape of the actin proteins changes.

"We found that during daytime, the actin has mostly the form of long filaments, while at night, the majority of it is in a globular form," Hoyle said. "We know that the actin filaments are very important in allowing cells to move." As a result of these changes, the fibroblasts travel to the site of the injury more slowly at night, when the actin is mostly spherical. In a later experiment in the study, the researchers observed the same effect in the skin of mice.

And when the team looked at medical records of human patients recovering from burns, they found evidence of exactly the same phenomenon: "Wounds incurred during the day were, on average, healed in 17 days compared to the healing times of wounds incurred at night, which was 28 days," Hoyle said.

It's still not clear exactly why the nighttime wounds take longer to heal, however. The researchers originally expected the fibroblasts to make up for lost ground during the day, but that doesn't happen, Hoyle said. "This is one of the most surprising results," Hoyle said. "What we see is a persistent 'time of wounding' effect. The cells wounded during the nighttime never catch up."

Hoyle said the finding could perhaps be used in the future to develop a technique to trick cells into thinking it's daytime, in case a procedure needs to be performed at night. Such interferences are technically possible, he added. In addition, Hoyle said that he hopes to study the healing processes further, as they are extremely complex and involve many other cells and proteins beyond fibroblasts and actin.

http://bit.ly/2zuYlfI

Drinking Alcohol Really Does Raise Your Cancer Risk, Doctors Warn

Drinking alcohol, even a light or moderate amount, increases the risk of several common cancers, according to a leading group of cancer doctors.

By Rachael Rettner, Senior Writer | November 8, 2017 05:14pm ET

This week, the American Society of Clinical Oncology (ASCO) issued a statement identifying alcohol as a "definite" risk factor for cancer. The statement is intended to raise awareness about the strong link between alcohol and cancer.

"People typically don't associate drinking beer, wine and hard liquor with increasing their risk of developing cancer in their lifetimes," Dr. Bruce Johnson, the president of ASCO, said in a statement. Indeed, a recent survey from the organization found that 70 percent of Americans didn't know that drinking alcohol is a risk factor for cancer. "However, the link between increased alcohol consumption and cancer has been firmly established," Johnson said.

It's estimated that, worldwide, about 5 percent of new cancers and 6 percent of cancer deaths each year are directly attributable to alcohol consumption, the ASCO statement said.

The statement also cites a recent report from the World Cancer Research Fund and the American Institute for Cancer Research, which concluded that there is convincing evidence that drinking alcohol can be a cause of seven cancers. These include breast cancer, colorectal

cancer, esophageal cancer, liver cancer and cancers of the oral cavity, pharynx and larynx (also referred to as "head and neck cancer").

Drinking even one alcoholic drink per day is linked with a 5 percent increase in the risk of breast cancer, a 17 percent increase in the risk of oropharyngeal cancer (a cancer of the middle part of the throat) and a 30 percent increase in the risk of esophageal cancer, compared with not drinking, according to a 2013 study cited by the ASCO statement.

Heavier drinking is linked with greater risks, the statement said. People who drink more than four alcoholic drinks a day have five times the risk of cancer of the oral cavity and pharynx, five times the risk of esophageal cancer and two times the risk of liver cancer, compared with those who don't drink.

"The good news is that, just like people wear sunscreen to limit their risk of skin cancer, limiting alcohol intake is one more thing people can do to reduce their overall risk of developing cancer," said Dr. Noelle LoConte, an associate professor of medicine at the University of Wisconsin and lead author of the ASCO statement.

For people who choose to drink alcohol, the Centers for Disease Control and Prevention recommends that men consume no more than two drinks per day and women consume no more than one drink per day to reduce the risk of alcohol-related harms, including cancer.

ASCO's statement also offered some recommendations to reduce excessive alcohol consumption in the general population, including increasing alcohol taxes and prices, enhancing enforcement of laws that prohibit the sale of alcohol to minors, restricting youth exposure to alcohol-related advertising and providing alcohol screening in doctors' offices.

http://bit.ly/2hnNZDQ

As epidemic rages, ER study finds opioids no better than Advil and Tylenol

Opioids currently only suggested for acute pain, but they may not even be best for that.

Beth Mole - 11/9/2017, 3:12 AM

The easiest way to avoid getting hooked on opioids may be to never take them in the first place. After all, an initial prescription of just a few days' worth of pills can trap patients into using the highly addictive, often deadly drugs for a year or more. But despite the dangers, many patients don't have the luxury of passing on potent pain killers—for instance, those stumbling into a hospital emergency room with a broken or badly bloodied limb.

At least, that's what doctors assumed.

"This change in prescribing habit," they write, "could potentially help mitigate the ongoing opioid epidemic by reducing the number of people initially exposed to opioids and the subsequent risk of addiction."

