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High doses of 60 plus-year-old chemo drug found to spur immune system attack on lymphoma

Cyclophosphamide not only kills cancer cells directly in large doses, but also spurs an immune system attack on the cells

More than 60 years ago, British physician Denis Parsons Burkitt and his associates achieved one of the signal successes in cancer medicine when they cured children in sub-Saharan Africa with a form of lymphoma by treating them with high doses of the chemotherapy drug cyclophosphamide. Now, Dana-Farber Cancer Institute researchers have shown that the traditional understanding of the drug's mode of action is incomplete.

In a paper in today's issue of the journal Cancer Discovery, the researchers demonstrate that large doses of cyclophosphamide not only kill cancer cells directly, as has been known, but also spur an immune system attack on the cells. The discovery resolves long-standing questions about how cyclophosphamide and other alkylating agents - among the oldest and most widely used types of chemotherapy - work, and suggests a novel way of sparking an immune system strike on certain cancers.

"Our results show that, at high doses, cyclophosphamide and other alkylating agents blur the line between chemotherapy and immunotherapy," said Dana-Farber's David Weinstock, MD, the senior author of the study. "These findings offer insights into how to switch on key immune system cells to augment existing therapies."

Cyclophosphamide was just the eighth anti-cancer drug to enter standard therapy when it was approved by the U.S. Food and Drug Administration in 1954. It became a mainstay of cancer treatment after Burkitt and others used high doses to cure children with what's now known as Burkitt lymphoma - which had a 100% mortality rate at the time - sometimes with only one dose. Cyclophosphamide and other alkylating agents are now used at lower doses to treat many types of cancer, including breast, ovarian, and pediatric cancers.

Alkylating agents work by attaching chemical components called alkyl groups to cancer cells' DNA, leading to breaks in the DNA molecule. The damage undermines the cells' ability to duplicate their DNA and, ultimately, to divide.

Over the years, clues emerged that there's more to the drugs' effectiveness than damaging DNA. Researchers discovered, for example, that while high doses are much more effective against certain cancers than low doses, they inflict about the same amount of DNA damage, suggesting that something else comes into play at high doses. Sporadic data pointed to the immune system.

Another clue came from pathology studies of Burkitt lymphoma tissue. "Burkitt lymphoma and other high-grade lymphomas with rearrangements in the MYC gene have a 'starry sky' appearance under the microscope, with large numbers of macrophages [a type of immune system cell] dispersed among the lymphoma cells," Weinstock remarked.

In the new study, investigators focused on the effect of high doses of cyclophosphamide on macrophages - cells that, under the right conditions, eat infected cells or cells in the process of dying. In mouse models implanted with human lymphoma tissue, the researchers showed that high doses of the drug, but not normal doses, damaged tumor cells in a way that severely stressed the lymphoma cells. The stressed cells responded by secreting cytokines, substances that summon macrophages to eat the tumor cells.

The researchers analyzed thousands of these macrophages to determine which genes were active, or expressed, in each of them. They found that one subset, which expresses the proteins CD36 and FcgRIV, has a particularly voracious appetite for stressed

lymphoma cells. Dubbed "super-macrophages," they devour lymphoma cells, Weinstock said.

Although high doses of cyclophosphamide and other alkylating agents may be too toxic for patients with diseases other than Burkitt lymphoma, researchers are investigating agents that mimic their ability to stress cancer cells, but with milder side effects.

The findings may be especially relevant for the treatment of "double-hit" lymphomas, which are marked by their aggressiveness and for a rearrangement in the MYC gene, Weinstock observed. Targeted therapies are currently lacking for this disease, which accounts for six to 10% of diffuse large B cell lymphomas and generally has poor outcomes for patients.

The lead author of the study is Chen Lossos of Dana-Farber. Co-authors are Amanda L. Christie, MSc, Alexandria Van Scoyk, Kay Shigemori, Kristen E. Stevenson, Sara Morrow, Olivia D. Plana, Kristen L. Jones, Huiyun Liu, Rebecca Modiste, and Quang-De Nguyen, PhD, of Dana-Farber; Yunpeng Liu and Michael T. Hemann, of the Broad Institute of MIT and Harvard University and the Koch Institute for Integrative Cancer Research at MIT; Kellie E. Kolb, Sanjay M. Prakadan, PhD, and Alex K. Shalek, PhD, of the Broad Institute, Institute for Medical Engineering and Science, the Koch Institute for Integrative Cancer Research at MIT, and the Ragon Institute of MGH, MIT, and Harvard; Cameron Fraser and Kristopher A. Sarosiek, PhD, of Harvard T.H. Chan School of Public Health and Harvard Medical School; Christian P. Pallasch of University Hospital of Cologne, Cologne, Germany; Jeffrey W. Craig, MD, Elizabeth A. Morgan, MD, and Jon C. Aster, MD, PhD, of Brigham and Women's Hospital; and Francisco Vega, MD, PhD, of University of Miami/Sylvester Comprehensive Cancer Center.

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http://bit.ly/2LGAMpR

A bacteria likely to reduce the cardiovascular risks of 1 in 2 people

University of Louvain research in world premiere

In 2007, Patrice Cani (FNRS-WELBIO researcher) and his team at the Louvain Drug Research Institute of University of Louvain, in close collaboration with Willem de Vos, professor at UWageningen, discovered the beneficial effects of an intestinal bacteria, Akkermansia muciniphila [(1),] able to moderate the development of obesity and type 2 diabetes, in mice. In 2017, the team discovered (still in the mouse) that the use of a pasteurized form of Akkermansia leads to an even greater protection than the living bacterium regarding various cardiovascular disease risk factors such as insulin resistance, hypercholesterolemia, or the storage of fat in adipose tissue.

Following these discoveries, the UCLouvain team, in collaboration with the Cliniques universitaires Saint-Luc [(2),] developed a clinical study in order to administer the bacteria to humans. For this, it was necessary to develop the capacity to produce the bacterium in large quantity and to make sure that the tests would be without risk for the participants.

The UCLouvain researchers administered Akkermansia to overweight or obese volunteers, all displaying insulin resistance (pre-diabetes type 2) and metabolic syndrome, in other words, having several elevated risk factors for cardiovascular diseases. The volunteers were randomly divided into 3 groups (placebo, live bacteria and pasteurized bacteria) and were asked not to change their dietary habits or their physical activity. Akkermansia was provided as a nutritional supplement.

The primary goal of this UCLouvain study was to demonstrate the feasibility of daily ingesting Akkermansia for 3 months, without risk. Clara Depommier and Amandine Everard, UCLouvain researchers, observed excellent compliance (the supplements were easy to ingest) and tolerance (there were no side effects) in the groups taking live or pasteurized bacteria.

The conclusions are clear: the tests in humans confirm what had already been observed in mice. Ingestion of the (pasteurized) bacterium prevented the deterioration of the health status of the subjects (pre-diabetes, cardiovascular risks). Even better, the researchers observed a decrease in inflammation markers in the liver, a slight decrease in the body weight of the subjects (2.3 kg on average [(3)]) as well as a lowering of cholesterol levels. In contrast, the metabolic parameters (insulin resistance or hypercholesterolemia) in placebo subjects continued to deteriorate over time.

Who does it benefit? According to the WHO, one in three people die every day from cardiovascular disease worldwide. In Western countries, one in two people is overweight and has increased cardiovascular risks. This research of the UCLouvain would limit these risks and therefore potentially have an impact (limit the effects) on half of the population, if properly used.

In conclusion, this pilot study demonstrates the feasibility of administrating (pasteurized) Akkermansia bacteria to humans in the form of a food supplement and reports encouraging results on the effectiveness of the Akkermansia-based dietary supplements to reduce cardio-metabolic risk factors. These results pave the way for a large-scale study, to confirm/elaborate these first results, but also endorse the commercialization of the bacteria as food supplements, by 2021.

A generic email address has been created for the public who wants more information about the current clinical study: akkermansia@uclouvain.be.

To carry out this research, Patrice Cani has benefited from several fundings, via the FNRS (Belgian Research National Funds), the EOS (EU Excellence of Science), the Funds Baillet-Latour, the WELBIO, the Bank Transatlantic Belgium, the Walloon Region (DGO6) and two European ERC grants (starting and proof of concept).

