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It may be possible to restore memory function in Alzheimer's, preclinical study finds

UB researchers corrected synaptic dysfunctions in the brain involved in memory loss, using an epigenetic approach

BUFFALO, N.Y. -- Research published today (Jan. 22) in the journal Brain reveals a new approach to Alzheimer's disease (AD) that may eventually make it possible to reverse memory loss, a hallmark of the disease in its late stages.

The team, led by University at Buffalo scientists, found that by focusing on gene changes caused by influences other than DNA sequences -- called epigenetics -- it was possible to reverse memory decline in an animal model of AD.

"In this paper, we have not only identified the epigenetic factors that contribute to the memory loss, we also found ways to temporarily reverse them in an animal model of AD," said senior author Zhen Yan, PhD, a SUNY Distinguished Professor in the Department of Physiology and Biophysics in the Jacobs School of Medicine and Biomedical Sciences at UB.

The research was conducted on mouse models carrying gene mutations for familial AD -- where more than one member of a family has the disease -- and on post-mortem brain tissues from AD patients.

AD is linked to epigenetic abnormality

AD results from both genetic and environmental risk factors, such as aging, which combine to result in epigenetic changes, leading to gene expression changes, but little is known about how that occurs.

The epigenetic changes in AD happen primarily in the later stages, when patients are unable to retain recently learned information and exhibit the most dramatic cognitive decline, Yan said. A key reason for the cognitive decline is the loss of glutamate receptors, which are critical to learning and short-term memory.

"We found that in Alzheimer's disease, many subunits of glutamate receptors in the frontal cortex are downregulated, disrupting the excitatory signals, which impairs working memory," Yan said.

The researchers found that the loss of glutamate receptors is the result of an epigenetic process known as repressive histone modification, which is elevated in AD. They saw this both in the animal models they studied and in post-mortem tissue of AD patients.

Yan explained that histone modifiers change the structure of chromatin, which controls how genetic material gains access to a cell's transcriptional machinery.

"This AD-linked abnormal histone modification is what represses gene expression, diminishing glutamate receptors, which leads to loss of synaptic function and memory deficits," Yan said.

Potential drug targets

Understanding that process has revealed potential drug targets, she said, since repressive histone modification is controlled or catalyzed by enzymes.

"Our study not only reveals the correlation between epigenetic changes and AD, we also found we can correct the cognitive dysfunction by targeting the epigenetic enzymes to restore glutamate receptors," Yan said.

The AD animals were injected three times with compounds designed to inhibit the enzyme that controls repressive histone modification.

"When we gave the AD animals this enzyme inhibitor, we saw the rescue of cognitive function confirmed through evaluations of recognition memory, spatial memory and working memory. We were quite surprised to see such dramatic cognitive improvement," Yan said. "At the same time, we saw the recovery of glutamate receptor expression and function in the frontal cortex."

The improvements lasted for one week; future studies will focus on developing compounds that penetrate the brain more effectively and are thus longer-lasting.

Epigenetic advantage

Brain disorders, such as AD, are often polygenetic diseases, Yan explained, where many genes are involved and each gene has a modest impact. An epigenetic approach is advantageous, she said, because epigenetic processes control not just one gene but many genes.

"An epigenetic approach can correct a network of genes, which will collectively restore cells to their normal state and restore the complex brain function," she explained.

"We have provided evidence showing that abnormal epigenetic regulation of glutamate receptor expression and function did contribute to cognitive decline in Alzheimer's disease," Yan concluded. "If many of the dysregulated genes in AD are normalized by targeting specific epigenetic enzymes, it will be possible to restore cognitive function and behavior."

The study was funded by a $2 million National Institutes of Health grant focused on novel treatment strategies for AD.

Other UB co-authors are Yan Zheng; Aiyi Liu; Zi-Jun Wang, PhD; Qing Cao, PhD; Lin Lin; Kaijie Ma; Freddy Zhang; Jing Wei, PhD; Emmanuel Matas, PhD and Jia Cheng, PhD. Additional co-authors are Guo-Jun Chen of Chongqing Medical University, PhD, and Xiaomin Wang, MD, PhD., of the Beijing Institute for Brain Disorders, Capital Medical University.

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Blood test may provide early diagnosis of Alzheimer's

Detecting a protein leaking from dying neurons could reveal signs of neurodegeneration before they become obvious.

Ben Lewis reports.

A simple blood test could detect the early danger signs of Alzheimer's disease long before confusion and memory loss set in, a new study suggests.

Researchers from Europe, the US and Australia, led by the German Centre for Neurodegenerative Diseases (DZNE) in Tübingen, have discovered a link between neurofilament light chain, a structural protein that forms part of the internal skeleton of neurons, and the later onset of the disease.

Writing in a paper published in *Nature Medicine*, they report using blood tests to detect the levels of the neurofilament light chain, allowing them to predict the development of Alzheimer's more than a decade before patients began to show cognitive impairments.

Long before outward symptoms of Alzheimer's disease develop, the brain starts changing and neurons slowly degrade. When those neurons are damaged or dying, proteins leak out into the cerebrospinal fluid that surrounds the brain, and from there into the bloodstream.

"Normally such proteins are rapidly degraded in the blood and are therefore not very suitable as markers for a neurodegenerative disease," says DZNE's Mathias Jucker, who led the research.

"An exception, however, is a small piece of so-called neurofilament that is surprisingly resistant to this degradation."

The researchers studied more than 400 people participating in the Dominantly Inherited Alzheimer's Network (DIAN) study, a group of families with genetic variations that lead to Alzheimer's in middle age.

Of the participants used to develop the blood test, 247 carried an early-onset genetic variant, and were compared with 162 of their unaffected relatives. The genetic variation all but guarantees the carrier will develop symptoms of dementia.

Those carrying the faulty gene variant had neurofilament light chain protein levels which were higher at baseline and rose over time. In contrast, protein levels were low and largely steady in people with the healthy form of the gene.

The rising levels of neurofilament light chain in the blood were also confirmed to predict cognitive decline. Thirty-nine of the patients revisited the clinic around two years after their last visit, and underwent brain scans and two cognitive tests.

Those whose blood protein levels had risen rapidly were most likely to show signs of brain degeneration and diminished cognitive abilities on their second visit.

"It is not the absolute neurofilament concentration, but its temporal evolution, which is meaningful and allows predictions about the future progression of the disease," says Jucker. "We were able to predict loss of brain mass and cognitive changes that actually occurred two years later."

Those changes in the blood became noticeable up to 16 years before the calculated onset of dementia symptoms.

It is hoped, however, that the test could help diagnose those at risk of a range of neurodegenerative conditions.

"We validated it in people with Alzheimer's disease because we know their brains undergo lots of neurodegeneration, but this marker isn't specific for Alzheimer's. High levels could be a sign of many different neurological diseases and injuries," says Brian Gordon from Washington University in St. Louis, US, who also worked on the research. While a commercial kit is available to test for protein levels in the blood, it has not been approved for use to diagnose or predict an individual's risk of brain damage.

Before that approval can be given, the researchers will need to establish the clinical relevance of protein levels in the blood – essentially, how much protein is too much. Another question also remains around the rate of change of protein levels, and how quickly protein levels can rise before it becomes a cause for concern.

http://bit.ly/2sHBZme

Famous freak wave recreated in laboratory mirrors Hokusai's 'Great Wave'

The Draupner wave was one of the first confirmed observations of a freak wave in the ocean; it was observed on the 1st of January 1995 in the North Sea by measurements made on the Draupner Oil Platform.

Freak waves are unexpectedly large in comparison to surrounding waves. They are difficult to predict, often appearing suddenly without warning, and are commonly attributed as probable causes for maritime catastrophes such as the sinking of large ships.

Figure 4. ***Still images of the free surface taken at intervals of 100ms (0.6s at field scale), showing the most successful reconstruction of the Draupner wave for $\Delta\theta$=120°. Breaking is observed in from of an upward projected jet, which does not limit wave crest height under these crossing-sea conditions.***

The team of researchers set out to reproduce the Draupner wave under laboratory conditions to understand how this freak wave was formed in the ocean. They successfully achieved this reconstruction by creating the wave using two smaller wave groups and varying the crossing angle - the angle at which the two groups travel.

Dr Mark McAllister at the University of Oxford's Department of Engineering Science said: 'The measurement of the Draupner wave in 1995 was a seminal observation initiating many years of research into the physics of freak waves and shifting their standing from mere folklore to a credible real-world phenomenon. By recreating the Draupner wave in the lab we have moved one step closer to understanding the potential mechanisms of this phenomenon.'

It was the crossing angle between the two smaller groups that proved critical to the successful reconstruction. The researchers found it was only possible to reproduce the freak wave when the crossing angle between the two groups was approximately 120 degrees.

When waves are not crossing, wave breaking limits the height that a wave can achieve. However, when waves cross at large angles, wave breaking behaviour changes and no longer limits the height a wave can achieve in the same manner.

Prof Ton van den Bremer at the University of Oxford said: 'Not only does this laboratory observation shed light on how the famous Draupner wave may have occurred, it also highlights the nature and significance of wave breaking in crossing sea conditions. The latter of these two findings has broad implications, illustrating previously unobserved wave breaking behaviour, which differs significantly from current state-of-the-art understanding of ocean wave breaking.'

To the researchers' amazement, the wave they created bore an uncanny resemblance to 'The Great Wave off Kanagawa' - also known as 'The Great Wave' - a woodblock print published in the early 1800s by the Japanese artist Katsushika Hokusai. Hokusai's image depicts an enormous wave threatening three fishing boats and towers over Mount Fuji which appears in the background. Hokusai's wave is believed to depict a freak, or 'rogue', wave.

The laboratory-created freak wave also bears strong resemblances with photographs of freak waves in the ocean. The researchers hope that this study will lay the groundwork for being able to predict these potentially catastrophic and hugely damaging waves that occur suddenly in the ocean without warning.

Experiments were carried out in the FloWave Ocean Energy Research facility at the University Of Edinburgh.

Dr Sam Draycott at the University of Edinburgh said: 'The FloWave Ocean Energy Research Facility is a circular combined wave-current basin with wavemakers fitted around the entire circumference. This unique capability enables waves to be generated from any direction, which has allowed us to experimentally recreate the complex directional wave conditions we believe to be associated with the Draupner wave event.'

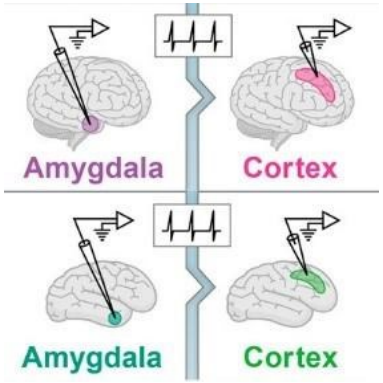
The research was led by Dr Mark McAllister and Prof Ton van den Bremer at the University of Oxford, in collaboration with Dr Sam Draycott at the University of Edinburgh. This project builds upon work previously carried out at the University of Oxford by Professors Thomas Adcock and Paul Taylor.

http://bit.ly/2WljEJo

All too human

The price we pay for our advanced brains may be a greater tendency to disorders

Prof. Rony Paz of the Weizmann Institute of Science suggests that our brains are like modern washing machines - evolved to have the latest sophisticated programming, but more vulnerable to breakdown and prone to develop costly disorders. He and a group of researchers recently conducted experiments comparing the efficiency of the neural code in non-human and human primates, and found that as the neural code gets more efficient, the robustness that prevents errors is reduced. Their findings, which recently appeared in Cell, may help to explain why disorders as ADHD, anxiety, depression, PTSD and even autism are common in humans.



The tradeoff in human brains (top) and monkey brains (bottom). The more evolutionarily advanced, the more efficient and the less robust each area proved to be. **Weizmann Institute of Science**

Paz, in the Institute's Neurobiology Department, says that anatomical differences between humans and other primates have been described - particularly our large pre-frontal cortex and its extended number of neurons. But differences in the neural code - the "software," in contrast with the "hardware" (the physical structure) - have not been explored.

Raviv Pryluk, a research student in Paz's group, devised a way to test and compare the efficiency of the neural code in several regions of the brain. "We defined efficient communication as that which uses the least amount of energy to transmit the maximal information - to

pass on as complicated message as possible with the fewest 'words'," says Pryluk.

The researchers recorded the electric activity of single neurons both in humans and in macaque monkeys in two regions: the pre-frontal cortex, where higher functions like decision making and rational thinking occur, and the amygdala, a more evolutionarily ancient region that is responsible for the "fight or flight" basic survival functions, as well as emotions. Paz and his group worked in collaboration with Prof. Itzhak Fried of Sourasky Medical Center in Tel Aviv and UCLA Medical School in Los Angeles. Patients with pharmacologically intractable epilepsy come to Fried to have electrodes implanted for diagnostic purposes, and these provide a rare opportunity to record the electric activity of single neurons in the human brain. Also participating in this research were Dr. Hagar Gelbard-Sagiv of Tel Aviv University and Dr. Yoav Kfir, at that time a research student in Paz's group.