Beyond that, the study flings into light the poor data backing current opioid prescription practices and the dwindling scenarios in which the dangerous drugs are firmly warranted. The implications are staggering given the current epidemic of opioid abuse and addiction gripping the country. In 2015, more than 30,000 people died of opioid overdoses, and currently an estimated 91 people die each day from the drugs.

Precarious prescriptions

The authors of the new trial, led by Andrew Chang of Albany Medical College in New York, note that common medical practice and guidelines, including those championed by the World Health Organization, suggest that opioids are simply more effective at treating acute pain than non-opioid medications—or combinations of them. Yet, the data backing that is shaky.

Ibuprofen and acetaminophen have completely different molecular activities in the central nervous system and brain—offering a one-two punch to pain when used in combination. Researchers haven't done the work to show that the duo are knocked out by opioids in terms of treating extreme pain in a limb. But a handful of studies on dental and post-operative patients clearly indicated that non-opioid drug pairs were just as effective. The studies compared a combination of ibuprofen and acetaminophen to a combo of codeine and

acetaminophen and found that no codeine-containing treatment—regardless of the dose—beat out the non-opioid blend.

"Plainly stated, the risks of opioids are addiction and death, and the benefits for chronic pain are often transient and generally unproven," then-CDC Director Tom Frieden said at the time.

Painful results

In the new trial, Chang and colleagues enrolled 411 patients who arrived in one of two Bronx, New York, emergency rooms with acute pain in a limb. The enrolled patients were all between 18 and 64 years old, cleared of complicating health conditions, had no history of allergies or signs of opioid addiction, and were on no medications that might interact with the pain treatments. When they arrived, the patients had a mean pain score of 8.7 on a standard 11-point scale.

Researchers then randomly assigned the patients to get one of four pain-pill combinations: 400mg of ibuprofen and 1,000mg of acetaminophen; 5mg of oxycodone and 325mg of acetaminophen; 5mg of hydrocodone and 300mg of acetaminophen; or 30mg of codeine and 300mg of acetaminophen. Each of the pill combinations looked identical to the patients—three opaque capsules.

Patients who needed more pain medication than the given treatment—which was determined at the discretion of the treating physician—could get a rescue dose of 5mg of oxycodone. Seventy-three of the 411 patients (~18 percent) got a rescue dose. But they were generally evenly distributed among the four treatment groups. In other words, there were no significant differences in the fraction of patients in each group getting a rescue dose.

Chang and colleagues note the main limitation of the study, which is that it only looked at pain treatment in a two-hour window. But, they note, "the goal was to determine if a single dose of an analgesic [pain reliever] would provide superior pain relief for patients while in the ED." It's possible that one combination could wear off faster, but they all have similar half-lives of three to four hours, they note.

"The trial by Chang et al provides important evidence that nonopioid analgesia can provide similar pain reduction as opioid analgesia for selected patients in the [emergency department] setting," emergency medicine physician Demetrios Kyriacou of Northwestern University concluded in an accompanying editorial. Still, researchers will need more data to know if pain patients in other clinical settings can skip the opioids.

JAMA, *2017. DOI: 10.1001/jama.2017.16190 (About DOIs).*

http://bit.ly/2i6l4oA

Frequent alcohol drinking kills new brain cells in adults, females are more vulnerable

Researchers from The University of Texas Medical Branch at Galveston recently discovered that alcohol killed the stem cells residing in adult mouse brains.

GALVESTON, Texas -- Because the brain stems cells create new nerve cells and are important to maintaining normal cognitive function, this study possibly opens a door to combating chronic alcoholism.

The researchers also found that brain stem cells in key brain regions of adult mice respond differently to alcohol exposure, and they show for the first time that these changes are different for females and males. The findings are available in Stem Cell Reports.

Chronic alcohol abuse can cause severe brain damage and neurodegeneration. Scientists once believed that the number of nerve cells in the adult brain was fixed early in life and the best way to treat alcohol-induced brain damage was to protect the remaining nerve cells.

"The discovery that the adult brain produces stem cells that create new nerve cells provides a new way of approaching the problem of alcohol-related changes in the brain," said Dr. Ping Wu, UTMB professor in the department of neuroscience and cell biology. "However, before the new approaches can be developed, we need to understand how alcohol impacts the brain stem cells at different stages in their growth, in different brain regions and in the brains of both males and females."

In the study, Wu and her colleagues used a cutting-edge technique that allows them to tag brain stem cells and observe how they migrate and develop into specialized nerve cells over time to study the impact of long-term alcohol consumption on them.

Wu said that chronic alcohol drinking killed most brain stem cells and reduced the production and development of new nerve cells.

The researchers found that the effects of repeated alcohol consumption differed across brain regions. The brain region most susceptible to the effects of alcohol was one of two brain regions where new brain cells are created in adults.