[(1)]Bacteria naturally present in large quantities in healthy people

[(2)]Prof. Jean-Paul Thissen, Prof. Michel Hermans, Prof. Dominique Maiter, Dr. Audrey Loumaye

[(3)]These results are statistically considered non-significant. That said, according to the precise analysis of the different intestinal bacteria (in collaboration with the team of Prof. Raes of the KULeuven), the observed effects are independent of a general modification of the microbiota and therefore probably specific to the action of Akkermansia.

http://bit.ly/2XtPacl

Study shows some generics can cost Medicare recipients more than brand-name drugs

Medicare enrollees may pay more out of pocket for high-priced specialty generic drugs than their brand-name counterparts

Medicare Part D enrollees may pay more out of pocket for high-priced specialty generic drugs than their brand-name counterparts, according to new research by health policy experts at Vanderbilt University Medical Center and the University of North Carolina at Chapel Hill.

Researchers examined differences in brand-name and generic or biosimilar drug prices, formulary coverage and expected out-of-pocket spending across all of the Medicare Part D plans available in the U.S. in the first quarter of 2018.

The study, published in the July issue of Health Affairs, found that current Medicare Part D beneficiaries can have higher out-of-pocket spending for generics than their branded counterparts if they use expensive specialty drugs and if the price differences between brands and generics are not large. This can be common for individuals prescribed specialty drugs typically used to treat rare or complex conditions such as cancer, rheumatoid arthritis or multiple sclerosis.

"Ironically, even if we assume that generic drugs have lower list prices than brands, for Medicare beneficiaries with $20,000 to $80,000 in annual drug spending, using only brand-name drugs could actually save them money," said Stacie Dusetzina, PhD, associate professor of Health Policy and Ingram Associate Professor of Cancer Research at VUMC, the study's lead author.

"This is happening because branded drug manufacturers now pay a discount in the donut hole, which gets counted as out-of-pocket

spending," she said. "This helps patients reach catastrophic coverage faster, where they pay 5% of the drug's price instead of 25%. Generic drug makers do not pay these same discounts, so patients have to spend more of their own money to make it to the catastrophic phase of the benefit."

In 2019, this means people using brand-name drugs who reach the donut hole, or coverage gap, have to spend $982 to get to the catastrophic coverage phase. People using generic drugs have to spend $3,730 to reach that point. The study also notes policy changes set to take effect in 2020 will only make the situation worse by increasing patient out-of-pocket spending requirements for the catastrophic phase coverage from $5,100 to $6,350.

In response, the Trump administration and the Medicare Payment Advisory Commission (MedPAC) have included recommendations to exclude the manufacturer discount from out-of-pocket spending calculations.

"While this would level the playing field between generic drugs and brands, it would do so by making brand-name drugs more expensive instead of making generic drugs less expensive," said Dusetzina. "Congressional committees have signaled interest in addressing this and other issues in Medicare Part D, including placing a cap on out-of-pocket spending.

"The Part D benefit needs a redesign so that it works for people needing expensive drugs. I hope Congress will take this opportunity to make changes to Part D, including making sure that generic drug users aren't overpaying for these drugs."

In addition to Dusetzina, study authors are Shelly Jazowski, a doctoral student in the Department of Health Policy and Management at the University of North Carolina at Chapel Hill (UNC-Chapel Hill) and predoctoral fellow in the Department of Population Health Sciences at Duke University; Ashley Cole, a fellow at the Cecil G. Sheps Center for Health Services Research at UNC-Chapel Hill; and Joel Nguyen, a doctoral student in the UNC Eshelman School of Pharmacy at UNC-Chapel Hill.

https://wb.md/30dOLrq

Five Things We Found in the FDA's Hidden Device Database

After two decades of keeping the public in the dark about millions of medical device malfunctions and injuries, the Food and Drug Administration has published the once hidden database online, revealing 5.7 million incidents publicly for the first time.

Sydney Lupkin

The newfound transparency follows a Kaiser Health News investigation that revealed device manufacturers, for the past two decades, had been sending reports of injuries or malfunctions to the little-known database, bypassing the public FDA database that's pored over by doctors, researchers and patients. Millions of reports, related to everything from breast implants to surgical staplers, were sent to the agency as "alternative summary" reports instead. Here's what we found in those newly public reports:

1. Blood glucose meters for patients with diabetes had more unique incidents than any other device in the database, logging 2.4 million reports over the past 20 years.

Almost all the products were made by LifeScan, which had been a Johnson & Johnson company until it was sold to a private equity firm in 2018. Common problems included displaying incorrect messages, losing power or being damaged before customers started using them, according to the database.

"When you're trying to manage a chronic disease, and especially if your numbers are dangerously high, that's life-threatening," said Linda Radach, who chairs the medical device committee for the Patient Safety Action Network.

LifeScan did not return requests for comment.

The FDA said the number of glucose meter problems in the alternative summary reporting database shouldn't be a surprise.

"Approximately 10% of the U.S. population has diabetes and most rely on these devices several times a day," said FDA spokesman Michael Felberbaum. The agency also sees a "high volume" of adverse events for glucose meters in its longtime public database, called MAUDE, he said.

He reiterated that the alternative summary reporting program was intended for "well-understood" adverse events "so that we could focus more resources on identifying and taking action on new safety signals and less understood risks."

2. There were 2.1 million reports for bad dental implants. And 114,200 were reported last year.

This kind of implant goes into the bone to support an artificial tooth or implant. Many of the reports were for problems with connections between the device and the bone.

"A lot of people have gone out and gotten these and probably don't know about these risks," said Madris Tomes, a former FDA manager who now runs a website to make the notoriously clunky MAUDE easier to work with.

Dental implants were among the last device types to lose permission to report harm via alternative summary reports instead of the public database. Although the device harm data doesn't include what happened to patients, Tomes said that if a dental implant has to be removed, it often can't be replaced because the underlying bone is so damaged.

Felberbaum said that the high number of reports for dental implants is expected because these are commonly used devices, and that more companies have brought new products to market in the past two decades.

3. There were 176 deaths reported through the alternative summary reporting system.

Alternative summary reports are not supposed to include deaths, except for cardiac arrest potentially caused by certain kinds of heart valves that were implanted at least five years beforehand. Those accounted for two-thirds of the deaths in the hidden database, KHN found.

The most recent death was reported last fall by Medtronic, and it was related to a MiniMed Paradigm insulin pump that was hard to program or calibrate. Deaths reported to the once-hidden database also included fatalities associated with two kinds of pacemakers, a breast implant, an intra-aortic balloon pump and a ventilator.

When asked why these were there, the FDA said its "standard practice" was to reach out to the manufacturer for more information when it detected an "ineligible event" in the alternative summary reports. Sometimes, a death was reported in error. Sometimes, the FDA required the manufacturer to report an incident to the public database as well. KHN found that of the 59 ineligible deaths, only eight appeared to be revised in updated alternative summary reports.

"In some cases, the FDA revoked ASR exemptions following continued reporting of ineligible events in ASRs," said Felberbaum, adding that ineligible deaths represented "0.001% of all reports received through the ASR program."

The FDA contacted Medtronic "a number of weeks ago" about the 2018 insulin pump death, said company spokeswoman Pamela Reese. The death was not reported to MAUDE because the "alleged" device malfunction "did not cause or contribute to the patient death," she said, adding that it was actually caused by "stroke and pneumonia." She said that the company was in compliance with reporting rules and that the FDA has not asked Medtronic any additional questions about it.

"One has to wonder what other information wasn't made public if something that clear-cut [the instruction not to include deaths in the ASR] was included and hidden from the public," said Diana Zuckerman, president of the nonprofit National Center for Health Research. "Did FDA notice?"

4. Surgical stapler-related malfunctions accounted for more than 66,000 previously hidden incidents since 2001.

The KHN investigation spotlighted problems with staplers, which tend to be used in minimally invasive surgery to cut and seal tissue and vessels quickly. Although the FDA received only 84 reports for stapler-related harm in the public database, it acknowledged earlier this year that it had received nearly 10,000 reports through alternative summary reporting.

The most common problems were staplers that failed to fire or fired malformed staples. Nearly 4,700 stapler problems were reported through the hidden database in 2017 alone. If a stapler fails to seal tissue properly during surgery, it can lead to serious bleeding or infection. An FDA advisory panel last month recommended the agency switch staplers to a higher-risk classification with more safety requirements.

5. Breast implant injuries and malfunctions accounted for nearly half a million unique reports over two decades, including implants that leaked, deflated or migrated.

More than 6,600 incidents have been reported in 2019 by three companies: Allergan, Mentor and Sientra. The most common problem was rupture.

Tomes was especially concerned about cancer attributed to breast implants, which was the subject of an investigation by the International Consortium of Investigative Journalists last fall. But without publicly available data tracking patient problems, which exists in adverse events data for drugs but not devices, it's impossible to say. "How is the public supposed to make sense of this if they've redacted patient safety codes?" she asked.