The findings of this research provided support for the "washing machine" theory of brain evolution: The neural code in the "more evolved" pre-frontal cortex is more efficient than the amygdala, both in humans and monkeys. And the neural code of both areas in the human brain was more efficient than its monkey counterpart. But the higher the efficiency of a particular neural code, the less it was robust to errors. Paz likens the amygdala to the washing machine drum: "It's not highly sophisticated, but it is less likely to fail - which is important to animals' survival," he says, adding: "The lower resistance of the human amygdala to errors may play a role in exaggerated survival-like responses in inappropriate contexts, such as those we see in PTSD and other anxiety disorders."

Pryluk: "Evolution works with trade-offs. There may be a zero-sum game between efficiency and robustness; and our complex, multidimensional brains have gained one at the price of the other."

Fried: "Comparing single-cell recordings from human and monkey brains is a large step forward toward answering the question of what makes the human brain unique." Paz adds: "Why, on the one hand, do humans have such superior learning, cognitive and adaptive abilities and, on the other, this tendency to anxiety, depression and other mental diseases? We have shown that these may be two sides of the same coin."

Prof. Rony Paz's research is supported by the Adelis Foundation; the Irving and Dorothy Rom Family Discovery Endowment Fund; the Irving B. Harris Fund for New Directions in Brain Research; the Bernard and Norton Wolf Family Foundation; the Leff Family; the Oster Family Foundation; Mr. and Mrs. Gary Clayman; Rosanne Cohen; the estate of Toby Bieber; and the European Research Council.

http://bit.ly/2UjlIjb

Test for esophageal cancer could save millions of lives

A tiny capsule, a string and a 2-centimeter sponge are the future of screening for deadly disease

Cancer of the esophagus claims more than 400,000 lives around the world each year. With no efficient, reliable method of screening for the disease, by the time symptoms become apparent, it's often too late to save the patient.

A Johns Hopkins researcher who has devoted his career to the detection and prevention of esophageal cancer today published a paper in the journal *Clinical Cancer Research* that he says could finally result in simple and inexpensive screening for the deadly disease.

The EsophaCap is packed into a gelatin capsule that dissolves in a patient's stomach. **Stephen Meltzer, M.D.**

In the article, gastroenterologist Stephen Meltzer, a professor of medicine and oncology at the Johns Hopkins University School of Medicine, along with a team of researchers, clinicians and biomedical engineers describe a test - the "EsophaCap" - that uses

specific genetic biomarkers to detect dangerous changes in the cells that line the inside of the esophagus.

Previous studies have demonstrated Meltzer's biomarkers' ability to detect a condition called Barrett's esophagus, which causes the body to replace the tissue that lines the organ with cells that can turn cancerous.

But large-scale methods to deploy those biomarkers as a screening tool have been elusive until now.

The principle behind the EsophaCap is simple, says Meltzer. The patient swallows a small capsule that has a long string attached to it. After the capsule makes its way down the esophagus and into the stomach - a process that takes only a minute or so - the gelatin coating on the capsule begins to dissolve.

From that capsule emerges a 2-centimeter polyurethane sponge, still attached to the string, much of which still hangs from the patient's mouth.

The screener gently pulls the string and the sponge begins its return journey, out of the stomach, into the esophagus and, finally, out of the patient's mouth.

As it makes its way up, the sponge comes into contact with the entire length and breadth of the esophagus, collecting genetic material all along the way. Then, as the sponge nears the top, the screener gives a final gentle tug, popping the sponge past the organ's upper sphincter muscle. The sponge emerges loaded with genetic material that holds the key to the patient's esophageal health.

The sponge is then sent to a company that performs simple genetic tests on the material to determine the patient's risk for esophageal cancer.

"Early detection is the whole ballgame when it comes to esophageal cancer," Meltzer says. "Patients have a much better chance to treat it - or even prevent it - if they know their risk. We believe this little sponge can bring easy and inexpensive screening to people around the world."

With nearly half a million new cases a year, esophageal cancer is the eighth most-common cancer worldwide, with the highest rates in parts of Africa and Asia.

In 2016, the United States saw nearly 17,000 new cases diagnosed and about 16,000 deaths from cancer of the esophagus. Those numbers have increased sharply in recent years.

The five-year survival rate for people with cancer confined to the esophagus is 43 percent. When it spreads to nearby tissues or organs, that rate falls to 23 percent. And esophageal cancer that spreads to distant parts of the body offers a five-year survival rate of only 5 percent.

In previous research, Meltzer has performed rigorous testing on the set of genetic biomarkers he uses to diagnose Barrett's esophagus. The gene combination of p16, NELL1, AKAP12 and TAC1 has yielded a sensitivity of nearly 92 percent and has offered reliable diagnoses.

Medicine has never had routine screening methods for the disease. Both endoscopy and biopsy are less-than-ideal, since they're inexact, expensive and rely on random tissue samples, rather than material from the whole esophagus lining.

"It's actually possible to miss early cancerous cells using endoscopy with biopsy and most patients with Barrett's don't ever undergo endoscopy," says Meltzer. "Right now, we're confident that we have the tools to identify this type of cancer. But we previously lacked a way to collect enough genetic material to confidently determine a patient's diagnosis. We believe that EsophaCap now provides a solution to this serious problem."

Meltzer administered the EsophaCap test to 94 people over the course of the study. Eighty-five percent of subjects were able to swallow the capsule, with 100 percent successful sponge retrieval.

Endoscopic evaluation of the patients after EsophaCap administration, Meltzer reported, showed no evidence of bleeding, pain, trauma or other adverse reactions to the test.

In the journal article, Meltzer reports that of the patients able to swallow the capsule, nearly half would be diagnosed with Barrett's esophagus - a rate far higher than that of the general U.S. population. He notes that most patients enrolled in the study were being treated for gastrointestinal symptoms. "That may explain why we saw a rate of Barrett's esophagus that was higher than in the general population," he says.

Additional authors of the study are Zhixiong Wang, Ph.D; Swetha Kambhampati, M.D.; Yulan Cheng, M.D.; Ke Ma, M.D.; Cem Simsek, M.D.; Alan H. Tieu, M.D.; John M. Abraham, Ph.D; Xi Liu, Ph.D; Vishnu Prasath, M.D.; Mark Duncan, M.D.; Alejandro Stark, B.S.; Alexander Trick, B.S.; Hua-Ling Tsai, Ph.D; Hao Wang, Ph.D.; Yulong He, Ph.D; Mouen A. Khashab, M.D.; Saowanee Ngamruengphong, M.D.; Eun Ji Shin, M.D. and Tza-Huei Wang, Ph.D.

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All the article's authors state that there are no conflicts of interest.

http://bit.ly/2CHaBcx

Human mutation rate has slowed recently

Researchers discovered that the human mutation rate is significantly slower than for our closest primate relatives.

This may be important for estimates of when the common ancestor for humans and chimpanzees lived

Aarhus University

Researchers from Aarhus University, Denmark, and Copenhagen Zoo have discovered that the human mutation rate is significantly slower than for our closest primate relatives. The new knowledge may be important for estimates of when the common ancestor for humans and chimpanzees lived - and for conservation of large primates in the wild.

Over the past million years or so, the human mutation rate has been slowing down so that significantly fewer new mutations now occur in humans per year than in our closest primate relatives. This is the conclusion of researchers from Aarhus University, Denmark, and Copenhagen Zoo in a new study in which they have found new mutations in chimpanzees, gorillas and orangutans, and compared these with corresponding studies in humans.

Using whole-genome sequencing of families, it is possible to discover new mutations by finding genetic variants that are only present in the child and not in the parents.

"Over the past six years, several large studies have done this for humans, so we have extensive knowledge about the number of new mutations that occur in humans every year. Until now, however, there have not been any good estimates of mutation rates in our closest primate relatives," says Søren Besenbacher from Aarhus University.

The study has looked at ten families with father, mother and offspring: seven chimpanzee-families, two gorilla families and one orangutan family. In all the families, researchers found more mutations than would be expected on the basis of the number of mutations that would typically arise in human families with parents of similar age. This means that the annual mutation rate is now about one-third lower in humans than in apes.

Time of speciation fits better with fossil evidence

The higher rates in apes have an impact on the length of time estimated to have passed since the common ancestor of humans and chimpanzees lived. This is because a higher mutation rate means that the number of genetic differences between humans and chimpanzees will accumulate over a shorter period.

If the new mutation rates for apes are applied, the researchers estimate that the species formation (speciation) that separated humans from chimpanzees took place around 6.6 million years ago. If the mutation rate for humans is applied, speciation should have been around 10 million years ago.

"The times of speciation we can now calculate on the basis of the new rate fit in much better with the speciation times we would expect from the dated fossils of human ancestors that we know of," explains Mikkel Heide Schierup from Aarhus University.

The reduction in the human mutation rate demonstrated in the study could also mean that we have to move our estimate for the split between Neanderthals and humans closer to the present.

Furthermore, the results could have an impact on conservation of the great apes. Christina Hvilsom from Copenhagen Zoo explains:

"All species of great apes are endangered in the wild. With more accurate dating of how populations have changed in relation to climate over time, we can get a picture of how species could cope with future climate change."

The study "Direct estimation of mutations in great apes reconciles phylogenetic dating" has been published in Nature Ecology and Evolution and is a collaboration between researchers from Aarhus University, Copenhagen Zoo and Universitat Pompeu Fabra in Barcelona.

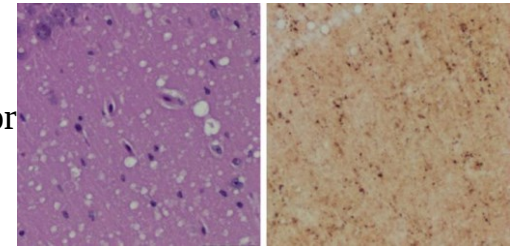
http://bit.ly/2CGn406

New skin test detects prion infection before symptoms appear

Proof-of-concept study demonstrates test's preclinical utility

Prions can infect both humans and animals, causing Creutzfeldt-Jakob disease (CJD) in humans, mad cow disease in cattle, and chronic wasting disease in elk and deer. The infectious, misfolded protein particles often go undetected as they destroy brain tissue, causing memory loss, mobility issues, and ultimately death. Preclinical detection of prions has proven difficult, but new research suggests skin samples hold early signs of prion disease that precede neurologic symptoms.

"Currently a definitive diagnosis of Creutzfeldt-Jakob disease is dependent on the examination of diseased brain tissue obtained at biopsy or autopsy. It has been impossible to detect at the early preclinical stage," said Wenquan Zou, MD, PhD, associate professor of pathology at Case Western Reserve University School of Medicine.



(Left) Staining shows spongiform degeneration. (Right) Staining shows intense misfolded prion protein. **Case Western Reserve University School of Medicine**

In a ground-breaking study published in *Nature Communications*, Zou and an international team of researchers successfully used two methods to detect prions in skin samples collected from inoculated rodents. The study provides the first proof-of-concept evidence that readily accessible skin samples could be used to detect prion disease early--before clinical symptoms appear.

In the new study, Zou and colleagues successfully detected prions in rodent skin samples as early as two weeks post-infection. They also detected prions in the skin of uninoculated rodents that were housed alongside inoculated cage mates, demonstrating that prion transmission can occur between cohabitating rodents.

Prions were detected in skin samples from the inoculated rodents before they showed any clinical signs of prion disease. The researchers first inoculated the brains of hamsters and humanized transgenic mice with rodent or human prion samples, respectively. Then, they collected skin and brain samples at different time points, and used two different methods to detect disease-associated prion

proteins in the tissues. In both hamsters and mice, the researchers detected prions in skin before they could be detected in brain tissue. The researchers concluded that skin prions could serve as a useful biomarker for preclinical diagnosis of prion diseases.

The study compared two highly-sensitive prion detection methods: RT-QuIC (real-time quaking-induced conversion) and sPMCA (serial protein misfolding cyclic amplification). "Both assays were able to efficiently amplify trace amounts of disease-associated prion protein found in the skin tissues of infected animals," said the study's first author Zerui Wang, MD, a PhD student from the First Hospital of Jilin University, China, working in the Zou laboratory. The tests use prions in tissue samples as a template and either normal brain tissue or synthetic prion protein as "building blocks" to dramatically amplify minute amounts of prions to detectable levels.