They also noted that female mice showed more severe deficits than males. The females displayed more severe intoxication behaviors and more greatly reduced the pool of stem cells in the subventricular zone.

Using this model, scientists expect to learn more about how alcohol interacts with brain stem cells, which will ultimately lead to a clearer understanding of how best to treat and cure alcoholism.

Other authors include UTMB's Erica McGrath, Junling Gao, Yong Fang Kuo, Tiffany Dunn, Moniqua Ray, Kelly Dineley, Kathryn Cunningham and Bhupendra Kaphalia.

http://bit.ly/2htyM7W

HPV vaccine also prevents uncommon childhood respiratory disease, study suggests

Recurrent respiratory papillomatosis is disappearing as a result of highly successful HPV vaccination program

The vaccine that protects against cancer-causing types of human papillomavirus (HPV) also prevents an uncommon but incurable childhood respiratory disease, according to a new study published in The Journal of Infectious Diseases. The findings suggest that the chronic and difficult-to-treat condition, recurrent respiratory papillomatosis, is disappearing in Australian children as a result of the nation's highly successful HPV vaccination program.

"This is a world-first finding of evidence that the HPV vaccine has actually prevented recurrent respiratory papillomatosis cases," said study author Julia M.L. Brotherton, MD, PhD, MPH, of the Victorian Cytology Service in Melbourne, Australia. "It's really exciting that we finally have a way to prevent this terrible disease. It adds to the list of strong reasons why you as a parent should choose to vaccinate your child."

The condition is thought to occur in children when HPV (specifically, HPV type 6 or 11) is spread from mother to child around the time of birth. In some children, the virus can cause wart-like, non-cancerous growths called papillomas to develop in the respiratory tract, eventually making it difficult to breathe.

The condition can be life-threatening, and repeated surgeries are usually required to keep the airway clear. Medical costs related to the disease in children total $123 million annually in the U.S., where approximately 800 children develop the condition each year, according to previously published estimates.

In the new study, Australian researchers report the initial results from a nationwide surveillance program created to monitor the disease, building on an existing program that monitors rare pediatric diseases using reports from clinicians. Seven cases of juvenile-onset recurrent respiratory papillomatosis were reported in 2012, the surveillance program's first full year.

The number of new cases reported annually declined over the next five years. Clinicians reported just one case in the entire country in 2016. None of the mothers of the children who were diagnosed with the disease from 2012-2016 had been vaccinated against HPV prior to their pregnancy.

Australia's publicly funded HPV immunization program provides the quadrivalent vaccine, which protects against four HPV types (types 6, 11, 16, and 18), through school-based programs. Nationwide, 86 percent of girls and 79 percent of boys 14-15 years of age have received the first dose of the vaccine, according to current estimates. Although rates have improved in the U.S., only 60 percent of teens 13-to-17-years-old had received one or more doses of the HPV

vaccine in 2016, the Centers for Disease Control and Prevention (CDC) recently reported. CDC currently recommends two doses of the vaccine for teens younger than 15 and three doses for those who start the vaccine series at ages 15 through 26.

In a related editorial commentary, Basil Donovan, MD, and Denton Callander, PhD, both of the Kirby Institute at the University of New South Wales in Sydney, Australia, and who were not involved in the study, called the downward trend in cases of recurrent respiratory papillomatosis in children encouraging. They also urged high-income countries with excellent HPV immunization rates to fully evaluate similar population-level impacts of their vaccination programs.

"National and individual vaccine hesitancy remains common," they wrote in their accompanying commentary, "and, unless these hesitant countries are persuaded by the ever-expanding benefits of quadrivalent HPV vaccination, millions of dollars in health spending along with countless unnecessary episodes of disease and death will occur in the coming decades."

Fast Facts

Recurrent respiratory papillomatosis is an uncommon but difficult-to-treat respiratory disease caused by certain types of human papillomavirus (HPV).

In children, the chronic disease is thought to occur when HPV is spread from mother to child around the time of birth, later causing recurring growths in the respiratory tract that usually require repeated surgeries to remove.

In Australia, where HPV vaccination rates are high, new cases of the disease in children declined between 2012 and 2016, suggesting an additional benefit from HPV immunization, which also protects against cancer-causing types of the virus.

Editor's note: The study was funded in part by Merck's Investigator Initiated Studies Program. The study authors' and editorial commentary authors' affiliations, acknowledgments, and disclosures of financial support and potential conflicts of interests, if any, are available in the study and the commentary, which are embargoed until 12:05 a.m. ET on Thursday, Nov. 9. For an embargoed copy of the study and the commentary, please contact Stephanie Goldina (312-558-1770, sgoldina@pcipr.com).

http://bit.ly/2zxlHS2

Mushrooms are full of antioxidants that may have antiaging potential

Mushrooms have higher quantities of two important anti-oxidants that may help with anti-aging treatments and strategies.