Plus: Thousands of medical device types are still eligible for reporting outside the FDA's public database.

There are still ways that device makers can avoid submitting individual injuries and malfunctions to the MAUDE database.

To replace the ASR program, the FDA has launched the Voluntary Summary Reporting Program. More than 5,600 device types — or 87% of them — are eligible for summary reporting of device malfunctions, according to FDA records.

Patient advocates say they fear that these will be just as difficult to tally and track as ASRs. For example, a summary report for 156 injuries would appear to be a single MAUDE report with a note that it represents 156 injuries, not one. "Why would you end one [hidden data program] just to start another?" Radach asked.

Methodology

To avoid double-counting adverse events, KHN counted each event identified with a unique report ID only once, unless otherwise noted. Although this isn't the norm, some companies appear to have recycled report IDs, using them for more than one event. As a result, our counts may be underestimated.

http://bit.ly/2NuIqpJ

Bonobo diet of aquatic greens may hold clues to human evolution

Bonobos foraging in swamps for iodine-rich aquatic herbs may explain how the nutritional needs of prehistoric humans in the region were met

by BioMed Central

Observations of bonobos in the Congo basin foraging in swamps for aquatic herbs rich in iodine, a critical nutrient for brain development and higher cognitive abilities, may explain how the nutritional needs of prehistoric humans in the region were met. This is the first report of iodine consumption by a nonhuman primate and it is published in the open access journal *BMC Zoology*.

Dr. Gottfried Hohmann, from the Max Planck Institute for Evolutionary Anthropology, the lead author of the study said: "Our results have implications for our understanding of the immigration of prehistoric human populations into the Congo basin.

Bonobos as a species can be expected to have similar iodine requirements to humans, so our study offers—for the first time—a possible answer on how pre-industrial human migrants may have survived in the Congo basin without artificial supplementation of iodine."

Credit: Zana Clay, LuiKotale Bonobo Project

The researchers made behavioural observations of two bonobo communities in the LuiKotale forest in Salonga National Park, Democratic Republic of Congo. These observations were combined with data on the iodine content of plants eaten by bonobos from an ongoing study by the Leibniz Institute for Zoo and Wildlife Research, Berlin.

They found that the aquatic herbs consumed by bonobos are a surprisingly rich natural source of iodine in the Congo basin, a region that was previously thought to be scarce in iodine sources.

Dr. Hohmann said: "Evolutionary scenarios suggest that major developments of human evolution are associated with living in coastal areas, which offer a diet that triggered brain development in hominins. The results of our study suggest that consumption of aquatic herbs from swamps in forest habitat could have contributed to satisfying the iodine requirements of hominin populations used to diets prevalent in coastal environments."

He added: "Our report potentially answers the question of how apes obtain iodine from natural food sources, when many populations inhabit areas considered to be iodine deficient. Other apes such as chimpanzees and gorillas have also been observed eating aquatic herbs, which suggests that they could be obtaining essential iodine from these sources."

The authors caution that without data on the iodine status of wild bonobos, it is difficult to tell how much iodine they absorb, although given the high concentrations in the herbs, it is likely to be substantial. The authors also stress that the iodine concentrations obtained at the field site of LuiKotale may not be reflective of the entire Congo basin.

Fishing for iodine: what aquatic foraging by bonobos tells us about human evolution, Hohmann et al. BMC Zoology 2019, DOI: 10.1186/s40850-019-0043-z

http://bit.ly/328BuSC

The neuroscience of autism: New clues for how condition begins

Scientists have uncovered details of a key cellular mechanism crucial for proper brain development; it involves a gene that, when mutated, had previously been linked to the development of autism

CHAPEL HILL, N.C. - UNC School of Medicine scientists unveiled how a particular gene helps organize the scaffolding of brain cells called radial progenitors necessary for the orderly formation of the brain. Previous studies have shown that this gene is mutated in some people with autism.

The discovery, published in Neuron, illuminates the molecular details of a key process in brain development and adds to the scientific understanding of the biological basis of autism spectrum disorder (ASD), a condition linked to brain development and estimated to affect about one in 59 children born in the United States.

"This finding suggests that ASD can be caused by disruptions occurring very early on, when the cerebral cortex is just beginning to construct itself," said study senior author Eva S. Anton, PhD, professor of cell biology and physiology at the UNC School of Medicine and member of the UNC Neuroscience Center and the UNC Autism Research Center.

The cerebral cortex - which in humans is responsible for higher brain functions including perception, speech, long-term memory,

and consciousness - is relatively large and dominant compared to other brain structures.

How the cortex constructs itself in the developing brain of a human or other mammal is far from fully understood. But scientists know that early in cortical development, precursor cells called radial glial cells (RGCs) appear at the bottom of the developing cortex in a regularly spaced or tiled pattern.

Each RGC sprouts a single stalk-like structure, called a basal process that extends to the top of the cortex. Collectively these RGCs and their basal processes form a scaffold, much like the scaffolds of a construction site.

RGCs divide to form young cortical neurons, and these baby neurons climb the scaffold to find their proper places in the developing brain. The cortex, thanks to this scaffolding system, normally develops a highly regular structure with six distinct layers of neurons required for the normal formation of functional neural cortical circuits.

Anton and colleagues discovered that a gene encoding for a protein called Memo1 is needed to organize the tiled radial glial cell scaffold. Mutations in the Memo1 gene also have been found in some people with autism and are suspected of causing the condition.

To explore Memo1's role in brain development and autism, Anton's team first engineered mice in which the Memo1 gene is deleted early in brain development in RGCs.

They found the resulting RGC scaffold is disrupted. Each RGC's stalk-like basal process formed too many branches and no longer forms a guiding scaffold, resulting in neuronal misplacement and disorganized layers.

The scientists traced this ill effect, in part, to unstable microtubules, which normally help reinforce the scaffold structure and serve as railways for the internal traffic of key molecules necessary for RGC function.

Intriguingly, studies of the brains of children with autism found patches of similar neuronal disorganization. The scientists then analyzed MEMO1 gene mutations reported recently in individuals with autism behaviors and intellectual disabilities.

They discovered the human MEMO1 genetic mutation resulted in a shortened form of the Memo1 protein and this can disrupt RGC development

Further supporting the autism connection, Anton and his colleagues discovered the mice lacking Memo1 in their RGCs behaved abnormally, showing a lack of explorative activity similar to those seen in some people with autism.

The findings overall suggest that Memo1-associated autism may be wired into the brain very early in development than are other forms of autism with origins in disrupted neuronal differentiation and connectivity.

"For disorders of brain development such as ASD, it is important to understand the origins of the problem even if we are still far away from being able to correct developmental disruptions occurring in utero," Anton said. "We need this foundational knowledge if we are to truly get to the root causes of these conditions and eventually develop better diagnostic or therapeutic strategies."

Anton and colleagues are continuing to evaluate MEMO1 in cortical development and autism, and as more human mutations are being identified in this gene family and other ASD genes, they plan to shift from experiments in mice to the study of human brain organoids - kind of mini brains that can be grown from patient derived stem cells with ASD related mutations.

The research was supported by grants from the National Institutes of Health (MH060929) and the National Institute of Neurological Disorders and Stroke (5P30NS045892-12).

The co-authors were Naoki Nakagawa PhD, Charlotte Plestant PhD, Keiko Yabuno-Nakagawa PhD, Jingjun Li PhD, Jason L. Stein PhD, all of UNC-Chapel Hill; Zoltan Molnar of University of Oxford, and Ali Badache PhD, of Centre de Recherche en Cancérologie de Marseille.

http://bit.ly/2FVdMQk

Antibiotics weaken flu defenses in the lung

Antibiotics can leave the lung vulnerable to flu viruses, leading to significantly worse infections and symptoms, finds a new study in mice led by the Francis Crick Institute.

The research, published in Cell Reports, discovered that signals from gut bacteria help to maintain a first line of defence in the lining of the lung. When mice with healthy gut bacteria were infected with the flu, around 80% of them survived. However, only a third survived if they were given antibiotics before being infected.

"We found that antibiotics can wipe out early flu resistance, adding further evidence that they should not be taken or prescribed lightly," explains Dr Andreas Wack, who led the research at the Francis Crick Institute. "Inappropriate use not only promotes antibiotic resistance and kills helpful gut bacteria, but may also leave us more vulnerable to viruses. This could be relevant not only in humans but also livestock animals, as many farms around the world use antibiotics prophylactically. Further research in these environments is urgently needed to see whether this makes them more susceptible to viral infections."