One of the methods, RT-QuIC, has been used to detect prion particles in symptomatic CJD patients. However, it normally requires invasive cerebrospinal fluid (CSF) sampling that may be contraindicated for certain patients. Additionally, "The CSF-based prion test results could be uncertain in some cases and not all CSF specimens from patients with prion disease are RT-QuIC positive," said Qingzhong Kong, PhD, associate professor of pathology at Case Western Reserve University School of Medicine and co-corresponding author on the study. "Although skin samples may not replace CSF in routine RT-QuIC-based prion disease diagnosis, they may be helpful when prion disease is suspected but CSF is either unavailable or RT-QuIC-negative."

The study results build upon previous work by Zou and colleagues showing that autopsy skin samples from human prion disease patients exhibit prion seeding and infectivity. The next step will be to develop and validate the skin prion tests for clinical use.

Said Zou, "Since the skin is readily accessible and skin biopsy is minimally invasive, detection of skin prions will be very useful for monitoring disease progression and assessing therapeutic efficacy during clinical trials or treatments when prion therapy becomes available in the future."

Zou and Kong were recently awarded a $2.9 million grant from the National Institutes of Health to validate the test methods using human skin samples. They will determine if skin prions could serve as a diagnostic biomarker for CJD or a source of prion transmission. The researchers believe the methods may also be adapted for diagnosis of other diseases involving misfolded proteins. "Sensitive, minimally invasive detection of various misfolded proteins in skin, such as tau in Alzheimer's disease and alpha-synuclein in Parkinson's disease, could be highly valuable for disease diagnosis and monitoring of disease progression and efficacy of treatments," Zou said. "It's possible that the skin will ultimately serve as a mirror for us to monitor these misfolded proteins that accumulate and damage the brain in patients with these conditions."

Wang, Z. et al. "Early preclinical detection of prions in the skin of prion-infected animals." Nature Communications *10:247 (2019).*

http://bit.ly/2DAdAoZ

Children who had a dengue infection could be protected from symptomatic Zika

A prior dengue virus infection could protect children from symptomatic Zika virus infection

ANN ARBOR--A prior dengue virus infection could protect children from symptomatic Zika virus infection, according to a study by an international group of researchers including those from the University of Michigan and the University of California, Berkeley.

"We don't think that that dengue immunity protects from being infected (with Zika), or at least it doesn't look like that is the case in our study. However, for children who were infected with Zika, prior dengue exposure protected them from symptomatic Zika disease,"

said study lead author Aubree Gordon, assistant professor of epidemiology at U-M's School of Public Health.

Gordon and her collaborators from UC-Berkeley, the Nicaragua Ministry of Health and Sustainable Sciences Institute in Managua, used data from their long-standing Pediatric Dengue Cohort Study, established in 2004 in Managua.

Of the roughly 3,700 participants (children ages 2-14), 3,027 had known dengue infection histories, with 743 of them having at least one prior dengue infection and 176 with a recent dengue infection. Through testing, researchers found that 1,356 of them had had a Zika infection, and of those, 560 had symptomatic Zika.

The researchers compared children who had experienced a prior dengue infection to those who had not, to establish whether prior dengue infection affected whether the children were infected with Zika and the severity of the infection.

Among children infected with Zika, researchers found that children with a prior dengue infection were 38 percent less likely to develop symptomatic Zika than children without prior dengue exposure.

While dengue has been endemic to the Americas, Zika wasn't reported in the region until 2015. The viruses are very similar: they are transmitted by the Aedes aegypti mosquitoes and can cause similar symptoms, including fever, rash, and joint and muscle pain.

Those who work on mosquito-borne diseases believe there is an immunological interaction between dengue and Zika, said study co-author Eva Harris, of UC-Berkeley.

Researchers are paying special attention to a phenomenon called 'antibody-dependent enhancement,' Harris said. In some cases, people who had a previous dengue infection develop antibodies that, instead of protecting their hosts, make them unable to fight a subsequent infection, enhancing it instead.

Harris' international team recently showed this was the case in children in the Nicaraguan cohort study. Researchers believe this mechanism might be behind the severe Zika cases that caused neurological issues.

"However, in the current study, we did not examine severe Zika outcomes," Harris said. "We analyzed uncomplicated Zika in our pediatric population and found that prior dengue infection actually protected against disease. This is consistent with our previous studies on the role of dengue antibodies in relation to uncomplicated dengue disease.

Gordon said further research is needed to examine the interaction.

"If there are interactions, if it protects you from dengue, that's great. Or if it helps protect you from being symptomatic, fine," she said. "But there is always the concern that the antibodies are protective to a certain point, and once they reach a certain level they are now a risk for severe disease. And so I think that needs to be looked at pretty closely."

The study, published on PLOS Medicine, *was supported by grants R01 AI099631 (AB), P01 AI106695 (EH) and U19 AI118610 (EH) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, as well as grant VE-1 (EH) from the Pediatric Dengue Vaccine Initiative of the Bill and Melinda Gates Foundation.*

http://bit.ly/2Rfa2vN

Fecal Transplants More Successful from "Super-Donors"

A review finds that for several conditions, poop from certain healthy people is more likely to provide relief for recipients.

Shawna Williams

Not all poop is equally valuable, at least when it comes to fecal transplants. Some people, it appears, generate waste that is better at alleviating conditions associated with gut microbiome imbalances than others, according to a review article published yesterday (January 21) in *Frontiers in Cellular and Infection Microbiology*.

"Strategies to find super-donors whose stool is especially effective as a curative are still in their infancy, although progress on this topic—or making synthetic super-donors from the stool of many

people—could greatly improve application of [faecal transplants],” Rob Knight, a microbiology researcher at the University of California, San Diego, who wasn’t involved in the review, tells *The Guardian*.

The authors of the paper looked at studies on the use of fecal microbiota transplants (FMT) to treat *Clostridium difficile* infection, inflammatory bowel disease, constipation, allergic colitis, and other conditions. They write in their conclusion that the existence of super-donors is “not yet robustly supported by empirical evidence,” but that there is some support for the phenomenon for conditions other than *C. difficile* infection. “[T]he efficacy of FMT likely depends on the ability of the donor to provide the necessary taxa capable of restoring metabolic deficits in recipients that are contributing toward disease,” the authors write. “Further characterization of super-donors will likely result in the development of more refined FMT formulations to help standardize therapy and reduce variability in patient response.”

The review follows another study on fecal transplants published earlier this month (January 15), in which researchers tested the therapy for ulcerative colitis. Of subjects who received three transplants over seven days from donors, 32 percent were in remission eight weeks later, compared with just 9 percent of patients who received control treatments with their own stool, the authors report.

Coauthor Sam Costello of the Queen Elizabeth Hospital in Adelaide, Australia, says in a statement that an important difference between this and previous studies was that the stool samples were processed anaerobically. “Many gut bacteria die with exposure to oxygen and we know that with anaerobic stool processing a large number of donor bacteria survive so that they can be administered to the patient,” Costello explains. “We believe that this may be the reason that we had a good therapeutic effect with only a small number of treatments.”

https://nyti.ms/2CKoN4B

Scientists Are Teaching the Body to Accept New Organs

Patients receiving new kidneys and livers must take damaging anti-rejection drugs for the rest of their lives. Now researchers hope to train the immune system instead of just tamping it down.

Gina Kolata

It was not the most ominous sign of health trouble, just a nosebleed that would not stop. So in February 2017, Michael Schaffer, who is 60 and lives near Pittsburgh, went first to a local emergency room, then to a hospital where a doctor finally succeeded in cauterizing a tiny cut in his nostril.

Then the doctor told Mr. Schaffer something he never expected to hear: “You need a liver transplant.”

Mr. Schaffer had no idea his liver was failing. He had never heard of the diagnosis: Nash, for nonalcoholic steatohepatitis, a fatty liver disease not linked to alcoholism or infections.

The disease may have no obvious symptoms even as it destroys the organ. That nosebleed was a sign that Mr. Schaffer’s liver was not making proteins needed for blood to clot. He was in serious trouble.

The news was soon followed by another eye-opener: Doctors asked Mr. Schaffer to become the first patient in an experiment that would attempt something that transplant surgeons have dreamed of for more than 65 years.

If it worked, he would receive a donated liver without needing to take powerful drugs to prevent the immune system from rejecting it.

Before the discovery of anti-rejection drugs, organ transplants were simply impossible. The only way to get the body to accept a donated organ is to squelch its immune response. But the drugs are themselves hazardous, increasing the risks of infection, cancer, high cholesterol levels, accelerated heart disease, diabetes and kidney failure.

Within five years of a liver transplant, 25 percent of patients on average have died. Within 10 years, 35 to 40 percent have died.

"Even though the liver may be working, patients may die of a heart attack or stroke or kidney failure," said Dr. Abhinav Humar, a transplant surgeon at the University of Pittsburgh Medical Center who is leading the study Mr. Schaffer joined. "It may not be entirely due to the anti-rejection meds, but the anti-rejection meds contribute."

Kidneys in particular may be damaged. "It is not uncommon to end up doing a kidney transplant in patients who previously had a lung or liver or heart transplant," Dr. Humar added.

Patients usually know about the drugs' risks, but the alternative is worse: death for those needing livers, hearts or lungs; or, for kidney patients, a life on dialysis, which brings an even worse life expectancy and quality of life than does a transplanted kidney.

A glimmer of hope

In 1953, Dr. Peter Medawar and his colleagues in Britain did an experiment with a result so stunning that he shared a Nobel Prize for it. He showed that it was possible to "train" the immune systems of mice so that they would not reject tissue transplanted from other mice.

His method was not exactly practical. It involved injecting newborn or fetal mice with white blood cells from unrelated mice. When the mice were adults, researchers placed skin grafts from the unrelated mice onto the backs of those that had received the blood cells.

The mice accepted the grafts as if they were their own skin, suggesting that the immune system can be modified. The study led to a scientific quest to find a way to train the immune systems of adults who needed new organs.

That turned out to be a difficult task. The immune system is already developed in adults, while in baby mice it is still "learning" what is foreign and what is not.

"You are trying to fool the body's immune system," Dr. Humar said. "That is not easy to do."

Most of the scientific research so far has focused on liver and kidney transplant patients for several reasons, said Dr. James Markmann, chief of the division of transplant surgery at Massachusetts General Hospital.

Those organs can be transplanted from living donors, and so cells from the donor are available to use in an attempt to train the transplant patient's immune system.

Far more people need kidneys than need any other organ — there are about 19,500 kidney transplants a year, compared with 8,000 transplanted livers. And those transplanted kidneys rarely last a lifetime of battering with immunosuppressive drugs.

"If you are 30 or 40 and get a kidney transplant, that is not the only kidney you will need," said Dr. Joseph R. Leventhal, who directs the kidney and pancreas transplant programs at Northwestern University.

Another reason to focus on kidneys: "If something goes wrong, it's not the end of the world," Dr. Markmann said. If an attempt to wean patients from immunosuppressive drugs fails, they can get dialysis to cleanse their blood. Rejection of other transplanted organs can mean death.

The liver intrigues researchers for different reasons. It is less prone to rejection by the body's immune system. When rejection does occur, there is less immediate damage to the organ.

And sometimes, after people have lived with a transplanted liver for years, their bodies simply accept the organ. A few patients discovered this by chance when they decided on their own to discard their anti-rejection drugs, generally because of the expense and side effects.

An estimated 15 to 20 percent of liver transplant patients who have tried this risky strategy have succeeded, but only after years of taking the drugs.

In one trial, Dr. Alberto Sanchez-Fueyo, a liver specialist at King's College London, reported that as many as 80 percent could stop

taking anti-rejection drugs. In general, those patients were older — the immune system becomes weaker with age. They had been long-term users of immunosuppressive drugs and had normal liver biopsies.

But the damage caused by immunosuppressive drugs is cumulative and irreversible, and use over a decade or longer can cause significant damage. Yet there is no way to predict who will succeed in withdrawing.

Tricking the immune system

The more researchers learned about the symphony of white blood cells that control responses to infections and cancers — and transplanted organs — the more they began to see hope for modifying the body's immune system.

Many types of white blood cells work together to create and control immune responses. A number of researchers, including Dr. Markmann and his colleague, Dr. Eva Guinan of the Dana-Farber Cancer Institute, chose to focus on cells called regulatory T lymphocytes.

These are rare white blood cells that help the body identify its own cells as not foreign. If these regulatory cells are missing or impaired, people can develop diseases in which the body's immune system attacks its own tissues and organs.

The idea is to isolate regulatory T cells from a patient about to have a liver or kidney transplant. Then scientists attempt to grow them in the lab along with cells from the donor.

Then the T cells are infused back to the patient. The process, scientists hope, will teach the immune system to accept the donated organ as part of the patient's body.

"The new T cells signal the rest of the immune system to leave the organ alone," said Angus Thomson, director of transplant immunology at the University of Pittsburgh Medical Center.