Mushrooms may contain unusually high amounts of two antioxidants that some scientists suggest could help fight aging and bolster health, according to a team of Penn State researchers.

In a study, researchers found that mushrooms have high amounts of the ergothioneine and glutathione, both important antioxidants, said Robert Beelman, professor emeritus of food science and director of the Penn State Center for Plant and Mushroom Products for Health. He added that the researchers also found that the amounts the two compounds varied greatly between mushroom species.

"What we found is that, without a doubt, mushrooms are highest dietary source of these two antioxidants taken together, and that some types are really packed with both of them," said Beelman.

Beelman said that when the body uses food to produce energy, it also causes oxidative stress because some free radicals are produced. Free radicals are oxygen atoms with unpaired electrons that cause damage to cells, proteins and even DNA as these highly reactive atoms travel through the body seeking to pair up with other electrons.

Replenishing antioxidants in the body, then, may help protect against this oxidative stress.

"There's a theory -- the free radical theory of aging -- that's been around for a long time that says when we oxidize our food to produce energy there's a number of free radicals that are produced that are side products of that action and many of these are quite toxic," said Beelman. "The body has mechanisms to control most of them, including ergothioneine and glutathione, but eventually enough accrue to cause damage, which has been associated with many of the diseases of aging, like cancer, coronary heart disease and Alzheimer's."

According to the researchers, who report their findings in a recent issue of Food Chemistry, the amounts of ergothioneine and glutathione in mushrooms vary by species with the porcini species, a wild variety, containing the highest amount of the two compounds among the 13 species tested.

"We found that the porcini has the highest, by far, of any we tested," said Beelman. "This species is really popular in Italy where searching for it has become a national pastime."

The more common mushroom types, like the white button, had less of the antioxidants, but had higher amounts than most other foods, Beelman said.

The amount of ergothioneine and glutathione also appear to be correlated in mushrooms, the researchers said. Mushrooms that are high in glutathione are also high in ergothioneine, for example.

Cooking mushrooms does not seem to significantly affect the compounds, Beelman said.

"Ergothioneine are very heat stable," said Beelman.

Beelman said that future research may look at any role that ergothioneine and glutathione have in decreasing the likelihood of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease.

"It's preliminary, but you can see that countries that have more ergothioneine in their diets, countries like France and Italy, also have lower incidences of neurodegenerative diseases, while people in countries like the United States, which has low amounts of ergothioneine in the diet, have a higher probability of diseases like Parkinson's Disease and Alzheimer's," said Beelman. "Now, whether that's just a correlation or causative, we don't know. But, it's something to look into, especially because the difference between the countries with low rates of neurodegenerative diseases is about 3 milligrams per day, which is about five button mushrooms each day."

Beelman worked with Michael D. Kalaras, postdoctoral assistant in food sciences; John P. Richie, professor of public health sciences and pharmacology; and Ana Calcagnotto, research assistant in public health sciences.

http://bit.ly/2zGf8dk

Smell test challenge suggests clinical benefit for some before development of Alzheimer's

Using a patient's sense of smell to treat Alzheimer's disease before it ever develops

New York, NY - Researchers at Columbia University Medical Center (CUMC) and the New York State Psychiatric Institute (NYSPI) may have discovered a way to use a patient's sense of smell to treat Alzheimer's disease before it ever develops. Having an impaired sense of smell is recognized as one of the early signs of cognitive decline, before the clinical onset of Alzheimer's disease. The researchers at CUMC and NYSPI have found a way to use that effect to determine if patients with mild cognitive impairment may respond to cholinesterase inhibitor drugs to treat Alzheimer's disease.

The findings were published online this week in the Journal of Alzheimer's Disease.

Cholinesterase inhibitors, such as donepezil, enhance cholinergic function by increasing the transmission of the neurotransmitter acetylcholine in the brain. Cholinergic function is impaired in individuals with Alzheimer's disease. Cholinesterase inhibitors, which block an enzyme that breaks down acetylcholine, have shown some effectiveness in improving the cognitive symptoms of Alzheimer's disease. However, they have not been proven effective as a treatment for individuals with mild cognitive impairment (MCI), a condition that markedly increases the risk of Alzheimer's disease.

"We know that cholinesterase inhibitors can make a difference for Alzheimer's patients, so we wanted to find out if we could identify patients at risk for Alzheimer's who might also benefit from this treatment," said D.P. Devanand, MBBS, MD, professor of psychiatry, scientist in the Gertrude H. Sergievsky Center at CUMC, and co-director of the Memory Disorders Clinic and the Late Life Depression Clinic at NYSPI. "Since odor identification tests have been shown to predict progression to Alzheimer's, we hypothesized that these tests

would also allow us to discover which patients with MCI would be more likely to improve with donepezil treatment."