The study found that type I interferon signalling, which is known to regulate immune responses, was key to early defence. Among the genes switched on by interferon is a mouse gene, Mx1, which is the equivalent of the human MxA gene. This antiviral gene produces proteins that can interfere with influenza virus replication. Although often studied in immune cells, the researchers found that microbiota-driven interferon signals also keep antiviral genes in the lung lining active, preventing the virus from gaining a foothold.

"We were surprised to discover that the cells lining the lung, rather than immune cells, were responsible for early flu resistance induced by microbiota," says Andreas. "Previous studies have focused on immune cells, but we found that the lining cells are more important for the crucial early stages of infection. They are the only place that the virus can multiply, so they are the key battleground in the fight against flu. Gut bacteria send a signal that keeps the cells lining the lung prepared, preventing the virus from multiplying so quickly.

"It takes around two days for immune cells to mount a response, in which time the virus is multiplying in the lung lining. Two days after infection, antibiotic-treated mice had five times more virus in their lungs. To face this bigger threat, the immune response is much stronger and more damaging, leading to more severe symptoms and worse outcomes."

To test whether the protective effect was related to gut bacteria rather than local processes in the lung, the researchers treated mice with antibiotics and then repopulated their gut bacteria through faecal transplant. This restored interferon signalling and associated flu resistance, suggesting that gut bacteria play a crucial role in maintaining defences.

"Taken together, our findings show that gut bacteria help to keep non-immune cells elsewhere in the body prepared for attack," says Andreas. "They are better protected from flu because antiviral genes are already switched on when the virus arrives. So when the virus infects a prepared organism, it has almost lost before the battle starts. By contrast, without gut bacteria, the antiviral genes won't come on until the immune response kicks in. This is sometimes too late as the virus has already multiplied many times, so a massive, damaging immune response is inevitable."

http://bit.ly/30eL70b

Promising approach: Prevent diabetes with intermittent fasting

Mice on an intermittent fasting regimen exhibited lower pancreatic fat

Intermittent fasting is known to improve sensitivity to the blood glucose-lowering hormone insulin and to protect against fatty liver.

DZD scientists from DIfE have now discovered that mice on an intermittent fasting regimen also exhibited lower pancreatic fat. In their current study published in the journal Metabolism, the researchers showed the mechanism by which pancreatic fat could contribute to the development of type 2 diabetes.

Fatty liver has been thoroughly investigated as a known and frequently occurring disease. However, little is known about excess weight-induced fat accumulation in the pancreas and its effects on the onset of type 2 diabetes. The research team led by Professor Annette Schürmann and Professor Tim J. Schulz of the German Institute of Human Nutrition (DIfE) has now found that overweight mice prone to diabetes have a high accumulation of fat cells in the pancreas.

Mice resistant to diabetes due to their genetic make-up despite excess weight had hardly any fat in the pancreas, but instead had fat deposits in the liver. "Fat accumulations outside the fat tissue, e.g. in the liver, muscles or even bones, have a negative effect on these organs and the entire body. What impact fat cells have within the pancreas has not been clear until now," said Schürmann, head of the Department of Experimental Diabetology at DIfE and speaker of the German Center for Diabetes Research (DZD).

Intermittent fasting reduces pancreatic fat

The team of scientists divided the overweight animals, which were prone to diabetes, into two groups: The first group was allowed to eat ad libitum - as much as they wanted whenever they wanted. The second group underwent an intermittent fasting regimen: one day the rodents received unlimited chow and the next day they were not fed at all.

After five weeks, the researchers observed differences in the pancreas of the mice: Fat cells accumulated in group one. The animals in group two, on the other hand, had hardly any fat deposits in the pancreas.

Pancreatic adipocytes mediate hypersecretion of insulin

In order to find out how fat cells might impair the function of the pancreas, researchers led by Schürmann and Schulz isolated adipocyte precursor cells from the pancreas of mice for the first time and allowed them to differentiate into mature fat cells. If the mature fat cells were subsequently cultivated together with the Langerhans islets of the pancreas, the beta cells of the "islets" increasingly secreted insulin.

"We suspect that the increased secretion of insulin causes the Langerhans islets of diabetes-prone animals to deplete more quickly and, after some time, to cease functioning completely. In this way, fat accumulation in the pancreas could contribute to the development of type 2 diabetes," said Schürmann.

Significance of pancreatic fat for diabetes prevention

Current data suggest that not only liver fat should be reduced to prevent type 2 diabetes. "Under certain genetic conditions, the accumulation of fat in the pancreas may play a decisive role in the development of type 2 diabetes," said Schulz, head of the Department of Adipocyte Development and Nutrition. Intermittent fasting could be a promising therapeutic approach in the future. The advantages: it is non-invasive, easy to integrate into everyday life and does not require drugs.

Intermittent Fasting

Intermittent fasting means not eating during certain time slots. However, water, unsweetened tea and black coffee are allowed around the clock. Depending on the method, the fasting lasts between 16 and 24 hours or, alternatively, a maximum of 500 to 600 calories are consumed on two days within a week. The best known form of intermittent fasting is the 16:8 method which involves eating only during an eight-hour window during the day and fasting for the remaining 16 hours. One meal - usually breakfast - is omitted.

Islets of Langerhans

The islets of Langerhans - also referred to as islet cells or Langerhans islets - are islet-like accumulations of hormone-producing cells in the pancreas. A healthy adult has about one million Langerhans islets.

Each "islet" has a diameter of 0.2-0.5 millimeters. The beta cells produce the blood glucose-lowering hormone insulin and make up about 65 to 80 percent of the islet cells. When blood glucose levels are elevated, these secrete insulin into the bloodstream so that the levels are normalized again.

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http://bit.ly/2NzQVQA

Explorers to voyage to Japan in primitive boat in hopes of unlocking an ancient mystery

Adventurers will attempt to paddle a primitive hand-hewn canoe across 200 kilometers of ocean

By Dennis Normile

In the next week or so, five adventurers will attempt to paddle a primitive hand-hewn canoe across 200 kilometers of ocean in hopes of revealing how humans originally populated East China Sea islands.

A team of five paddlers will attempt to cross 200 kilometers of open ocean in a primitive log boat. **National Museum of Nature and Science/Tokyo**

The 40-hour trip, from Taiwan to Yonaguni, the westernmost of Japan's Okinawa Islands, is the culmination of a 6-year effort to experimentally determine what kinds of craft Paleolithic peoples may have built and used, and how they navigated over long ocean voyages.

Archeological sites show humans first arrived in Japan more than 30,000 years ago. They likely reached the main islands from northeast Asia via a land bridge from Siberia and by crossing the straits in watercraft from the Korean Peninsula.

But how Paleolithic humans settled the Ryukyus, the present-day Okinawa Islands that stretch 1200 kilometers from Taiwan to Japan's Kyushu Island, "is really a big mystery," says Yousuke Kaifu, an archaeologist at Japan's National Museum of Nature and Science in Tokyo who dreamed up the expedition.

The "very difficult" sea voyages were undoubtedly made in boats built of materials that have not survived, he says. And sailing boats had not yet appeared, So Kaifu's team has been building and testing watercraft that prehistoric seafarers might have paddled.

The voyagers will cross from Taiwan to Yonaguni in Japan, (red arrow) allowing a strong current to pull them northward as they paddle eastward. **A. Cuadra/*Science***

Yonaguni can be seen from Taroko Mountain in northeastern Taiwan. So ancient peoples presumably knew of the island, even though it can't be seen from shore, Kaifu says. To show the Taiwan-to-Yonaguni crossing could have been done, Kaifu starting to plan the "holistic reenactment" voyage in 2013.

The team first built boats made of bundled bulrushes, similar in design to reed boats used by prehistoric peoples around the world; and then bamboo rafts, relying on traditional techniques used by Taiwan's Amis tribe. Short-distance trial runs showed these crafts were slow and that currents pulled them off-course. The team concluded they were not suitable for long-distance voyages.

For their full-scale trip, Kaifu's team—all seasoned ocean kayakers—will be paddling a log boat or dugout canoe of a type found in China and Japan dating back 8000 years. The team used simple stone axes, modeled on Paleolithic era archeological findings in Japan, to chop down a 1-meter-thick tree and then hew it into a 7-meter-long, 350-kilogram dugout. It proved lighter, more buoyant, and about 50% faster than the other craft. To emulate the ancients in other ways, the crew will not use modern navigational tools. Instead, the team includes a Maori man from New Zealand who can navigate by following the stars and judging winds and ocean swells.

Whatever happens, the results should be interpreted cautiously, says Helen Farr, an archeologist at the University of Southampton in the United Kingdom. Sea level would have been about 100 meters lower than it is now, she notes, and that could have affected the routes chosen by voyagers, among other things. Still, she praises the experiment, saying that it could "inform our understanding" of the challenges of early seafaring—and the skills, technologies, and social organization required for such a journey.