Dr. Markmann, working with liver transplant patients, and Dr. Leventhal, working with kidney transplant patients, are starting studies using regulatory T cells.

At Pittsburgh, the plan is to modify a different immune system cell, called regulatory dendritic cells. Like regulatory T cells, they are rare and enable the rest of the immune system to distinguish self from non-self.

One advantage of regulatory dendritic cells is that researchers do not have to isolate them and grow them in sufficient quantities. Instead, scientists can prod a more abundant type of cell — immature white blood cells — to turn into dendritic cells in petri dishes.

"It takes one week to generate dendritic cells," Dr. Thomson said. In contrast, it can take weeks to grow enough regulatory T cells.

The regulatory T cells also have to remain in the bloodstream to control the immune response, while dendritic cells need not stay around long — they control the immune system during a brief journey through the circulation.

"Each of us is taking advantage of a different approach," Dr. Markmann said. "It is not clear yet which is best. But the field is at a fascinating point."

What about patients who already had an organ transplant? Is it too late for them?

"I get asked that question almost every day I am seeing patients," Dr. Leventhal said.

For now, the answer is that it is too late. These patients are not candidates for these new strategies to modify the immune system. But researchers hope that situation will change as they learn more.

'Somebody has to be first'

When Michael Schaffer, the Pittsburgh patient, was told that he needed a liver and that he could be the first patient in the group's clinical trial, he shrugged. "Someone has to be first," he said.

Mr. Schaffer began a search to find a living donor, a close relative willing to undergo a major operation to remove a lobe of liver — or a stranger whose cells were compatible and who was willing to donate.

The Pittsburgh scientists told him how to proceed. Ask immediate family, then relatives, friends and colleagues. If that failed, he would have to start advertising with fliers and posts on Facebook.

Mr. Schaffer is one of eight brothers. Four were older than 55, too old to safely undergo removal of part of their liver. The three younger brothers were in poor health.

He moved on to nieces and nephews. Three agreed to donate, and one, Deidre Cannon, 34, who was a good match, went forward with the operation.

It took place on Sept. 28, 2017. Afterward, Mr. Schaffer was taking 40 pills a day to prevent infections and to tamp down his immune system while his body learned to accept the new organ.

But now he has tapered down to one pill, a low dose of just one of the three anti-rejection drugs he started with. And doctors hope to wean him even from that.

His case may be intriguing, but he is just one patient. The scientists plan to try the procedure on 12 more patients and, if it succeeds, to expand the study to include many more patients at multiple test sites.

For Mr. Schaffer, it has all been worthwhile. He is active, working with a teenage grandson to replace the tiles on his kitchen floor. He shovels snow and mows lawns as a favor for his neighbors, and helps take care of his grandchildren after school.

“My goal is to live to be 100 and get shot in bed by a jealous husband,” Mr. Schaffer said.

Gina Kolata writes about science and medicine. She has twice been a Pulitzer Prize finalist and is the author of six books, including “Mercies in Disguise: A Story of Hope, a Family's Genetic Destiny, and The Science That Saved Them.”

http://bit.ly/2WjtYkO

Final verdict on finasteride: Safe, effective prevention for prostate cancer

Results over two decades show that finasteride has the lasting effect of reducing prostate cancer risk

Finasteride, a generic hormone-blocking drug, was found to reduce the risk of prostate cancer by 25 percent in the landmark Prostate Cancer Prevention Trial (PCPT). Long- term data, published today in the *New England Journal of Medicine*, show that reduction in prostate cancer risk has continued and fewer than 100 men on the trial died from the disease.

SWOG Cancer Research Network, an international cancer clinical trials group funded by the National Cancer Institute (NCI), part of the National Institutes of Health, opened the PCPT for enrollment 25 years ago. The PCPT enrolled 18,882 men from 1993 to 1997, making it one of the largest prostate cancer clinical trials ever conducted. New results, which reported participant deaths over two decades, show that finasteride has the lasting effect of reducing prostate cancer risk. Results also eliminate concerns over initial findings of a possible risk of more aggressive cancers with finasteride use.

"Finasteride is safe, inexpensive, and effective as a preventive strategy for prostate cancer," said Ian Thompson, Jr, MD, principal investigator of the PCPT for SWOG. "Doctors should share these results with men who get regular prostate-specific antigen tests that screen for the presence of prostate cancer. The drug will have its greatest effect in this group of men."

Thompson is chair of SWOG's genitourinary cancer committee and serves as president of CHRISTUS Santa Rosa Hospital - Medical Center in San Antonio, Texas and as emeritus professor at the University of Texas Health Science Center. Along with SWOG biostatisticians Catherine Tangen, DrPH, and Phyllis Goodman, MS,

of Fred Hutchinson Cancer Research Center, Thompson sought to determine whether the increased number of high-grade cancers detected through the PCPT years ago would result in more prostate cancer deaths over time.

SWOG published the first PCPT results in 2003. Investigators reported a significant, positive result: finasteride reduced prostate cancer risk by 25 percent. But the study also cast a shadow on the drug, the first 5-alpha-reductase inhibitor which targets and blocks the action of androgens like testosterone and is commonly used to treat lower urinary tract problems in men and also male pattern baldness. The results showed that finasteride increased the number of high-grade prostate cancers - a finding that resulted in a drug label warning posted by the U.S. Food and Drug Administration. That warning persists to this day.

So is finasteride safe in the long run? Thompson, Tangen, and Goodman matched participants to the National Death Index, a centralized database of death record information managed by the U.S. Centers for Disease Control and Prevention. This analysis allowed the SWOG team to determine if a trial participant had died, and if so, the cause of death. With almost 300,000 person-years of follow-up and a median follow-up of 18.4 years, they found 42 deaths due to prostate cancer on the finasteride arm and 56 on the placebo arm. Thus, there was no statistically significant increased risk of prostate cancer death with finasteride.

In the NEJM letter, the team notes that a cheap, reliable prostate cancer prevention drug will have a big impact on public health. Due to a rise in screening for the disease, prostate cancer diagnoses are on the rise, with the American Cancer Society estimating that 164,690 American men would be diagnosed in 2018. While many of these cancers will be slow-growing, and not life-threatening, they are still often treated with surgery and radiation, resulting in common complications such as impotence and incontinence.

"There are significant negative consequences to patients' health and quality of life that can result from prostate cancer treatment, as well as to their finances and their peace of mind," Thompson said. "If we can save people from surgeries, and scores of examinations and tests, and spare them from living for years with fear, we should. The best-case scenario for patients is prevention, and this trial has found an inexpensive medication that gets us there."

The NCI and the National Institutes of Health funded the study through grants CA037429 and CA182883.

Other members of the SWOG study team include Amy K. Darke, MS, of Fred Hutch; M. Scott Lucia, MD of University of Colorado, Denver; Leslie G. Ford, MD, of the Division of Cancer Prevention at the NCI; Lori M. Minasian, MD, of the Division of Cancer Prevention at the NCI; Howard L. Parnes, MD, of the Division of Cancer Prevention at the NCI; and Michael L. LeBlanc, PhD, of Fred Hutch.

http://bit.ly/2Rfe5rZ

What makes the deadly pufferfish so delectable

Researchers have identified the major compounds responsible for the taste of pufferfish

Some people consider pufferfish, also known as fugu, a delicacy because of its unique and exquisite flavor, which is perhaps seasoned by knowledge that consumption of the fish could be deadly. Now, researchers have identified the major compounds responsible for the taste of pufferfish, minus the thrill of living dangerously. They report their results in ACS' *Journal of Agricultural and Food Chemistry*.

Researchers have identified the key compounds responsible for the taste of pufferfish (Takifugu obscurus). **Yuan Liu**

Pufferfish get their name from their ability to inflate to a much larger size when threatened by predators. But if that defense mechanism fails, the predator may not survive long after its meal: The liver, ovaries, eyes and skin of most species of pufferfish contain tetrodotoxin, a potent neurotoxin. Although specially trained chefs

can prepare fugu that's safe to eat, Yuan Liu and colleagues wondered if they could reproduce the flavor of pufferfish without the life-threatening toxin.

The researchers analyzed the key taste-active compounds in *Takifugu obscurus*, a species of pufferfish found mainly in the East and South China Seas. First, the team ground up pufferfish muscle tissue and cooked, filtered and centrifuged it to produce a liquid pufferfish extract. They then analyzed the extract and found amounts of 28 potential taste compounds, such as free amino acids, nucleotides and inorganic ions. Taste tests with trained panelists revealed that 12 of these compounds, when added to water, best simulated the flavor of pufferfish, which involved strong umami (savory) and kokumi (mouthfulness) components. When the researchers added two flavor peptides they isolated in a prior study, the imitation pufferfish extract tasted even more like the real thing.

These authors acknowledge funding from the National Natural Science Foundation of China.

The abstract that accompanies this study is available here.

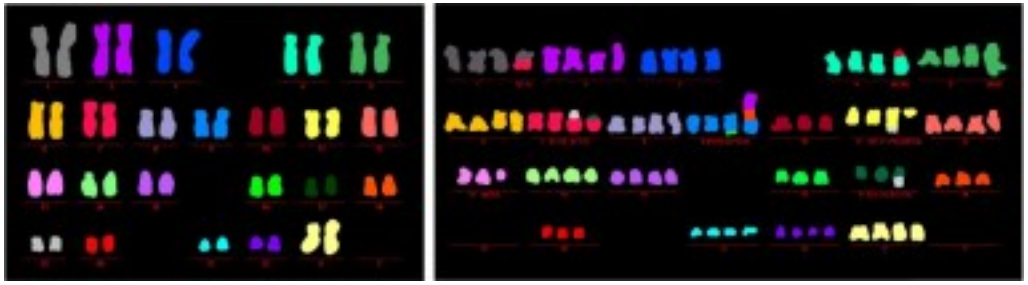
http://bit.ly/2RUjdap

In surprising reversal, scientists find a cellular process that stops cancer before it starts

Salk research shows that cellular recycling process, thought to fuel cancer's growth, can actually prevent it

LA JOLLA - Just as plastic tips protect the ends of shoelaces and keep them from fraying when we tie them, molecular tips called telomeres protect the ends of chromosomes and keep them from fusing when cells continually divide and duplicate their DNA. But while losing the plastic tips may lead to messy laces, telomere loss may lead to cancer.

Salk Institute scientists studying the relationship of telomeres to cancer made a surprising discovery: a cellular recycling process called autophagy--generally thought of as a survival mechanism--actually promotes the death of cells, thereby preventing cancer initiation.



Left: The 23 pairs of chromosomes of cells in which autophagy is functioning look normal and healthy with no structural or numerical aberrations (each color represents a unique chromosome pair). Right: the chromosomes of cells in which autophagy is not functioning bypass crisis, showing both structural and numerical aberrations, with segments added to, deleted from, and/or swapped between chromosomes--a hallmark of cancer.

Credit: Salk Institute

The work, which appeared in the journal *Nature* on January 23, 2019, reveals autophagy to be a completely novel tumor-suppressing pathway and suggests that treatments to block the process in an effort to curb cancer may unintentionally promote it very early on.

"These results were a complete surprise," says Jan Karlseder, a professor in Salk's Molecular and Cell Biology Laboratory and the senior author of the paper. "There are many checkpoints that prevent cells from dividing out of control and becoming cancerous, but we did not expect autophagy to be one of them."

Each time cells duplicate their DNA to divide and grow, their telomeres get a little bit shorter. Once telomeres become so short that they can no longer effectively protect chromosomes, cells get a signal to stop dividing permanently. But occasionally, due to cancer-causing viruses or other factors, cells don't get the message and keep on dividing. With dangerously short or missing telomeres, cells enter a state called crisis, in which the unprotected chromosomes can fuse and become dysfunctional--a hallmark of some cancers.

Karlseder's team wanted to better understand crisis--both because crisis often results in widespread cell death that prevents precancerous cells from continuing to full-blown cancer and because the mechanism underlying this beneficial cell death isn't well-understood.

"Many researchers assumed cell death in crisis occurs through apoptosis, which along with autophagy is one of two types of programmed cell death," says Joe Nassour, a postdoctoral fellow in the Karlseder lab and the paper's first author. "But no one was doing experiments to find out if that was really the case."

To investigate crisis and the cell death that typically ensues, Karlseder and Nassour used healthy human cells to run a series of experiments in which they compared normally growing cells with cells they forced into crisis. By disabling various growth-limiting genes (also known as tumor-suppressor genes), their group enabled the cells to replicate with abandon, their telomeres getting shorter and shorter in the process.

To know which type of cell death was responsible for the major die-off in crisis, they examined morphological and biochemical markers of both apoptosis and autophagy. Although both mechanisms were responsible for a small number of cells dying in the normally growing cells, autophagy was by far the dominant mechanism of cell death in the group in crisis, where many more cells died.