In this year-long study, 37 participants with MCI underwent odor identification testing with the University of Pennsylvania Smell Identification Test (UPSIT). The test was administered before and after using an atropine nasal spray that blocks cholinergic transmission.

The patients were then treated with donepezil for 52 weeks, and were periodically reevaluated with the UPSIT and with memory and cognitive function tests. Those who had a greater decline in UPSIT scores, indicating greater cholinergic deficits in the brain, after using the anticholinergic nasal spray test saw greater cognitive improvement with donepezil.

In addition, short-term improvement in odor identification from baseline to eight weeks tended to predict longer-term cognitive improvement with donepezil treatment over one year.

"These results, particularly if replicated in larger populations, suggest that these simple inexpensive strategies have the potential to improve the selection of patients with mild cognitive impairment who are likely to benefit from treatment with cholinesterase inhibitors like donepezil," said Dr. Devanand.

The study is titled: "Change in Odor Identification Impairment is Associated with Improvement with Cholinesterase Inhibitor Treatment in Mild Cognitive Impairment." The other contributors are Cody Lentz (CUMC), Richard E. Chunga (NYSPI), Adam Ciarlegilio (CUMC, NYSPI), Jennifer M. Scodes (Columbia's Mailman School of Public Health), Howard Andrews (CUMC, Mailman), Peter W. Schofield (University of Newcastle, Callaghan, Australia), Yaakov Stern (CUMC), Edward D. Huey (CUMC), Karen Bell (CUMC), and Gregory H. Pelton (NYSPI, CUMC).

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Disclosures

Dr. Bell owns stock in Baxter. Dr. Devanand has received consulting fees for serving on Astellas' Scientific Advisory Board, Axovant's Educational Advisory Board, Eisai's Data Safety Monitoring Board, and Genentech's Scientific Advisory Board, and has received grants from Avanir. Dr. Stern has received consulting fees from Lilly USA, LLC, Takeda Global Research & Development Center, Inc, and Axovant Sciences, Inc. The other contributors report no financial or other conflicts of interest.

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Site of asteroid impact changed the history of life

An asteroid, also known as the Chicxulub Impactor, hit Earth some 66 million years ago, causing a crater 180 km wide.

The impact of the asteroid heated organic matter in rocks and ejected it into the atmosphere, forming soot in the stratosphere.

Soot is a strong, light-absorbing aerosol that caused global climate changes that triggered the mass extinction of dinosaurs, ammonites, and other animals, and led to the macroevolution of mammals and the appearance of humans.

Based on results of a new study, the researchers say that the probability of the mass-extinction occurring was only 13 percent. This is because the catastrophic chain of events could only have occurred if the asteroid had hit the hydrocarbon-rich areas occupying approximately 13 percent of the Earth's surface.

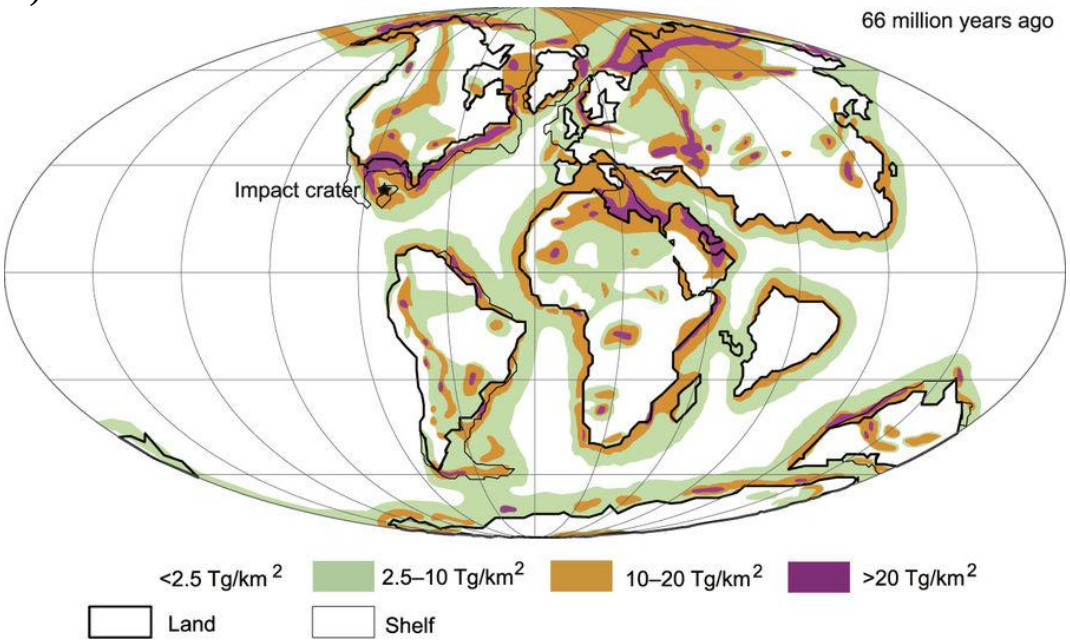
Led by Tohoku University Professor Kunio Kaiho, the researchers came by their hypothesis by calculating the amount of soot in the stratosphere and estimating climate changes caused by soot using a global climate model developed at the Meteorological Research Institute. The results are significant because they explain the pattern of extinction and survival.