Even failure might be informative, says Robin Dennell, an archeologist at the University of Exeter in the United Kingdom who has studied the peopling of the Ryukyus. "It might show us how the islands were … *not* colonized," he says, "and that might encourage a search for alternatives." He also likes how the project is leading modern humans to "admire what people were able to do over 30,000 years ago."

http://bit.ly/2LHIL63

Saturn's Icy Moon Enceladus Is Likely the 'Perfect Age' to Harbor Life

Below the ice-covered surface of Saturn's moon Enceladus hides a vast ocean.

By Yasemin Saplakoglu, Staff Writer

BELLEVUE, Wash. — This sprawling ocean is likely 1 billion years old, which means it's the perfect age to harbor life, said Marc Neveu, a research scientist at NASA Goddard Space Flight Center last Monday (June 24) during a talk at the 2019 Astrobiology Science Conference.

Neveu and his colleagues used simulations to calculate Enceladus' age using data gathered by the Cassini spacecraft, which orbited Saturn for 13 years.

The scientist and his team published their findings last April in the journal Nature Astronomy.

One of Cassini's major discoveries was that Enceladus had an ocean filled with hydrothermal vents.

"It's very surprising to see an ocean today," Neveu told Live Science after the talk.

"It's a very tiny moon and, in general, you expect tiny things to not be very active [but rather] like a dead block of rock and ice."

But not only does the tiny moon most likely have an ocean, this Washington-state-size icy moon has the habitat needed for life, including sources of chemical energy and sources of essential elements such as carbon, nitrogen, hydrogen and oxygen, Neveu said.

"But there's [another] dimension of habitability...time," Neveu said. If the ocean is too young – for example, only a couple of million years old – there probably wouldn't have been enough time to mix those ingredients together to create life, he said.

What's more, that's not enough time for little sparks of life to spread enough for us Earthlings to detect them.

On the other hand, if the ocean is too old, it's as if the planet's "battery" is running out of juice; the chemical reactions needed to sustain life might stop, Neveu said.

In this world, the elements that needed to dissolve would have dissolved, all the minerals needed to form would have formed, he said.

The moon would've then reached an equilibrium, meaning that the reactions to sustain life wouldn't take place.

That means Enceladus' ocean may be the perfect age to harbor life.

Neveau and his team estimated the ocean's age with a little bit of guesswork.

They ran about 50 simulations, plugging in various parameters based on measurements Cassini took, such as the details of Saturns' moons' orbits, the radioactivity of the rocks on Enceladus, and their own guesses as to the age of the moon and how it formed.

The simulation that best-replicated the icy moon's current conditions estimated that the ocean was 1 billion years old.

However, Neveu cautions that this age estimation was based on a single simulation.

And though it matches a lot of the conditions seen on Enceladus, it doesn't match all of them.

"For example, if you took the present day, the ocean would be refrozen in that simulation which is not what we're seeing." So the age of the ocean, should be taken with a grain of salt, Neveu said.

Neveu and his team are now working to make their simulation run faster.

The hope is that, with the faster run time, and slightly improved models, they can more precisely date Enceladus' oceans. "We want to know this before we go back to search for life," he said.

http://bit.ly/2RZJcKa

879% drug price hike is one of 3,400 in 2019 so far; rate of hikes increasing

Despite public and political pressure, pharma keeps on ratcheting up prices.

Beth Mole

Pharmaceutical companies raised the prices of more than 3,400 drugs in the first half of 2019, surpassing the number of drug hikes they imposed during the same period last year, according to an analysis first reported by NBC News.

The average price increase per drug was 10.5%, a rate around five times that of inflation. About 40 of the drugs saw triple-digit increases. That includes a generic version of the antidepressant Prozac, which saw a price increase of 879%.

The surge in price hikes comes amid ongoing public and political pressure to drag down the sky-rocketing price of drugs and healthcare costs overall. In May of 2018, President Trump boldly announced that drug companies would unveil “voluntary massive drops in prices” within weeks. But no such drops were ever announced. Trump then went on to publicly shame Pfizer for continuing to raise drug prices. The company responded with a short-lived pause on drug price increases mid-way through last year, but it resumed increasing prices in January—as did dozens of other pharmaceutical companies.

"Requests and public shaming haven't worked," Michael Rea, chief executive of RX Savings Solutions, told Reuters last December. His company helps health plans and employers seek lower-cost prescription medicines. It also conducted the new analysis on drug prices.

In December, Rea predicted that the number of 2019 increases would be even greater than in past years. It appears he is correct.

The more than 3,400 drug price increases in the first half of 2019 is a 17% increase over the number of drug price hikes in the first half of 2018. In addition to the Prozac generic, the drugs that saw triple-digit increases included the topical steroid Mometasone, which had a price increase of 381%. A pain reliever and cough medication (Promethazine/Codeine) saw a 326% hike while the ADHD treatment Guanfacine 2mg saw its price rise 118%.

In May, the Trump administration finalized a rule that will require drug companies to include drug list prices in television advertisements. The rule is slated to go into effect sometime this summer.

https://n.pr/2XWte9e

Scientists Make Model Embryos From Stem Cells To Study Key Steps In Human Development

Scientists have created living entities that resemble very primitive human embryos, the most advanced example of these structures yet created in a lab.

Rob Stein

The researchers hope these creations, made from human embryonic stem cells, will provide crucial new insights into human development and lead to new ways to treat infertility and prevent miscarriages, birth defects and many diseases. The researchers say this is the first time scientists have created living models of human embryos with three-dimensional structures.

The researchers reported their findings Monday in a paper published in the journal *Nature Cell Biology*. But the research is stirring debate about how far scientists should go in creating living models of human embryos, sometimes called embryoids.

"It's very exciting work," says Insoo Hyun, a bioethicist at the Case Western Reserve University and Harvard Medical School who was not involved in the research. "But it does send folks down the road to thinking very seriously about where the limits may be ethically for this work."

For decades, scientists have worked to understand some of the earliest steps that enable an embryo to develop into a fetus. But some of the most crucial ones have been a mystery. That's because they occur in a woman's womb and can't be studied. Scientists are prohibited from studying human embryos in their labs beyond 14 days of development.

As a result, these very early stages of development have been "a complete black box," says Ali Brivanlou, a molecular biologist at Rockefeller University in New York who heads the lab where the new research was conducted. So Brivanlou and his colleagues decided to try to use human embryonic stem cells to create living models of human embryos they could study in the lab.

"We came up with a model of human embryos that is developed outside of the womb and is not the product of the sperm and the eggs but is the product of human embryonic stem cells that self-organize into complicated structures," Brivanlou says.

The researchers placed human embryonic stem cells into dishes containing a gel and added a protein to coax the cells into organizing themselves into three-dimensional hollow balls that resemble early embryos.

"Our experimental model looks like a ball — a shell — of cells. This is more or less what the embryonic tissue looks like at this stage," says Mijo Simunovic, the study's first author.

Moreover, the balls of cells then took a crucial next step: They broke the symmetry of the sphere, which starts the development of more complex structures that eventually lead to the development of a human being. "This process of symmetry breaking is a major holy grail of development biology," Brivanlou says. "Life is a continuation of symmetry-breaking events."

Finally being able to re-create and now study that first symmetry-breaking moment is thrilling, humbling and "mind blowing," he says. "I really feel like I'm looking at one of the most mysterious aspects of our own existence."

Brivanlou, Simunovic and their colleagues hope their creations will lead to fundamental discoveries that could have many implications, including a better understanding of the origins of many diseases.

"We're very excited about this," Simunovic says. "This is the first time we've been able to achieve this."

Other scientists agree.

"Scientifically, this research is important," says Dr. George Daley, a leading stem-cell scientist and the dean of the Harvard Medical School. "We really don't have access to the earliest stages of development. And here we have this remarkable tool in a petri dish."

But Daley and Hyun say this kind of research has already started to raise some questions. "The question becomes: How long do you allow these structures to develop and when do they start to raise some of the ethical challenges that we've seen in the history of human embryo biology?" Daley says.

A long-standing guideline known as the 14-day rule prohibits scientists from thoroughly studying these and more advanced structures in real human embryos in their labs, because they have to discontinue their experiments after 14 days. Brivanlou's synthetic embryos may eventually get close to something equivalent to a real 14-day-old human embryo, and beyond. "It certainly hints that science is headed towards a challenge to that rule," Daley says.

Hyun agrees.

"As the embryo models become much more complete and much further along in showing us how the human body develops after fertilization, one might begin to wonder: At what point do these models effectively just become the real thing?" Hyun says.