The researchers then explored what happened when they prevented autophagy in the crisis cells. The results were striking: without cell death via autophagy to stop them, the cells replicated tirelessly. Furthermore, when the team looked at these cells' chromosomes, they were fused and disfigured, indicating that severe DNA damage of the kind seen in cancerous cells was occurring, and revealing autophagy to be an important early cancer-suppressing mechanism.

Finally, the team tested what happened when they induced specific kinds of DNA damage in the normal cells, either to the ends of the chromosomes (via telomere loss) or to regions in the middle. Cells with telomere loss activated autophagy, while cells with DNA damage to other chromosomal regions activated apoptosis. This shows that apoptosis is not the only mechanism to destroy cells that may be precancerous due to DNA damage and that there is direct cross-talk between telomeres and autophagy.

The work reveals that, rather than being a mechanism that fuels unsanctioned growth of cancerous cells (by cannibalizing other cells to recycle raw materials), autophagy is actually a safeguard against such growth. Without autophagy, cells that lose other safety measures, such as tumor-suppressing genes, advance to a crisis state of unchecked growth, rampant DNA damage--and often cancer. (Once cancer has begun, blocking autophagy may still be a valid strategy of "starving" a tumor, as a 2015 study by Salk Professor Reuben Shaw, a coauthor on the current paper, discovered.)

Karlseder, who holds the Donald and Darlene Shiley Chair, adds, "This work is exciting because it represents so many completely novel discoveries. We didn't know it was possible for cells to survive crisis; we didn't know autophagy is involved with the cell death in crisis; we certainly didn't know how autophagy prevents the accumulation of genetic damage. This opens up a completely new field of research we are eager to pursue."

Next the researchers plan to more closely investigate the split in cell-death pathways whereby damage to chromosome ends (telomeres) leads to autophagy while damage to other parts of chromosomes leads to apoptosis.

Other authors included Robert Radford, Adriana Correia, Javier Miralles Fusté, Brigitte Schoell and Anna Jauch.

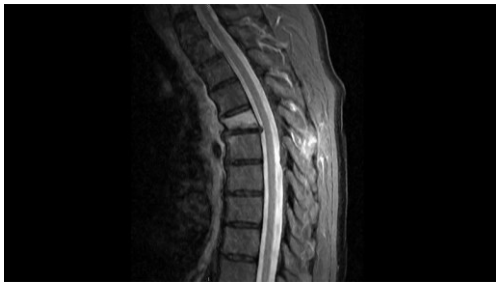
The work was funded by the European Molecular Biology Organization (EMBO), the Hewitt Foundation, the Paul F. Glenn Center for Biology of Aging Research, the Salk Institute Cancer Center (core grant P30CA014195), the National Institutes of Health (R01CA227934, GM087476, R01CA174942), the Donald and Darlene Shiley Chair, the Helmsley Foundation, the Auen Foundation and the Highland Street Foundation.

https://go.nature.com/2TgG3FH

Japan's approval of stem-cell treatment for spinal-cord injury concerns scientists

Chief among their worries is insufficient evidence that the therapy works.

David Cyranoski



A stem cell treatment for spinal cord injuries will soon be available in Japan. **Steven Needell/SPL**

Japan has approved a stem-cell treatment for spinal-cord injuries. The event marks the first such therapy for this kind of injury to receive government approval for sale to patients.

"This is an unprecedented revolution of science and medicine, which will open a new era of healthcare," says oncologist Masanori Fukushima, head of the Translational Research Informatics Center, a Japanese government organization in Kobe that has been giving advice and support to the project for more than a decade.

But independent researchers warn that the approval is premature. Ten specialists in stem-cell science or spinal-cord injuries, who were approached for comment by *Nature* and were not involved in the work or its commercialization, say that evidence that the treatment works is insufficient. Many of them say that the approval for the therapy, which is injected intravenously, was based on a small, poorly designed clinical trial.

They say that the trial's flaws — including that it was not double-blinded — make it difficult to assess the treatment's long-term efficacy, because it is hard to rule out whether patients might have recovered naturally. And, although the cells used — known as mesenchymal stem cells (MSCs) — are thought to be safe, the infusion of stem cells into the blood has been connected with dangerous blood clots in the lungs. And all medical procedures carry risks, which makes them hard to justify unless they are proven to offer a benefit.

Path to approval

That the treatment won approval to be sold to patients is concerning, says James Guest, a neurosurgeon at the Miami Project to Cure Paralysis at the University of Miami in Florida. "This approval is an unfortunate step away from everything researchers have learned over the past 70 years about how to conduct a valid clinical trial," he says.

One of the inventors of the treatment, neurosurgeon Osamu Honmou of Sapporo Medical University in Japan, says he is preparing to publish a scientific paper that will discuss the clinical-trial and safety issues. "I think it is very safe." He says he did not do a double-blinded study because Japan's regulations do not require it. "The most important point is that the efficacy is dramatic and definitive," says Fukushima.

The unpublished results describe a trial of 13 people, who had experienced spinal-cord injuries in the past 40 days. The team found that infusions of stem cells extracted from the patients' bone marrow helped them to regain some lost sensation and movement.

On the basis of these results, Japan's health ministry last month gave conditional approval for the treatment, called Stemirac. It is made by extracting mesenchymal stem cells from a person and multiplying them in the lab. In the clinical trial, about 50 million to 200 million MSCs were intravenously infused back into patients 40 days after their injury to help repair the damage. The team can market and sell the therapy as long as they collect data from the participants over the next seven years, to show that it works. People could start paying for the treatment in the next few months.

Whereas many governments require new treatments to undergo rigorous clinical trials with hundreds of patients before the therapies can be sold, Japan has a programme to fast track the development of

regenerative medicines, which approves therapies that show only hints of efficacy, on the condition that the researchers collect follow-up data.

Mode of action

Honmou says that after 6 months, 12 of the 13 patients improved by at least one level on the American Spinal Injury Association impairment scale, an internationally recognized system that ranks people's ability to contract muscles and sense touch on parts of the body.

The team thinks the stem cells might repair damage to the spinal cord through any of several mechanisms, including reducing inflammation and protecting existing neurons. They also say that some of the infused stem cells develop into neurons that can replace those damaged in the injury. Honmou says that he and others have demonstrated these mechanisms in animal studies[1].

The claim that MSCs can become neurons, in particular, concerns some of the independent scientists *Nature* consulted. Studies in the early to mid 2000s found that MSCs could take on certain features of neurons, such as expressing some of the same proteins[2,3], but the idea that they can function as neurons has been widely discarded.

So it is very unlikely that the MSCs converted to neurons in the trial, says Bruce Dobkin, a neurologist at the University of California, Los Angeles. Other studies in animals and people have found that MSCs infused intravenously tend to get stuck in the lungs.

"The fact that the cells are trapped in the lungs makes it difficult to see how they can be effective in the spinal cord," says Pamela Robey, a stem-cell researcher at the US National Institutes of Health in Bethesda, Maryland.

Jeffery Kocsis, a neurologist at Yale University in New Haven, Connecticut, who has been collaborating with Honmou and others on the team for more than 20 years, calls the results "potentially interesting" . "While use of these cells may [have some] benefit," he says, "continued work will be necessary to fully substantiate efficacy."

Burden of proof

Some of the independent scientists also expressed concerns about the lack of double-blinding. This is the gold standard for assessing a treatment's efficacy, because neither the physicians nor patients know who is receiving the experimental treatment. As a result, it reduces bias that could prevent scientists from discovering whether a treatment works, says Guest.

Double-blinded studies can be difficult to achieve. In this case, Guest says, it would have been easy.

Instead, the results could be explained by natural healing and physical rehabilitation in the months after an injury, says Dobkin. "This trial, as designed, cannot reveal efficacy," he says.

Fukushima, however, says that the consistent improvement and high rate of success in their trial patients — even among those who were judged to have no hope of recovery — is "unprecedented". This could not have been achieved by natural healing with rehabilitation, he says.

But once the treatment is sold to patients, it will be even harder for the team to gather evidence that it is effective, says Arnold Kriegstein, a stem-cell researcher at the University of California, San Francisco. Paying for treatments can increase the likelihood that the patient will experience a placebo effect, and makes it impossible to perform a blinded trial, because people cannot be charged for a placebo procedure.

Kriegstein worries that the product could remain on the market without ever providing evidence that it works. "I do not think it is morally justified to charge patients for an unproven therapy that has risks," he says.

doi: 10.1038/d41586-019-00178-x **References**

http://bit.ly/2RRJfuS

The helix, of DNA fame, may have arisen with startling ease

New study suggests spiraling may have occurred billions of years ago when RNA's chemical ancestors spun into spiraled strands

Trying to explain how DNA and RNA evolved to form such neat spirals has been a notorious enigma in science. But a new study suggests the rotation may have occurred with ease billions of years ago when RNA's chemical ancestors casually spun into spiraled strands.

Artwork for the study shows the chemical structure of the helix that self-assembled in the lab, producing surprisingly bountiful results. **Georgia Tech / Nick Hud**

In the lab, researchers at the Georgia Institute of Technology were surprised to see them do it under conditions thought to be common on Earth just before first life evolved: in plain water, with no catalysts, and at room temperature.

The neat spiraling also elegantly integrated another compound which today forms the backbone of RNA and DNA. The resulting structure had features that strongly resembled RNA.

Pivotal twists

The study has come a step closer to answering a chicken-egg question about the evolutionary path that led to RNA (from which DNA later evolved): Did the spiral come first, and did this structure influence which molecular components made it later into RNA because they fit well into the spiral?

"The spiraling could have had a reinforcing effect. It could have facilitated the molecules getting connected together that have the same chirality (curve) to connect into a common backbone that is compatible with the helical twist," said the study's principal investigator Nicholas Hud, a Regents Professor in Georgia Tech's School of Chemistry and Biochemistry.

The researchers published the new study in the journal *Angewandte Chemie* in December 2018. The research was funded by the National Science Foundation and the NASA Astrobiology Program under the Center for Chemical Evolution. The center is headquartered at Georgia Tech, and Hud is its principal investigator.

The study's resulting polymers were not RNA but could be have been an important intermediate step in the early evolution of RNA. For building blocks, the researchers used base molecules referred to as "proto-nucleobases," highly suspected to be precursors of nucleobases, main components that transport genetic code in today's RNA.

Nucleobase paradox

The study had to work around a paradox in chemical evolution:

Making RNA or DNA using their actual nucleobases in the lab without the aid of the enzymes of living cells that usually do this job is more than a herculean task. Thus, although RNA and DNA are ubiquitous on Earth now, their evolution on pre-life Earth would appear to have been an anomaly requiring erratic convergences of extreme conditions.

By contrast, the Georgia Tech researchers' model of chemical evolution holds that precursor nucleobases self-assembled easily to into ancestral prototypes -- that were polymer-like and referred to as assemblies -- which later evolved into RNA.

"We would call these 'proto-nucleobases' or 'ancestral nucleobases,'" Hud said. "For our overall model of chemical evolution, we're saying that these proto-nucleobases, which self-assemble into these long strands, could have been part of a very early stage before modern nucleobases were incorporated."

One main suspected proto-nucleobase in this experiment -- and in previous experiments on the possible the evolution of RNA -- was

triaminopyrimidine (TAP). Cyanuric acid (CA) was another. The researchers highly suspect TAP and CA were parts of a proto-RNA.

The chemical bonds that hold together assemblies of the two suspected proto-nucleobases were surprisingly strong but non-covalent, which is akin to connecting two magnets. In RNA the main bonds holding together modern nucleobases are covalent bonds, akin to welding, and enzymes make those bonds in cells today.

Helical biases

A helix can spiral two ways, left-handed or right-handed. In chemistry, a molecule can also be handed, or chiral, making for "L" or "D" forms of the molecule.

Incidentally, the building blocks of today's RNA and DNA are all the D form, which make a right-handed helix. Why they evolved like this is still a mystery.

Batches of TAP and CA the researchers started out with produced roughly equal amounts of right and left-handed helices, but something stood out: Whole regions of a batch were biased in one direction and were separate from other regions that spiraled mostly the other way.

"The propensity for the molecules to choose one helical direction was so strong that large regions of the batches were made up predominantly of assemblies that were unidirectionally twisted," Hud said.

This was surprising because the individual molecules of TAP and CA had no chirality of their own, neither L nor D. Still, the twists had a preferred direction.

'world record'

The researchers added two more experiments to test how strongly their RNA-like assemblies preferred making one-handed helices.

First, they introduced a smidgeon of compounds similar to TAP and CA, but which had L or D chirality, to nudge the spiraling direction. The whole batch conformed to the chirality of the respective additive, resulting in assemblies twisting in a unified direction as helices do in RNA and DNA today.