During the study, Kaiho thought that the amount of soot and temperature anomaly might have been affected by the amount of sedimentary organic-matter. So, he analyzed the amount of sedimentary organic-matter in the Earth to obtain readings of temperature anomaly caused by soot in the stratosphere.

Naga Oshima of the Meteorological Research Institute conducted the global climate model calculations to obtain temperature anomalies caused by various amounts of soot injected into the stratosphere.

Kaiho clarified the relationship between the findings and concluded that the significant cooling and mass-extinction event could have only have occurred if the asteroid had hit hydrocarbon-rich areas occupying

approximately 13 percent of the Earth's surface (orange areas in Fig. 4).



Global map showing the amount of organic matter in sedimentary rocks ejected if the Chicxulub asteroid hit various locations at the end of the Cretaceous. Shaded areas denote the following burned organic carbon weights in each area burned by the asteroid impact: white: <22,000 Tg; olive: 22,000–89,000 Tg; orange: 89,000–220,000 Tg; and magenta: 220,000–890,000 Tg. These areas correspond to 0–4 °C, 4–8 °C, 8–11 °C, and ≥11 °C cooling (global mean surface air temperature anomalies) and 0–6 °C, 6–13 °C, 13–17 °C, and ≥17 °C cooling on land by soot only, respectively, when the asteroid hit each area (Table 3). Mass extinction could have been caused by 8–11 °C or more cooling[1] when the asteroid hit an orange or magenta area, which occupied approximately 13% of the Earth's surface. The map is based on Courtillot et al.[53]; thin lines indicate continental crust shelf edges. **Kunio Kaiho**

If the asteroid had hit a low-medium hydrocarbon area on Earth (occupying approximately 87 percent of the Earth's surface), mass extinction could not have occurred and the Mesozoic biota could have persisted beyond the Cretaceous/Paleogene boundary. The site of the asteroid impact, therefore, changed the history of life on Earth.

According to the study, soot from hydrocarbon-rich areas caused global cooling of 8-11°C and cooling on land of 13-17°C. It also caused a decrease in precipitation by approximately 70-85 percent on land and a decrease of approximately 5-7°C in seawater temperature at a 50-m water depth, leading to mass extinction of life forms including dinosaurs and ammonites.

At the time, these hydrocarbon-rich areas were marine coastal margins, where the productivity of marine algae was generally high and sedimentary rocks were thickly deposited. Therefore, these areas contained a high amount of organic matter, part of which became soot from the heat of the asteroid's impact.

Thus, the researchers concluded that the Chicxulub impact occurred in a hydrocarbon-rich area and is a rare case of mass extinction being caused at such an impact site.

Kaiho and Oshima are doing further studies to clarify the frequency of all the cooling events by impacts. Kaiho's team is analyzing climate change caused by large volcanic eruptions that may have contributed to other mass extinctions. It is hoped that the results will lead to further understanding of the processes behind those mass extinctions.

http://bit.ly/2zFMXeL

Brain chemistry study shows chronic fatigue syndrome, Gulf War illness as unique disorders

Researchers at Georgetown University Medical Center have found distinct molecular signatures in two brain disorders long thought to be psychological in origin -- chronic fatigue syndrome (CFS) and Gulf War Illness (GWI).

WASHINGTON -- In addition, the work supports a previous observation by GUMC investigators of two variants of GWI. The disorders share commonalities, such as pain, fatigue, cognitive dysfunction and exhaustion after exercise.

Their study, published in Scientific Reports, lays groundwork needed to understand these disorders in order to diagnosis and treat them effectively, says senior investigator, James N. Baraniuk, MD,

professor of medicine at Georgetown University School of Medicine. Narayan Shivapurkar, PhD, assistant professor of oncology at the medical school worked with Baraniuk on the research.

The changes in brain chemistry -- observed in levels of miRNAs that turn protein production on or off -- were seen 24 hours after riding a stationary bike for 25 minutes.

"We clearly see three different patterns in the brain's production of these molecules in the CFS group and the two GWI phenotypes," says Baraniuk. "This news will be well received by patients who suffer from these disorders who are misdiagnosed and instead may be treated for depression or other mental disorders."