In fact, the embryoids have shown early signs of a crucial structure known as the primitive streak, which is another cutoff for studying human embryos in the lab. "The research is unpredictable. The cells are self-organizing in a way that sometimes surprises the researchers — they get a level of complexity that they did not expect," Hyun says. "There are dangers lurking ahead."

Because of this, the International Society for Stem Cell Research is planning to revise its guidelines for this kind of research, Daley says. "It's time to start to think about reevaluating the limits on these kinds of experiments," Daley says. "The science has progressed to the point where those guidelines now have to look again at the 14-day rule."

The Rockefeller University scientists agree that researchers and bioethicists need to discuss the issues raised by this research. But they insists the models do not have the same moral status of a human embryo and are nowhere near anything that could ever become a baby. "These are not actual human embryos," Simunovic says. "And they would never become human embryos if we let them grow." But the researchers do plan to try to develop even more sophisticated embryoids. "Now we build up this model with complexity to study more complex events," Simunovic says.

http://bit.ly/2Jq1D6W

Ancient DNA sheds light on the origins of the Biblical Philistines

Ancient genomes suggest that the Philistines descended from people who migrated across the Mediterranean and reached the shores of the southern Levant at the beginning of the Iron Age

An international team, led by scientists from the Max Planck Institute for the Science of Human History and the Leon Levy Expedition, retrieved and analyzed, for the first time, genome-wide data from people who lived during the Bronze and Iron Age (~3,600-2,800 years ago) in the ancient port city of Ashkelon, one

of the core Philistine cities during the Iron Age. The team found that a European derived ancestry was introduced in Ashkelon around the time of the Philistines' estimated arrival, suggesting that ancestors of the Philistines migrated across the Mediterranean, reaching Ashkelon by the early Iron Age. This European related genetic component was subsequently diluted by the local Levantine gene pool over the succeeding centuries, suggesting intensive admixture between local and foreign populations. These genetic results, published in *Science Advances*, are a critical step toward understanding the long-disputed origins of the Philistines.

The Philistines are famous for their appearance in the Hebrew Bible as the arch-enemies of the Israelites. However, the ancient texts tell little about the Philistine origins other than a later memory that the Philistines came from "Caphtor" (a Bronze Age name for Crete; Amos 9:7). More than a century ago, Egyptologists proposed that a group called the Peleset in texts of the late twelfth century BCE were the same as the Biblical Philistines. The Egyptians claimed that the Peleset travelled from the "the islands," attacking what is today Cyprus and the Turkish and Syrian coasts, finally attempting to invade Egypt. These hieroglyphic inscriptions were the first indication that the search for the origins of the Philistines should be focused in the late second millennium BCE. From 1985-2016, the Leon Levy Expedition to Ashkelon, a project of the Harvard Semitic Museum, took up the search for the origin of the Philistines at Ashkelon, one of the five "Philistine" cities according to the Hebrew Bible. Led by its founder, the late Lawrence E. Stager, and then by Daniel M. Master, an author of the study and director of the Leon Levy Expedition to Ashkelon, the team found substantial changes in ways of life during the 12th century BCE which they connected to the arrival of the Philistines. Many scholars, however, argued that these cultural changes were merely the result of trade or a local imitation of foreign styles and not the result of a substantial movement of people.

This new study represents the culmination of more than thirty years of archaeological work and of genetic research utilizing state of the art technologies, concluding that the advent of the Philistines in the southern Levant involved a movement of people from the west during the Bronze to Iron Age transition.

Genetic discontinuity between the Bronze and Iron Age people of Ashkelon

The researchers successfully recovered genomic data from the remains of 10 individuals who lived in Ashkelon during the Bronze and Iron Age. This data allowed the team to compare the DNA of the Bronze and Iron Age people of Ashkelon to determine how they were related. The researchers found that individuals across all time periods derived most of their ancestry from the local Levantine gene pool, but that individuals who lived in early Iron Age Ashkelon had a European derived ancestral component that was not present in their Bronze Age predecessors.

"This genetic distinction is due to European-related gene flow introduced in Ashkelon during either the end of the Bronze Age or the beginning of the Iron Age. This timing is in accord with estimates of the Philistines arrival to the coast of the Levant, based on archaeological and textual records," explains Michal Feldman of the Max Planck Institute for the Science of Human History, leading author of the study. "While our modelling suggests a southern European gene pool as a plausible source, future sampling could identify more precisely the populations introducing the European-related component to Ashkelon."

Transient impact of the "European related" gene flow

In analyzing later Iron Age individuals from Ashkelon, the researchers found that the European related component could no longer be traced. "Within no more than two centuries, this genetic

footprint introduced during the early Iron Age is no longer detectable and seems to be diluted by a local Levantine related gene pool," states Choongwon Jeong of the Max Planck Institute of the Science of Human History, one of the corresponding authors of the study.

"While, according to ancient texts, the people of Ashkelon in the first millennium BCE remained 'Philistines' to their neighbors, the distinctiveness of their genetic makeup was no longer clear, perhaps due to intermarriage with Levantine groups around them," notes Master.

"This data begins to fill a temporal gap in the genetic map of the southern Levant," explains Johannes Krause of the Max Planck Institute for the Science of Human History, senior author of the study. "At the same time, by the zoomed-in comparative analysis of the Ashkelon genetic time transect, we find that the unique cultural features in the early Iron Age are mirrored by a distinct genetic composition of the early Iron Age people."

http://bit.ly/329acvm

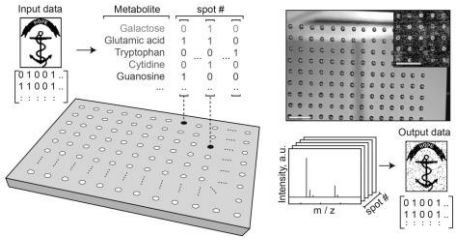
Molecular thumb drives: Researchers store digital images in metabolite molecules

It's possible to store and retrieve data stored in artificial metabolomes

PROVIDENCE, R.I. [Brown University] -- DNA molecules are well known as carriers of huge amounts of biological information, and there is growing interest in using DNA in engineered data storage devices that can hold vastly more data than our current hard drives. But new research shows that DNA isn't the only game in town when it comes to molecular data storage.

A study led by Brown University researchers shows that it's possible to store and retrieve data stored in artificial metabolomes -- arrays of liquid mixtures containing sugars, amino acids and other types of small molecules. For a paper published in the journal PLOS ONE, the researchers showed that they could encode kilobyte-scale image files into metabolite solutions and read the information back out again.

"This is a proof-of-concept that we hope makes people think about using wider ranges of molecules to store information," said Jacob Rosenstein, a professor in Brown's School of Engineering and senior author of the study. "In some situations, small molecules like the ones we used here can have even greater information density than DNA."



In a step toward molecular storage systems that could hold vast amounts of data in tiny spaces, Brown University researchers have shown it's possible to store image files in solutions of common biological small molecules. **Jacob Rosenstein et. al.**

Another potential advantage, Rosenstein says, stems from the fact that many metabolites can react with each other to form new compounds. That creates the potential for molecular systems that not only store data, but also manipulate it -- performing computations within metabolite mixtures.

The idea behind molecular computing grows out of an increasing need for more data storage capacity. By 2040, the world will have produced as much as 3 septillion (that's 3 followed by 24 zeros) bits of data by some estimates. Storing, searching and processing all of that data is a daunting challenge, and there simply may not be enough chip-grade silicon on Earth to do this with traditional semiconductor chips. Funded by a contract with the Defense Advanced Research Projects Administration (DARPA), a group of engineers and chemists at Brown has been working on a variety of techniques for using small molecules to create new information systems.

For this new study, the group wanted to see if artificial metabolomes could be a data-storage option. In biology, a metabolome is the full array of molecules an organism uses to regulate its metabolism.

"It's not hard to recognize that cells and organisms use small molecules to transmit information, but it can be harder to generalize and quantify," said Eamonn Kennedy, a postdoctoral associate at Brown and first author of the study. "We wanted to demonstrate how a metabolome can encode precise digital information."

The researchers assembled their own artificial metabolomes -- small liquid mixtures with different combinations of molecules. The presence or absence of a particular metabolite in a mixture encodes one bit of digital data, a zero or a one. The number of molecule types in the artificial metabolome determines the number of bits each mixture can hold. For this study, the researchers created libraries of six and 12 metabolites, meaning each mixture could encode either six or 12 bits. Thousands of mixtures are then arrayed on small metal plates in the form of nanoliter-sized droplets. The contents and arrangement of the droplets, precisely placed by a liquid-handling robot, encodes the desired data.