"It was the new world record for the smallest amount of a chiral dopant (additive) that would flip a whole solution," said Suneesh Karunakaran, the study's first author and a graduate researcher in Hud's lab. "This demonstrated how easy it would be in nature to get abundant amounts of unified helices."

Second, they put the sugar compound ribose-5-phosphate together with TAP to more closely emulate the current building blocks of RNA. The ribose fell into place, and the resulting assembly spiraled in a direction dictated by the ribose chirality.

"This molecule easily formed an RNA-like assembly that was surprisingly stable, even though the pieces were only held together by non-covalent bonds," Karunakaran said.

Evolution revolution

The study's results under such simple conditions represent a leap forward in experimental evidence for how the helical twist of biomolecules could have already been in place long before life emerged.

The research also expands a growing body of evidence supporting an unconventional hypothesis by the Center for Chemical Evolution, which dispenses with the need for a narrative that rare cataclysms and unlikely ingredients were necessary to produce life's early building blocks.

Instead, most biomolecules likely arose in several gradual steps, on quiet, rain-swept dirt flats or lakeshore rocks lapped by waves. Precursor molecules with the right reactivity enabled those steps readily and produced abundant materials for further evolutionary steps.

Basement engineer

In the lab, helix self-assemblage was so productive that it outstripped a detection device's capacity to examine the output. Regions a square

millimeter or more in size were packed with unidirectionally spiraled polymer-like assemblies.

"To look at them I had to make adjustments to the equipment," said Karunakaran. "I punched holes in a foil and put it in front of the beam of our spectropolarimeter."

That worked but needed improvement, so Hud took to his basement at home to build an automated scanner that could handle the experiment's bountiful results. It revealed large regions of helices with the same handedness.

Brian J. Cafferty, Angela Weigert-Muñoz and Gary B. Schuster of Georgia Tech co-authored the research. It was funded by the National Science Foundation and the NASA Astrobiology Program under the NSF Center for Chemical Evolution (grant CHE-1504217). Nicholas Hud is also Associate Director of the Parker H. Petit Institute for Bioengineering and Bioscience. Any findings, recommendations or conclusions are those of the authors and not necessarily of the funding agencies.

http://bit.ly/2RPIxhA

Gum Disease Could Drive Alzheimer's: Study

An enzyme of the bacteria* Porphyromonas gingivalis *has been found in the brains of patients with the disorder, and causes neurodegeneration in mice.

Ashley Yeager

Traces of the bacterium *Porphyromonas gingivalis*, which causes chronic gum disease, have been found in the brains of people who had Alzheimer's disease. The result suggests the bacterium may play a role in driving the development of the disease, researchers reported yesterday (January 23) in *Science Advances*.

Researchers looked at brain tissue from autopsies of individuals with and without Alzheimer's disease and found a majority of those with the disease had higher levels of an enzyme called gingipains, which is produced by *P. gingivalis*. They also studied the enzyme's effects in the brains of mice, and found that it caused the animals to develop signs of Alzheimer's.

The results indicate gingipains is the "main cause of Alzheimer's disease," study coauthor Steve Dominy, a neurologist at Cortexyme, Inc., a company developing treatments for the disease, tells *Newsweek*. The new study is one of a growing number that suggest microbes play a role in Alzheimer's disease.

"I'm fully on board with the idea that this microbe could be a contributing factor. I'm much less convinced that [it] causes Alzheimer's disease," Robert Moir, a neurobiologist at Massachusetts General Hospital in Boston who was not involved in the study, tells *Science*.

In the study, Dominy and his colleagues swabbed *P. gingivalis* onto the gums of healthy mice every other day for 6 weeks. The bacterium took hold, and the team later detected it in the mice's brains, where they also found dying neurons and higher levels of β-amyloid protein than in control animals, indicating the infected animals had developed signs of Alzheimer's disease.

In cell cultures, different forms of the gingipain enzyme damaged tau, another protein associated with Alzheimer's, and that damage may cause tau to develop into tangles, which are another indicator or Alzheimer's neurodegeneration, the researchers found in additional experiments.

The team also gave the mice a drug that bound to the gingipain enzyme. The drug cleared the infection from the animals' brains and reduced β-amyloid production and neurodegeneration.

The study "is clearly very comprehensively approached," James Noble, a neurologist at Columbia University who has studied the link between periodontal disease and Alzheimer's but was not involved in the new work, tells *Science*. "These are strange ideas, but they seem to be getting some traction."

https://bbc.in/2B3FRCA

'High' survival for many cancers diagnosed at stages 1-3

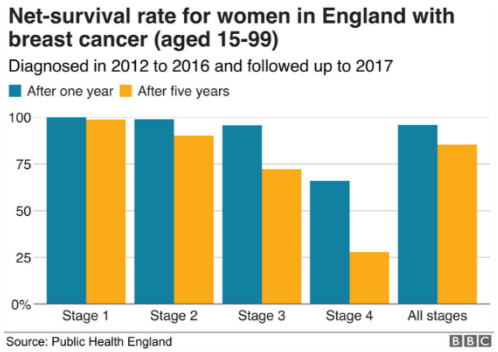
Adults diagnosed with stage-1 skin, prostate or breast cancer have the same chance of still being alive a year later as the general population, data from the Office for National Statistics and Public Health England suggests.

For many cancers, one-year survival rates are high if they are diagnosed in stages 1-3, but lower in stage 4. Pancreatic cancer has the lowest rates of survival, for men and women. The estimates are based on cancer diagnoses in England from 2012-16.

Sarah Caul, head of cancer analysis at the ONS, said this was the first time it had looked at five-year survival rates based on what stage the disease was at when diagnosed. "This research shows a mixed picture but does stress the need for awareness and early diagnosis," she said.

Late-stage drop

Among women diagnosed with breast cancer, the most common cancer in women, 90% will survive for a year unless they are diagnosed at stage 4, when the figure drops to 66%.



In men with prostate cancer, survival rates a year after diagnosis are very nearly 100% for stages 1-3, dropping to 87.6% for stage-4 diagnosis. However, five-year survival rates for both cancers fall away more steeply if diagnosis was made at stage 3 or later.

For stage 1-4 diagnoses, skin cancer (melanoma) has the highest one-year survival rate, of 97.4% for men and 98.6% for women, and pancreatic cancer has the lowest, at 23.7% and 25.3%.

And 10-year survival rates are highest for skin cancer and lowest for lung cancer - for both men and women.

Most lung cancers are diagnosed at a late stage, probably because symptoms tend not to appear until the cancer is more developed.

European comparison

Overall, data shows cancer survival in England has been improving steadily since 2006. But the rates are still lower than similar countries in Europe and around the world, recent studies suggest.

The differences in survival are thought to be down to lower numbers of cases being diagnosed early in England.

Cancer survival figures are also published by the Northern Ireland Cancer Registry, the Scottish Cancer Registry and the Welsh Cancer Intelligence and Surveillance Unit.

'More equipment'

Ruth Thorlby, assistant director of policy at think tank the Health Foundation, said improving cancer survival figures reflected sustained investment over the past two decades.

But she said more had to be done if the prime minister's plan to improve survival through earlier diagnosis was to be achieved.

She said it would require "capital investment for additional diagnostic equipment, such as MRI and CT scanners, significant increases in the cancer workforce to diagnose, treat and support cancer patients, and help for staff to improve complex services and get the most out of new advances in cancer care".

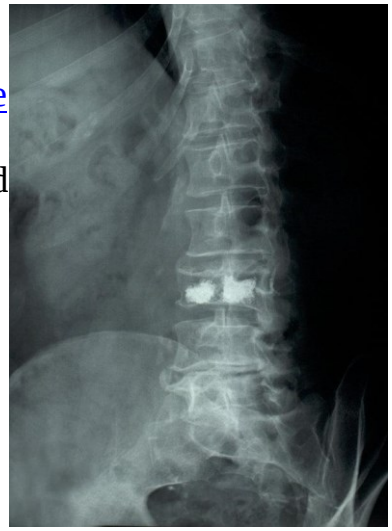
https://nyti.ms/2Sa39jT

Spinal Fractures Can Be Terribly Painful. A Common Treatment Isn't Helping.

Injections of bone cement into fractured vertebrae fail to relieve pain any more than a placebo does, researchers found.

By Gina Kolata

Scientists warned osteoporosis patients on Thursday to avoid two common procedures used to shore up painful fractures in crumbling spines.



The treatments, which involve injecting bone cement into broken vertebrae, relieve pain no better than a placebo does, according to an expert task force convened by the American Society for Bone and Mineral Research.

The task force noted that the pain goes away or diminishes within six weeks without the procedure. Patients should take painkillers instead, the experts said, and maybe try back braces and physical therapy.

An X ray showing cement injected into a collapsed lumbar vertebra in a 65-year-old patient. Scientists say the procedure, while common, does not effectively relieve pain. **Scott Camazine, via Getty Images**

Patients also should take osteoporosis drugs to slow bone loss, said Dr. Peter Ebeling, head of the department of medicine at Monash University in Australia and lead author of the new report, which was published in the Journal of Bone and Mineral Research.

A patient who has had a spine fracture and does not take the drugs has a one-in-five chance of developing another fracture in the next year. With the medications, the odds are one in 20.

The new advice may not sit well with many doctors and patients. For chronic pain caused by fractured vertebrae, there are few good treatments. And many patients believe the procedures eased their pain and increased their mobility.

“That’s why people don’t want to let go of this,” said Dr. Alan S. Hilibrand, a professor of neurological surgery at Jefferson University and a spokesman for the American Academy of Orthopaedic Surgeons.

Surgeons use two methods to deliver the bone cement.

In one operation, vertebroplasty, the cement is injected directly into the injured vertebra. In a newer procedure, kyphoplasty, doctors inflate a balloon to elevate the broken bone into position, and then inject the cement.

The treatments are widely advertised and promoted by companies that make surgical devices and bone cement, as well as groups such as the National Osteoporosis Foundation.

Insurers generally cover the treatments. Medicare pays about $2,400 to $3,000 for vertebroplasty, and $6,500 to $10,000 for kyphoplasty, depending on where the procedure is performed.

To assess the effectiveness of the two methods, the task force reviewed previously published data.

Vertebroplasty was tested in five rigorous trials with placebo controls, the task force found. Subjects who received sham procedures reported just as much pain relief.

Moreover, for those who had the treatment, pain relief did not last, said Dr. Bart Clarke, president of the A.S.B.M.R., who wrote a perspective accompanying the task force report.

After a month, pain among these patients was no less than it was among patients who did not have cement injections.

Kyphoplasty has not been subjected to such rigorous evaluations, but it has been compared with vertebroplasty in a few small trials.In terms of pain relief, the two procedures were roughly equivalent.

“If one of these procedures is going to be offered, the patient should be informed that there is a minimal chance it will help,” said Dr. Ebeling, who conducted one of the first randomized trials of vertebroplasty.

“The natural history is that pain will get better over the next four to six weeks,” he added. “That’s what I tell my patients.”

Australia's health care system stopped paying for the procedures in 2010, after two placebo-controlled trials failed to find a significant effect, and their use dropped by about 70 percent, Dr. Ebeling said.

The problem for doctors and patients is that even if the pain diminishes with time, patients may be desperate for relief in the short term. The cement injections can seem to offer that.

Suppose a patient is incapacitated by pain from a broken vertebra, said Dr. Joshua A. Hirsch, a back-pain specialist at Massachusetts General Hospital. Is it so bad to offer bone cement?

"You have a choice," said Dr. Hirsch. "Opiates and lying in bed with diminished activity, or a procedure that can mobilize patients and improve them."

Then there are the difficult patients, perhaps 10 percent of the total, whose severe pain lingers for months.

Dr. Hilibrand said he agrees with the task force's findings, but if patients "still have recalcitrant pain one to three months after the fracture, this is an option. Do you withhold treatment and have them continue to suffer?"

Dr. David Kallmes, a radiologist at the Mayo Clinic and one of the first doctors to cast doubt on vertebroplasty, said he understands the appeal.

"I have seen miracles with vertebroplasty," he said. "But the data are the data."

He tries to talk patients out of the treatment, describing the risks, which are small but real, including bleeding, infections, leakage of the cement, and new fractures from the procedures.

He explains the lack of benefit. But if a patient insists, he sometimes performs the procedure anyway.

"If it's not done by me, it will get done by Joe down the road," he said.

https://bbc.in/2sOlTXS

Mother's appeal after boy diagnosed with autism when he just needed antibiotics

A mother is calling for greater awareness of a little-known condition she believes changed her easy-going son overnight.

Alison Maclaine fears some children are being misdiagnosed with autism and mental health issues when they are really suffering an infection which can be treated simply with antibiotics.

Her eight-year-old son Jack suffered distressing personality changes and "lost a year of his life".