Chronic fatigue syndrome affects between 836,000 and 2.5 million Americans, according to a National Academy of Medicine report. The disorder was thought to be psychosomatic until a 2015 review of 9,000 articles over 64 years of research pointed to unspecified biological causes. Still, no definitive diagnosis or treatment is available.

Gulf War Illness has developed in more than one-fourth of the 697,000 veterans deployed to the 1990-1991 Persian Gulf War, Baraniuk and his colleagues have reported in earlier work.

Gulf War veterans were exposed to combinations of nerve agents, pesticides and other toxic chemicals that may have triggered the chronic pain, cognitive, gastrointestinal and other problems, Baraniuk says. Although the mechanisms remain unknown, the study provides significant insights into brain chemistry that can now be investigated.

This study focused on spinal fluid of CFS, GWI and control subjects who agreed to have a lumbar puncture. Spinal taps before exercise showed miRNA levels were the same in all participants. In contrast, miRNA levels in spinal fluid were significantly different after exercise. The CFS, control and two subtypes of GWI groups had distinct patterns of change. For example, CFS subjects who exercised had reduced levels of 12 different mRNAs, compared to those who did not exercise.

The miRNA changes in the two GWI subtypes add to other differences caused by exercise. One subgroup developed jumps in heart rate of over 30 beats when standing up that lasted for two to three days after exercise. Magnetic resonance imaging showed they had smaller brainstems in regions that control heart rate, and did not activate their brains when doing a cognitive task. In contrast, the other subgroup did not have any heart rate or brainstem changes, but did recruit additional brain regions to complete a memory test. The two groups were as different from each other as they were from the control group.

Finding two distinct pathophysiological miRNA brain patterns in patients reporting Gulf War disease "adds another layer of evidence to support neuropathology in the two different manifestations of Gulf War disease," he says. Baraniuk adds that miRNA levels in these disorders were different from the ones that are altered in depression, fibromyalgia, and Alzheimer's disease, further suggesting CFS and GWI are distinct diseases.

The study was supported by funding from The Sergeant Sullivan Center, Dr. Barbara Cottone, Dean Clarke Bridge Prize, Department of Defense Congressionally Directed Medical Research Program (CDMRP) W81XWH-15-1-0679, and National Institute of Neurological Diseases and Stroke R21NS088138 and RO1NS085131.

Baraniuk and Shivapurkar are named as inventors on a patent application that has been filed by Georgetown University related to the technology described.

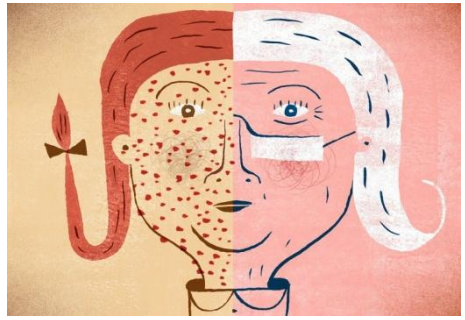
http://nyti.ms/2jmzqwY

No Excuses, People: Get the New Shingles Vaccine

Prominent experts sound positively excited about a newly approved shingles vaccine

Paula Span

Medical researchers and government health policymakers, a cautious lot, normally take pains to keep expectations modest when they're discussing some new finding or treatment.



David Plunkert

They warn about studies' limitations. They point out what isn't known. They emphasize that correlation doesn't mean causation.

So it's startling to hear prominent experts sound positively excited about a new shingles vaccine that an advisory committee to the Centers for Disease Control and Prevention approved last month.

"This really is a sea change," said Dr. Rafael Harpaz, a veteran shingles researcher at the C.D.C.

Dr. William Schaffner, preventive disease specialist at the Vanderbilt University School of Medicine, said, "This vaccine has spectacular initial protection rates in every age group. The immune system of a 70- or 80-year-old responds as if the person were only 25 or 30."

"This really looks to be a breakthrough in vaccinating older adults," agreed Dr. Jeffrey Cohen, a physician and researcher at the National Institutes of Health.

What's causing the enthusiasm: Shingrix, which the pharmaceutical firm GlaxoSmithKline intends to begin shipping this month. Large international trials have shown that the vaccine prevents more than 90 percent of shingles cases, even at older ages.

The currently available shingles vaccine, called Zostavax, only prevents about half of shingles cases in those over age 60 and has demonstrated far less effectiveness among elderly patients.

Yet those are the people most at risk for this blistering disease, with its often intense pain, its threat to vision and the associated nerve pain that sometimes last months, even years, after the initial rash fades.

Almost all older Americans harbor the varicella zoster virus that causes shingles; they acquired it with childhood chickenpox, whether they knew they had the disease or not.

The virus stays dormant until, for unknown reasons, it erupts decades later. The risk rises sharply after age 50.