The plates are then dried, leaving tiny spots of metabolite molecules, each holding digital information. The data can then be read out using a mass spectrometer, which can identify the metabolites present at each spot on the plate and decode the data.

The researchers used the technique to successfully encode and retrieve a variety of image files of sizes up to 2 kilobytes. That's not big compared to the capacity of modern storage systems, but it's a solid proof-of-concept, the researchers say. And there's plenty of potential for scaling up. The number of bits in a mixture increases with the number of metabolites in an artificial metabolome, and there are thousands of known metabolites available for use.

There are some limitations, the researchers point out. For example, many metabolites chemically interact with each other when placed in the same solution, and that could result in errors or loss of data. But that's a bug that could ultimately become a feature. It may be possible to harness those reactions to manipulate data -- performing in-solution computations.

"Using molecules for computation is a tremendous opportunity, and we are only starting to figure out how to take advantage of it," said Brenda Rubenstein, a Brown assistant professor of chemistry and co-author of the study.

"Research like this challenges what people see as being possible in molecular data systems," Rosenstein said. "DNA is not the only molecule that can be used to store and process information. It's exciting to recognize that there are other possibilities out there with great potential."

Other authors on the paper are Christopher Arcadia, Joseph Geiser, Peter Weber and Christopher Rose. The research was supported by DARPA (W911NF-18-2-0031).

http://bit.ly/2JhX6Vo

First complete wiring diagram of an animal's nervous system

First complete wiring diagram of the nervous system of C. elegans

BRONX, NY--In a study published online today in *Nature*, researchers at Albert Einstein College of Medicine describe the first complete wiring diagram of the nervous system of an animal, the roundworm Caenorhabditis elegans, used by scientists worldwide as a model organism. The study includes adults of both sexes and reveals substantial differences between them.

The findings mark a major milestone in the field of "connectomics," the effort to map the myriad neural connections in a brain, brain region, or nervous system to find the specific nerve connections responsible for particular behaviors.

"Structure is always central in biology," said study leader Scott Emmons, Ph.D., professor of genetics and in the Dominick P. Purpura Department of Neuroscience and the Siegfried Ullmann Chair in Molecular Genetics at Einstein. "The structure of DNA revealed how genes work, and the structure of proteins revealed how enzymes function. Now, the structure of the nervous system is revealing how animals behave and how neural connections go wrong to cause disease."

Researchers have hypothesized that some neurological and psychiatric disorders, such as schizophrenia and autism, are "connectopathies," that is, problems caused by "faulty wiring." "This hypothesis is strengthened by the finding that several mental disorders are associated with mutations in genes that are thought to determine connectivity," said Dr. Emmons. "Connectomics has the potential to help us understand the basis of some mental illnesses, possibly suggesting avenues for therapy."

A Model Organism

Because C. elegans is so tiny--adults are just one millimeter long and have only about 1,000 cells--its simple nervous system of a few hundred neurons (302 in the hermaphrodite/female sex, 385 in the male) makes it one of the best animal models for understanding the billions-times-more-complex human brain. It was also the first multi-cellular organism to have its entire genome sequenced.

Dr. Emmons' study builds on the groundbreaking work of the late British biologist Sydney Brenner, who in 2002 shared the Nobel Prize in Physiology or Medicine for his C. elegans research. Dr. Brenner's laboratory, in an effort led by laboratory member John White, published the first map of the C. elegans nervous system in 1986, after painstakingly analyzing neural structures visible on thousands of serial electron micrographs of the roundworm. Each image consisted of a cross-sectional "slice" a thousand times thinner than a human hair. He and his colleagues manually "connected the dots" between each slice, linking the structures from one image to another to create detailed representations of the nerves and the 5,000 or so connections (synapses) among them.

The tour de force effort by Drs. Brenner and White, 20 years in the making, launched the field of connectomics and established the roundworm as an essential animal model for the study of biology and human disease. But their map, informally called "The Mind of a Worm," skipped large portions of the worm's body and included just one of the sexes--the hermaphrodite, or female--not the male.

Taking Up the Baton

For the new study, Dr. Emmons' team analyzed new roundworm electron micrographs as well as Dr. Brenner's old ones and pieced them together using specially developed software to create complete wiring diagrams of entire adult animals of both C. elegans sexes. The diagrams include all connections between individual neurons, connections from neurons to the worm's muscles and other tissues, such as the gut and skin, and synapses between the muscle cells, with estimates of the strength of those synapses.

"While the synaptic pathways in the two sexes are substantially similar, a number of the synapses differ in strength, providing a basis for understanding sex-specific behaviors," said Dr. Emmons. The primary sex differences pertain to reproductive functions: in vulval and uterine muscles and the motor neurons that control them in the hermaphrodite; and in the large number of additional neurons, sex muscles, and connections in the tail that generate the circuits for copulation in the male. But beyond these, a surprising number of synapses between neurons in central pathways shared by both sexes also appear to differ considerably in strength.

"These connected networks serve as starting points for deciphering the neural control of C. elegans behavior," said Dr. Emmons. "Since the roundworm nervous system contains many of the same molecules as the human nervous system, what we learn about the

former can help us understand the latter." Dr. Emmons is currently studying how the roundworm connectome is encoded by its genome.

The study is titled, "Whole-Animal Connectomes of both C. elegans Sexes." Additional Einstein authors are: Steven J. Cook, Ph.D., Travis A. Jarrell, Ph.D., Christopher Brittin, Ph.D., Yi Wang, Ph.D., Maksim A. Yakovlev, Ken C. Q. Nguyen, Leo T.-H. Tang, Ph.D., Hannes E. Bülow, Ph.D., and David H. Hall, Ph.D. The other contributors include: Adam E. Bloniarz, Ph.D., at Google, Emily A. Bayer, Ph.D., at Columbia University, Janet S. Duerr, Ph.D., at Ohio University, and Oliver Hobert, Ph.D., at Hughes Medical Institute, Columbia University.

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The authors declare no conflicts of interests.

http://bit.ly/2XuzrJN

Scientists see how a protein preserves vision in a unique group of diabetic patients

Protein identified that protects against diabetic retinopathy

日本のニュース

An analysis of samples obtained from a well-studied cohort of over 1,000 patients affected by type 1 diabetes (T1D) for 50 years or longer has identified a protein that protects against an eye condition called diabetic retinopathy (DR) - one of the most common consequences of diabetes - which impacts most diabetic patients after 20 years of living with the disease.

Injecting the protein into rodents blocked DR without causing severe side effects, suggesting that preserving or administering the protein could help avoid debilitating eye damage in diabetic patients.

Many patients with long-term diabetes develop eye disorders such as DR, which has become a leading cause of vision loss in developed countries. Interestingly, 35% of these patients never develop severe DR even after decades of being diabetic, suggesting they may harbor protective factors against such complications.

To solve this mystery, Hishashi Yokomizo and colleagues turned to the Medalist cohort, a unique group of patients affected by T1D for at least 50 years.

They compared protein profiles in the retina or vitreous fluid from a total of 43 deceased Medalist patients with either severe or no-to-mild DR, 21 non-Medalist patients with diabetes, and 13 non-diabetic controls. The authors discovered that the patients who were protected from advanced DR had higher levels of RBP3, a protein secreted by light-sensing cells in the eyes.

Injecting RBP3 into the eyes of mice protected the animals against induced DR, and analysis showed that the protein inhibited the harmful effects of the growth factor VEGF and curtailed the secretion of inflammatory molecules in retinal cells.

Future work should aim to replicate these results in people with short-term T1D or type 2 diabetes, the authors say.

http://bit.ly/2LGmuFV

Immune cells invade aging brains, disrupt new nerve cell formation, Stanford study finds

Immune cells infiltrate the rare newborn nerve-cell nurseries of the aging brain

A study by Stanford University School of Medicine investigators has revealed that immune cells infiltrate the rare newborn nerve-cell nurseries of the aging brain. There's every reason to think those interlopers are up to no good. Experiments in a dish and in living animals indicate they're secreting a substance that chokes off new nerve cell production.

While most of the experiments in the study were carried out in mice, the central finding -- the invasion, by immune cells called killer T cells, of neurogenic niches (specialized spots in the brain where new nerve cells, or neurons, are generated) -- was corroborated in tissue excised from autopsied human brains.

The findings could accelerate progress in hunting down the molecules in the body that promote the common deterioration of brain function in older individuals and in finding treatments that might stall or even reverse that deterioration. They also signify a crack in the wall of dogma that's deemed the healthy brain impervious to invasion by the body's immune cells, whose unbridled access to the organ could cause damage.