And she said she was left "in despair" that she and her family had "no quality of life".

Now Alison believes he was suffering from Paediatric Acute-onset Neuropsychiatric Syndrome (PANDAS), triggered by a streptococcal infection - a condition that can be treated with simple antibiotics and anti-inflammatories.

Something wrong

Jack went to bed one Friday in January last year, looking forward to a football tournament he was playing in the next day.

But on arrival at the venue on Saturday morning he became overwhelmed with anxiety. After several attempts, he was unable to enter the building.

At home in Dumfries, Alison realised something was very wrong.

She told the BBC: "He started to repeatedly apologise. He said he didn't deserve to have fun, didn't deserve to have friends, didn't deserve to have nice things, didn't deserve to play football.

"That eventually led to 'I don't deserve to live, when I get home I am just going to sit outside until I freeze to death'."

When it came to bedtime, Jack refused to have covers and pillows and started to repeat that he needed to die, until he fell asleep.

The following day saw his behaviour sink further.

Alison said: "One of the worst things in the world must be listening to your child telling you he wanted to die and asking you to help him."

What is PANS/PANDAS?

According to the charity PANS PANDAS UK, PANS (Paediatric Acute-onset Neuropsychiatric Syndrome) is a neuropsychiatric condition which is triggered by a misdirected immune response which results in an inflammation of a child's brain.

PANDAS is a subset of PANS, triggered by a misdirected immune response to a streptococcal infection which results in an inflammation of a child's brain.

Happening very quickly, this can cause a child to exhibit symptoms including anxiety, aggressive behaviour, depression, clumsiness, insomnia and the onset of obsessive-compulsive disorder.

It was first recognised in the United States in 1998 where PANS PANDAS charities estimate as many as one in 200 children could be affected.

In 2018, the World Health Organisation recognised the condition, but in the UK it is not widely known.

There is no clear test for the condition so doctors often have to rule out psychiatric conditions. The immediate response to antibiotic or anti-inflammatory treatment is often what confirms the condition.

The charity PANS PANDAS UK said a failure to understand the condition in the UK means that children are regularly wrongly referred to Child and Adolescent Mental Health Services (CAMHS).

'Absolute despair'

Jack then became aggressive and withdrew from his beloved younger sister Cara. He would become irritable and angry and started to regress, playing with baby toys.

Over the next several months he was repeatedly diagnosed as having autism and severe anxiety.

But Alison, herself a psychiatrist, disagreed.

She said: "It got to the point where I really felt absolute despair. "I felt that he had no quality of life, we had no quality of life. There were times when I contemplated things."

That despair led to Alison doing her own research and the discovery of PANS and PANDAS.

Alison said reading the symptoms was like reading a description of her son and his behavioural changes.

Jack was finally diagnosed privately by a consultant paediatrician in England and treated with simple antibiotics.

They worked overnight and Alison had her son back.

She said: "Jack responded dramatically to the treatment. He hadn't left the street in five months except for school. After two days on antibiotics he wanted to come to Morrisons with me and Cara. It felt like Jack was back."

Alison is frustrated now, believing if Jack had been given got antibiotics when he first presented to the GP in January, the outcome would have been different.

She said: "It is so frustrating knowing the treatment was so simple. Now I hate to think there are other children in the situation that they have this disorder that has not been picked up on and have been sent down a mental health/psychological route which can't fix the problem."

Dr Tim Ubhi, who diagnosed Jack's condition, said: "The problem here is if we do not recognise this condition and we ignore it, potentially there are children out there who are suffering who could actually get treated and actually improve their symptoms.

"So we have a responsibility as physicians to think about this as a condition and do the work to actually create an awareness of what the condition is doing in the UK."

A Scottish government spokeswoman said: "We appreciate that watching any loved one suffer is heartbreaking, even more so when it is a child.

"We are working together with partners to improve the outcomes and support for adults and children with rare conditions, and ensure that everyone receives the appropriate treatment.

"Ministers are unable to make or influence clinical decisions or definitions, and it would not be appropriate for them to do so."

http://bit.ly/2UmMmb0

Muscle memory discovery ends 'use it or lose it' dogma

New research shows that extra nuclei gained during exercise persist even after a muscle shrinks from disuse, disease or aging -- and can be mobilized rapidly to facilitate bigger gains on retraining

The old adage "use it or lose it" tells us: if you stop using your muscles, they'll shrink. Until recently, scientists thought this meant that nuclei - the cell control centers that build and maintain muscle fibers - are also lost to sloth.

But according to a review published in *Frontiers in Physiology*, modern lab techniques now allow us to see that nuclei gained during training persist even when muscle cells shrink due to disuse or start to break down. These residual 'myonuclei' allow more and faster growth when muscles are retrained - suggesting that we can "bank" muscle growth potential in our teens to prevent frailty in old age. It also suggests that athletes who cheat and grow their muscles with steroids may go undetected.

Our biggest cells are in our muscles, and they're all fused together

Syncytium. Sounds like a neo-noir comic book series. It's actually a special type of tissue in your body, where cells are fused together extra close - so close, that they behave a like a giant single cell.

"Heart, bone and even placenta are built on these networks of cells," says Lawrence Schwartz, Professor of Biology at the University of Massachusetts. "But by far our biggest cells - and biggest syncytia - are our muscles." Like the Sin City series, it appeared at first that everything was black and white with syncytia.

"Muscle growth is accompanied by the addition of new nuclei from stem cells to help meet the enhanced synthetic demands of larger muscle cells," explains Schwartz. "This led to the assumption that a given nucleus controls a defined volume of cytoplasm - so that when a muscle shrinks or 'atrophies' due to disuse or disease, the number of myonuclei decreases."

A muscle can gain nuclei, but never loses them

This assumption long seemed valid, with many researchers reporting the presence of disintegrating nuclei in muscle tissue during atrophy induced by inactivity, injury or paralysis. But modern cell-type-specific dyes and genetic markers have shown that the dying nuclei other researchers had detected were in fact inflammatory and other cells recruited to atrophic muscle.

The new evidence paints a very different picture of muscle syncytium.

"Two independent studies - one in rodents and the other in insects - have demonstrated that nuclei are not lost from atrophying muscle fibers, and even remain after muscle death has been initiated."

This suggest that once a nucleus has been acquired by a muscle fiber, it belongs to the muscle syncytium - probably for life. But Schwartz, for one, is unsurprised by the new findings.

"Muscles get damaged during extreme exercise, and often have to weather changes in food availability and other environmental factors that lead to atrophy. They wouldn't last very long giving up their nuclei in response to every one of these insults."

"Use it or lose it - until you use it again"

Since myonuclei are the synthetic engine of muscle fibers, retaining them should enable muscle size and strength to recover more quickly after one of these insults, and help to explain the phenomenon of 'muscle memory'.

"It is well documented in the field of exercise physiology that it is far easier to reacquire a certain level of muscle fitness through exercise than it was to achieve it the first place, even if there has been a long intervening period of detraining. In other word, the phrase "use it or lose it" is might be more accurately articulated as 'use it or lose it, until you work at it again'."

As such, the findings have important implications beyond understanding muscle biology.

"Informing public health policy, the discovery that myonuclei are retained indefinitely emphasizes the importance of exercise in early life. During adolescence muscle growth is enhanced by hormones, nutrition and a robust pool of stem cells, making it an ideal period for individuals to "bank" myonuclei that could be drawn upon to remain active in old age."

The findings also support frequent drugs testing for competitive athletes, with permanent bans for proven steroid cheats since they will benefit from the steroids long after their use has ended.

"Anabolic steroids produce a permanent increase in users' capacity for muscle development. In keeping with this, studies show that mice given testosterone acquire new myonuclei that persist long after the steroid use ends."

Please link to the original research article in your reporting: *https://www.frontiersin.org/articles/10.3389/fphys.2018.01887/full*

http://bit.ly/2CKuNu5

Study suggests aspirin may help some patients survive head and neck cancer

Regular use of NSAIDs may help some patients survive head and neck cancer

Regular use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may help some patients with head and neck cancer survive the disease, according to a study led by Professor Jennifer Grandis at the University of California, San Francisco. The study, which will be published January 25 in the *Journal of Experimental Medicine*, indicates that NSAIDs are effective in patients with mutations in a gene called *PIK3CA*, and the researchers suggest this is because NSAIDs lower the levels of an inflammatory molecule called prostaglandin E_2. The researchers note, however, that they are not yet able to make any specific recommendations about the type, timing, or dosage of NSAIDs such patients should take, and that their results need to be corroborated by a prospective clinical trial.

Head and neck squamous cell carcinoma (HNSCC) accounts for about 4% of all cancers in the US and continues to have high rates of patient mortality. Risk factors for HNSCC include smoking, alcohol use, and human papillomavirus infection, but several studies have shown that regular use of aspirin can reduce the risk of developing the disease. However, whether aspirin or other NSAIDs can promote the survival of patients who have already developed HNSCC is unclear; studies investigating this question have so far produced conflicting results.

One possibility is that NSAIDs are only effective against some types of HNSCC. Around 35% of HNSCC tumors carry mutations that activate the *PIK3CA* gene, which encodes the catalytic subunit of a key signaling enzyme called PI3Ka. The team of researchers led by Dr. Grandis investigated whether regular NSAID use specifically improved the survival of HNSCC patients with alterations in the *PIK3CA* gene.

The team, which also included researchers from the University of Pittsburgh School of Medicine and the University of Arizona, analyzed a group of 266 HNSCC patients who had had their tumors surgically removed and, in most cases, were then treated with adjuvant chemotherapy and/or radiotherapy.

Patients without any alterations in their *PIK3CA* gene were no better off if they also took NSAIDs on a regular basis (defined as taking two or more doses per week for at least six months). By contrast,

regular NSAID usage dramatically enhanced the survival of patients whose *PIK3CA* gene was mutated and/or amplified. Among these patients, NSAIDs increased the overall five-year survival rate from 45% to 78%.

NSAIDs also reduced the growth of tumors in mice injected with cancer cells harboring a mutant *PIK3CA* gene. By analyzing these mice, Grandis and colleagues found that NSAIDs likely inhibit tumor growth by reducing the production of prostaglandin E_2. This proinflammatory molecule has been implicated in a variety of cancers and can be induced by the PI3Ka signaling pathway. NSAIDs may therefore also be effective against a variety of cancers that contain activating mutations in the *PIK3CA* gene. Indeed, previous studies have shown that regular aspirin usage can aid the survival of colorectal cancer patients carrying mutated *PIK3CA*.

"The present study is the first to demonstrate that regular NSAID usage confers a significant clinical advantage in patients with *PIK3CA*-altered HNSCC," Grandis says. "Inconsistencies in the type, timing, and dosages of NSAIDs taken by patients in this study limit our ability to make specific therapeutic recommendations. But the magnitude of the apparent advantage, especially given the marked morbidity and mortality of this disease, warrants further study in a prospective, randomized clinical trial."

Hedberg et al., 2019. J. Exp. Med.
http://jem.rupress.org/cgi/doi/10.1084/jem.20181936?PR

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A Drunk Man Swallowed a Live, Venomous, Spiny Catfish. Here's What Happened.

Fish-swallowing game was a "bizarre" tradition among some young people

By Rafi Letzter, Staff Writer | January 25, 2019 07:12am ET

There are all sorts of drinking traditions. Some people sing songs as they down their alcohol. Others dance to thumping music.

Somewhere in the vicinity of Rotterdam, in the Netherlands, a group of young men, apparently inspired by the American television show "Jackass," got in the habit of capping off their boozing by swallowing live fish. This, it turns out, is a bad idea. Especially in the event that the fish have evolved to fight back.

The bronze catfish skeleton, minus its tail, can now be found in the Natural History Museum Rotterdam alongside its amputated pectoral fin. **Benoist et al.**

According to a recent case report published on Jan. 17 in the journal Acta Oto-Laryngologica Case Reports, the young men typically swallowed live goldfish out of their home aquarium — small, squishy creatures that don't put up much of a fight. The fun stopped on April 3, 2016, when one of the men tried to take their tradition a bit further by swallowing a bronze catfish (*Corydoras aeneus*), a popular aquarium fish with some powerful natural defenses.

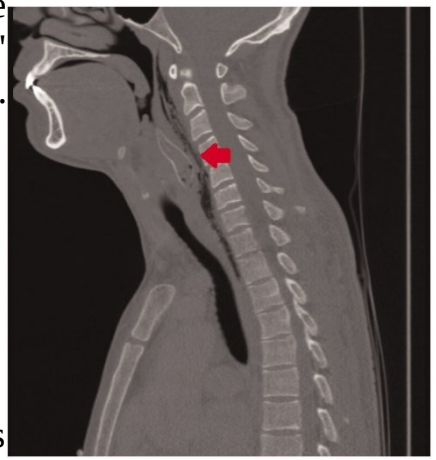
Perhaps unsurprisingly, the night ended with the 28-year-old man in the emergency room, where puzzled doctors carefully removed the spiny fish from the man's throat.