Shingles is hardly a minor menace. "A million cases occur in the United States each and every year," Dr. Schaffner said. "If you're fortunate enough to reach your 80th birthday, you stand a one-in-three to one-in-two chance of shingles."

Preventing the great majority of these cases — along with the risk of lingering and debilitating nerve pain, called postherpetic neuralgia — would represent a major advance in public health.

So while the old vaccine will remain on the market, the C.D.C. committee voted to make Shingrix the preferred vaccine and recommended it for all adults over age 50 — a group younger by a decade than those earlier encouraged to get Zostavax.

The committee also recommended Shingrix for adults who've previously gotten Zostavax, since a smaller study in people over age 65 demonstrated effectiveness and safety in those already vaccinated.

The Food and Drug Administration approved Shingrix last month.

Once the C.D.C.'s director endorses the committee's recommendations, and the agency publishes them, insurers — including Medicare and Medicaid — will start covering the vaccine.

"By early 2018, it should be broadly available to consumers in the U.S.," said Dr. Thomas Breuer, chief medical officer of GSK Vaccines. (Canada has also approved Shingrix; it awaits approval in Australia, Japan and Europe.)

What makes the new vaccine so promising, especially for older adults?

* It provides better protection against shingles from the start. Though Zostavax, introduced in 2006, can reduce shingles cases by about half (and postherpetic neuralgia by two-thirds), that overall rate conceals big differences by age.

That vaccine's effectiveness drops from 64 percent for people in their 60s to 38 percent among those over age 70, and falls still lower for people in their 80s.

But the new vaccine protects nearly as well in older groups as in the middle-aged. Shingrix racked up a 97 percent effectiveness rate in adults over age 50 and, in a separate study of people over age 70, prevented 90 percent of shingles in those 70 to well past age 80.

"In groups such as the elderly, who often don't maintain vigorous responses to vaccines, this represents extremely strong disease

protection," said Dr. Kathleen Dooling, an epidemiologist at the C.D.C.

* Shingrix's protection appears to last longer. Among seniors, the effectiveness of Zostavax wanes with disappointing speed. "After 11 years, the protection was close to zero," Dr. Harpaz said.

Regulators don't yet have 11 years of data on Shingrix, but in some samples, it remained effective for six years or longer, according to GSK. That should greatly reduce the incidence of postherpetic neuralgia, too, assuming the 42 million people in their 50s start getting vaccinated.

* The new vaccine may protect people with compromised immune systems.

A substantial number of older Americans have suppressed immunity because they're undergoing chemotherapy or transplants, have H.I.V. or take steroids. For them, the previous vaccine was off-limits because it was made with a weakened live virus.

Yet immune suppression itself leaves the people vulnerable to shingles. Shingrix, a recombinant vaccine made from a glycoprotein and a combination of immunity boosters called adjuvants, doesn't pose the same danger.

The C.D.C. committee held off on recommending Shingrix for the immunocompromised, because GSK is still running trials with these patients. But since the F.D.A. did not declare Shingrix contraindicated for them when approving it, they can get the vaccine once it's available.

Public health advocates do foresee a couple of potential problems.

First, Shingrix requires two doses, administered at least two months apart. Prodding the older population to get a single shot has proved tough: barely 31 percent of those over age 60 have been vaccinated against shingles. How much harder will it be to persuade people to get two Shingrix injections?

Further, "it tends to be a bit of an ouch-y vaccine," Dr. Schaffner cautioned.

In studies, most older recipients said they'd experienced pain, redness or swelling in their upper arms for a day or two after the shot, and 8.5 percent of those over age 70 deemed those symptoms uncomfortable enough to interfere with normal activities.

About half of those over age 70 reported more systemic side effects like fatigue, fever or aching joints, lasting one to two days. Physicians and pharmacists should prepare people for such reactions, Dr. Schaffner said.

"If people anticipate it, they'll cope with it better. They'll take a couple of Tylenol" — and not worry that something is seriously wrong.

They may feel pocketbook pain, too. Zostavax is the most expensive adult vaccine, and at $140 for each dose (plus the cost of administering the injection), Shingrix will be pricier still.

The 50- to 65-year-old cohort, many of whom have coverage under employee health plans, may not find that much of a barrier. At older ages, cost matters more.

Medicare will cover Shingrix under Part D (like its predecessor), not under Part B like the flu vaccine. That complicates reimbursement for those seeking vaccination in doctors' offices, so Medicare patients will probably find it simpler to head for a pharmacy.

But not all Medicare recipients have Part D, and those that do could face co-payments.

Still, it's no contest: The hazards of shingles and its complications dwarf any problems yet reported with Shingrix.

"Compared to shingles, a little arm pain for a day or so is a small price to pay," Dr. Schaffner said. "If you know people who've had this illness, you'll be first in line for this vaccine."