"Most animals know better"

Most animals know better than to eat bronze catfish, said Kees Moeliker, a director at the Rotterdam Natural History Museum who reviewed the catfish remains after doctors removed them from the man's throat. That's for a good reason: Their cute 2- to 3-inch bodies (5 to 8 centimeters) are defended with spines, mounted on their pectoral fins. When the fish get stressed out — say, for example, when they're being swallowed by a predator — those spines become erect and can pump venom into the mouths of their attackers.

Because of this, bronze catfish "don't have predators like birds and other fishes," Moeliker told Live Science. "Those who give it a try die, and natural selection does its work."

Indeed, in the man's case, it appears that he quickly realized that he had made a grave mistake, according to a video of the incident that was described by the case report authors. Unfortunately, the video was not available for Live Science to review or share. But the report includes a vivid description of what it showed. In the video, a crowd of men stood around drinking and shouting "grote vis, grote vis!" (Dutch for "Big fish! Big fish!") One guy, holding a glass of clear water with the live catfish in it, tips it back, attempting to swallow it whole. Four seconds later, he spit the water and the fish out into his hands, and threw it on the table, where it floundered, appearing "distressed" and "agonized," according to the report. That might have been the end of it, if someone hadn't plucked the flopping catfish off the table and handed it to a third man, a 28-year-old whose trauma would become the subject of the case report. This unfortunate fellow swallowed some beer, and then dropped the still-living creature into his throat.



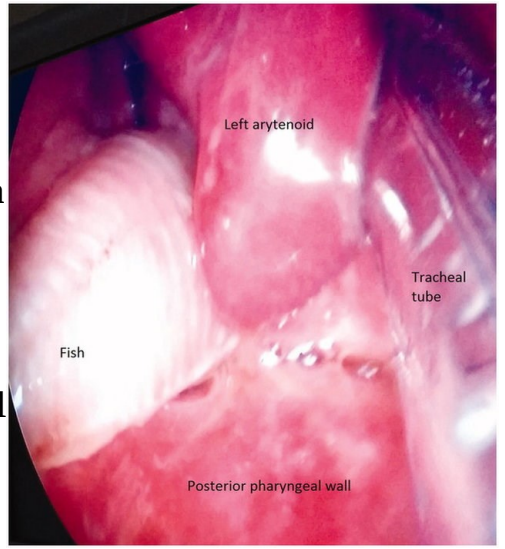
A CT scan shows where the main body of the fish lodged itself. **Benoist et al.**

Immediately, it was obvious something had gone wrong. The man tried to swallow more beer but couldn't. Ten seconds later, he was "gagging vigorously" and vomiting liquid. "In extreme distress," he shoved two fingers down his throat, trying to make himself gag but no luck. Someone administered what the doctors described as a "wrongly-applied Heimlich maneuver," which again failed to produce the fish. The man spewed some blood into a bucket, and then the camera switched off.

Even so, the man apparently waited "several hours" before going to the hospital, after trying but failing to dislodge the fish with "more beer, honey and ice cream."

A "fish-like" structure

When the man finally made it to the emergency room, doctors looked down his throat using a tool called a laryngoscope, and spotted what they described as "a fish-like structure," according to the report.



An image shows what that catfish looked like in the man's throat prior to removal. **Benoist et al.**

"This is definitely in the top three of weirdest medical cases I've encountered," said case report co-author Dr. Linda Benoist, a medical resident at Rotterdam's University Medical Center who treated the patient. Benoist told Live Science that she had been aware that the fish-swallowing game was a "bizarre" tradition among some young people in the area.

The catfish, she said, was already dead when the patient arrived, pressed up against the entrance to the man's esophagus, at the bottom of his throat. (The fish had probably suffocated, Moeliker said, noting that a few swallows of beer do not contain enough water for a fish to breathe in).

The man needed surgery to remove the fish, with the surgeons paying very close attention to carefully remove the fish's spines from the delicate tissue in the throat. .

Fortunately, the procedure was a success. Though not much is known about the effects of bronze catfish venom on humans, it didn't appear

to complicate the situation. As of the man's most recent follow-up with doctors, in March 2017, he is doing well.

The fish, meanwhile, ended up preserved at the Rotterdam Natural History Museum, which is right next door to the hospital. It joined an exhibit called "Dead Animal Tales" on dramatic collisions between animals and humans, Moeliker said.

Asked whether the drinking game is dangerous when only goldfish are involved, Benoist said, "I'm not an expert in goldfish swallowers, but I can imagine that fish species without [spikes] would slide easier into the stomach."

Still, the researchers did highlight some other case studies where people choked on live fish, including one instance where a fisherman attempted to kiss a fish but it slid into his throat. Live Science recommends eating fish dead and in bite-size pieces.

http://bit.ly/2DCOTYQ

Apollo Astronauts May Have Found the Oldest-Known Earth Rock on the Moon

One of Earth's oldest rocks may have been dug up on the moon.

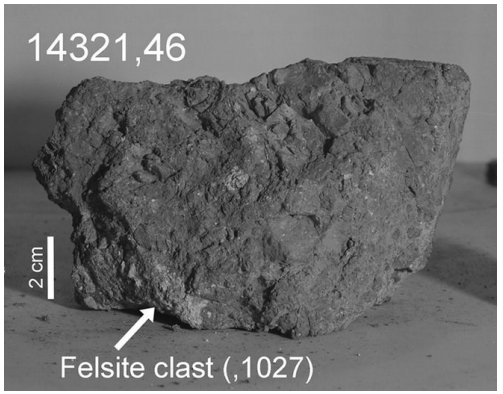
By Mike Wall, Space.com Senior Writer

A chunk of material brought back from the lunar surface by Apollo astronauts in 1971 harbors a tiny piece of Earth, a new study suggests. The Earth fragment was likely blasted off our planet by a powerful impact about 4 billion years ago, according to the new research.

"It is an extraordinary find that helps paint a better picture of early Earth and the bombardment that modified our planet during the dawn of life," study co-author David Kring, a Universities Space Research Association (USRA) scientist at the Lunar and Planetary Institute in Houston, said in a statement. (Biologists generally believe that life got a foothold on Earth between 4.1 billion and 3.8 billion years ago.)

The research team — led by Jeremy Bellucci, of the Swedish Museum of Natural History, and Alexander Nemchin, of the Swedish Museum and Curtin University in Australia — analyzed lunar samples collected by members of the Apollo 14 mission, which explored the lunar surface for a few days in early February 1971.

The scientists found that one rock contained a 0.08-ounce (2 grams) fragment composed of quartz, feldspar and zircon, all of which are rare on the moon but common here on Earth. Chemical analyses indicated that the fragment crystallized in an oxidized environment, at temperatures consistent with those found in the near subsurface of the early Earth, study team members said.



A moon rock brought back by Apollo 14 astronauts in 1971 may contain a tiny piece of the ancient Earth (the "felsite clast" identified by the arrow).
NASA/LPI/USRA/Bellucci et al.

The available evidence suggests that the fragment crystallized 4.1 billion to 4 billion years ago about 12 miles (20 kilometers) beneath Earth's surface, then was launched into space by a powerful impact shortly thereafter.

The voyaging Earth rock soon made its way to the moon, which was then about three times closer to our planet than it is today. (The moon is still retreating from us, at a rate of about 1.5 inches, or 3.8 centimeters, per year.) The fragment endured further trauma on the lunar surface. It was partially melted, and probably buried, by an impact about 3.9 billion years ago, then excavated by yet another impact 26 million years ago, the researchers said.

This latest collision created the 1,115-foot-wide (340 meters) Cone Crater, whose environs Apollo 14 astronauts Alan Shepard and Edgar Mitchell explored and sampled 47 years ago. (The third Apollo 14 crewmember, Stuart Roosa, stayed in lunar orbit aboard the mission's command module.)

An Earth origin for the ancient fragment isn't a slam dunk, study team members stressed. However, it is the simplest explanation; a lunar birth would require a rethink of the conditions present in the moon's interior long ago, the researchers said.

The new study was published online Thursday (Jan. 24) in the journal Earth and Planetary Science Letters.

http://bit.ly/2G3L0h9

Flu viruses resistant to new drug Xofluza uncovered in Japan

Mutated influenza viruses resistant to baloxavir marboxil, a new flu drug sold as Xofluza, were detected in patients last month, the National Institute of Infectious Diseases has said.

This was the first confirmation by a national research institute of such mutations in flu viruses since the drug was put into practical use last March, the health ministry said.

According to the NIID, Xofluza-resistant viruses were found in two of four primary school students in Yokohama in generic screenings in December conducted after they developed flu symptoms earlier the same month.

The mutated viruses were 76 to 120 times more resistant to the new anti-flu drug developed by Shionogi & Co. than unmutated ones detected in the other two children. In clinical trials of baloxavir marboxil, resistant viruses were detected in 23.4 percent of participating patients younger than 12 years old.

The NIID said that it will continue to keep an eye on mutated flu viruses and provide related information swiftly.

Sales of Xofluza have been increasing because only one dose of the drug is enough for treatment, according to the drug maker and other sources.

The health ministry said last week that the number of influenza patients per medical institution in Japan in the week through Jan. 20 had hit the second-highest level since the survey started in 1999.

The average number of flu patients at some 5,000 medical institutions across the country that are regularly monitored grew by 15.37 from the previous week to 53.91, following the record high of 54.33, marked in the previous year, the ministry announced Friday.

The total number of flu patients during the week is estimated at some 2.13 million, up by some 495,000 from the previous week.

https://bbc.in/2DFk8mh

The GM chickens that lay eggs with anti-cancer drugs

Researchers have genetically modified chickens that can lay eggs that contain drugs for arthritis and some cancers.

By Pallab Ghosh Science correspondent, BBC News

The drugs are 100 times cheaper to produce when laid than when manufactured in factories.

The researchers believe that in time production can be scaled up to produce medicines in commercial quantities.

The chickens do not suffer and are "pampered" compared to farm animals, according to Dr Lissa Herron, of Roslin Technologies in Edinburgh.

"They live in very large pens. They are fed and watered and looked after on a daily basis by highly trained technicians, and live quite a comfortable life.

"As far as the chicken knows, it's just laying a normal egg. It doesn't affect its health in any way, it's just chugging away, laying eggs as normal."

Scientists have previously shown that genetically modified goats, rabbits and chickens can be used to produce protein therapies in their milk or eggs. The researchers say their new approach is more efficient, produces better yields and is more cost-effective than these previous attempts.

"Production from chickens can cost anywhere from 10 to 100 times less than the factories. So hopefully we'll be looking at at least 10 times lower overall manufacturing cost" said Dr Herron.

Image copyright Norrie Russell, The Roslin Institute Image caption Battery Pharming: these eggs contain drugs produced at a tenth of the cost of normal production in laboratories

The biggest saving comes from the fact that chicken sheds are far cheaper to build and run than highly sterile clean rooms for factory production.

Many diseases are caused because the body does not naturally produce enough of a certain chemical or protein. Such diseases can be controlled with drugs that contain the deficient protein. These drugs are synthetically produced by pharmaceutical companies and can be very expensive to manufacture.

Dr Herron and her colleagues managed to reduce the costs by inserting a human gene - which normally produces the protein in humans - into the part of the chickens' DNA involved with producing the white in the chickens' eggs.

No yoke!

After cracking the eggs and separating the white from the yoke, Dr Herron discovered that the chicken had relatively large quantities of the protein.

The team has focused on two proteins that are essential to the immune system: one is IFNalpha2a, which has powerful antiviral and anti-cancer effects, and the other is macrophage-CSF, which is being developed as a therapy that stimulates damaged tissues to repair themselves.

Three eggs are enough to produce a dose of the drug, and chickens can lay up to 300 eggs per year. With enough chickens, the researchers believe they can produce drugs in commercial quantities.

The development of drugs for human health, and the regulatory hoops required, will take between 10 and 20 years. The researchers are hopeful of using chickens to develop drugs for animal health.

These include drugs which boost the immune systems of farm animals as an alternative to antibiotics, which would reduce the risk of the development of new strains of antibiotic-resistant superbugs.

And there is the potential to use the healing properties of macrophage-CSF to treat pets, according to Dr Herron.

"For example, we could use it in regenerating the liver or the kidneys of a pet that has suffered damage to these organs. The drugs currently available are a bit too pricey so we hope that we might be able to get into that a little more."

Professor Helen Sang, of the University of Edinburgh's Roslin Institute, said: "We are not yet producing medicines for people, but this study shows that chickens are commercially viable for producing proteins suitable for drug discovery studies and other applications in biotechnology."