"The textbooks say that immune cells can't easily get into the healthy brain, and that's largely true," said Anne Brunet, PhD, professor of genetics and senior author of the study. "But we've shown that not only do they get into otherwise healthy aging brains -- including human brains -- but they reach the very part of the brain where new neurons arise."

Lead authorship of the study, to be published online July 3 in *Nature*, is shared by medical student Ben Dulken, PhD, graduate student Matthew Buckley and postdoctoral scholar Paloma Navarro Negredo, PhD.

The cells that aid memory

Many a spot in a young mammal's brain is bursting with brand new neurons. But for the most part, those neurons have to last a lifetime. Older mammals' brains retain only a couple of neurogenic niches, consisting of several cell types whose mix is critical for supporting neural stem cells that can both differentiate into neurons and generate more of themselves. New neurons spawned in these niches are considered essential to forming new memories and to learning, as well as to odor discrimination.

In order to learn more about the composition of the neurogenic niche, the Stanford researchers catalogued, one cell at a time, the activation levels of the genes in each of nearly 15,000 cells extracted from the subventricular zone (a neurogenic niche found in mice and human brains) of healthy 3-month-old mice and healthy 28- or 29-month-old mice.

This high-resolution, single-cell analysis allowed the scientists to characterize each cell they looked at and see what activities it was engaged in. Their analysis confirmed the presence of nine familiar cell types known to compose the neurogenic niche. But when Brunet and her colleagues compared their observations in the brains of young mice (equivalent in human years to young adults) with what they saw in the brains of old mice (equivalent to people in their 80s), they identified a couple of cell types in the older mice not typically expected to be there -- and barely present in the young mice. In particular, they found immune cells known as killer T cells lurking in the older mice's subventricular zone.

The healthy brain is by no means devoid of immune cells. In fact, it boasts its own unique version of them, called microglia. But a much greater variety of immune cells abounding in the blood, spleen, gut and elsewhere in the body are ordinarily denied entry to the brain, as the blood vessels pervading the brain have tightly sealed walls. The resulting so-called blood-brain barrier renders a healthy brain safe from the intrusion of potentially harmful immune cells on an inflammatory tear as the result of a systemic illness or injury.

"We did find an extremely sparse population of killer T cells in the subventricular zone of young mice," said Brunet, who is the Michele and Timothy Barakett Endowed Professor. "But in the older mice, their numbers were expanded by 16-fold."

That dovetailed with reduced numbers of proliferation-enabled neural stem cells in the older mice's subventricular zone. Further experiments demonstrated several aspects of the killer T cells' not-so-mellow interaction with neural stem cells. For one thing, tests in laboratory dishware and in living animals indicated that killer T cells isolated from old mice's subventricular zone were far more disposed than those from the same mice's blood to pump out an inflammation-promoting substance that stopped neural stem cells from generating new nerve cells.

Second, killer T cells were seen nestled next to neural stem cells in old mice's subventricular zones and in tissue taken from the corresponding neurogenic niche in autopsied brains of old humans; where this was the case, the neural stem cells were less geared up to proliferate.

Possible brain-based antigens

A third finding was especially intriguing. Killer T cells' job is to roam through the body probing the surfaces of cells for biochemical signs of a pathogen's presence or of the possibility that a cell is becoming, or already is, cancerous. Such telltale biochemical features are called antigens. The tens of billions of killer T cells in a human body are able to recognize a gigantic range of antigens by means of receptors on their own surfaces. That's because every unexposed, or naïve, killer T cell has its own unique receptor shape. When an initially naïve killer T cell is exposed to an unfamiliar antigen that fits its uniquely shaped receptor, it reacts by undergoing multiple successive rounds of replication, culminating in a large set of warlike cells all sharing the same receptor and all poised to destroy any cells bearing the offending antigen. This process is called clonal expansion.

The killer T cells found in old mice's brains had undergone clonal expansion, indicating likely exposure to triggering antigens. But the receptors on those killer T cells differed from the ones found in the old mice's blood, suggesting that the brain-localized killer T cells hadn't just traipsed through a disrupted blood-brain barrier via passive diffusion but were, rather, reacting to different, possibly brain-based, antigens.

Brunet's group is now trying to determine what those antigens are. "They may bear some responsibility for the disruption of new neuron production in the aging brain's neurogenic niches," she said.

Brunet is a member of Stanford Bio-X, the Stanford Cancer Institute, the Stanford Cardiovascular Institute and the Wu Tsai Neurosciences Institute at Stanford.

Other Stanford study co-authors are basic life research scientist Naresha Saligrama, PhD, DVM; neuropathology fellow Romain Cayrol, MD, PhD; former postdoctoral scholars Dena Leeman, PhD, and Katja Hebestreit, PhD; MD-PhD students Benson George and John Pluvinage; Tony Wyss-Coray, PhD, professor of neurology and neurological sciences; Irving Weissman, MD, professor of pathology and of developmental biology and director of the Stanford Institute for Stem Cell Biology; Hannes Vogel, MD, professor of pathology and of pediatrics; and Mark Davis, PhD, professor of microbiology and immunology and director of the Stanford Institute for Immunity, Transplantation and Infection.

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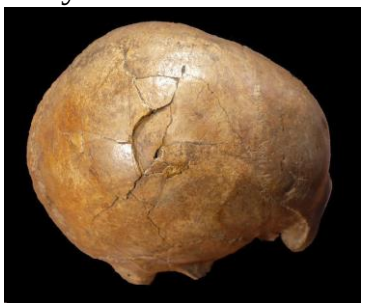
http://bit.ly/2YzHSQA

Cold Case Closed: Scientists Pin 33,000-Year-Old Murder on a Left-Handed Paleo Killer

One of the coldest cases on record — a man's mysterious death about 33,000 years ago — has finally been solved

By Laura Geggel, Associate Editor

One of the coldest cases on record — a man's mysterious death about 33,000 years ago — has finally been solved: a left-handed murderer killed the man by smashing his skull with two consecutive blows, a new study finds. What was the murder weapon? A bat-like object, meaning the victim was likely clubbed to death, the researchers found.



The Cioclovina skull has two large fractures on it, likely from interpersonal violence during the Upper Paleolithic. **Kranioti, EF. et al. PLOS ONE. 2019.**

"What our study shows is that this man was killed as a result of blunt force trauma" to his skull, said study senior author Katerina Harvati, a professor of paleoanthropology at the University of Tübingen in Germany. "The extent of the injuries that he sustained would have led to death. As to how or why this came about, we can only speculate."

All that's left of the ancient murder victim is a skull, known as the Cioclovina calvaria (a calvaria is a skullcap). In 1941, phosphate miners found it in the Pestera Cioclovina cave, in South Transylvania, Romania, along with stone tools from the Upper Palaeolithic Aurignacian culture and several cave bear fossils.

Other studies have shown that the skull belonged to an adult man. However, researchers couldn't agree on how this man's injuries were inflicted or whether the skull was damaged before or after he died. So, a team of international researchers from Greece, Romania and Germany took another look at it.

"The Cioclovina individual is particularly important, as it is one of the earliest and relatively complete skulls of modern Europeans from the Upper Paleolithic period (a period starting around 40,000 to 45,000 years, when the major dispersal of modern humans in Europe occurred)," Harvati told Live Science in an email. "Human remains from this period are very rare and often very fragmentary."

Harvati and her team took a CT scan of the skull to get a detailed look at its two fractures. Then, they took 12 synthetic bone spheres and subjected them to different traumas, dropping them from heights (to model a possible fall), hitting them with rocks and clubbing them with bats.

"Our results clearly showed that the fracture patterns observed on this skull could not have been produced after death, or from an accidental fall," Harvati said. "Instead, they closely matched with the expected patterns for blunt force trauma (i.e., trauma inflicted with a blunt instrument, such as a club, for example) to the head."

The locations of the injuries also revealed clues about the murderer. It appears that the murderer was face-to-face with the victim during the assault and likely a lefty, because the injury was on the skull's right side, "although the possibility of [the murderer] holding the object with both hands cannot be dismissed," the researchers wrote in the study.

During the Upper Paleolithic, people were creative; they developed cultural and technological innovation, symbolic behavior and artistic expression. But their world was a violent place. "We show that they were also capable of murder," Harvati said.

It's not surprising that the Upper Paleolithic was a violent time, but "this is still a very valuable study," said Niels Nørkjær Johannsen, an associate professor in the Department of Archaeology and Heritage Studies at Aarhus University, in Denmark, who was not involved with the research.

Some people might say "'Isn't that a matter of course?'" that the man died of violence, Johannsen told Live Science. But it's important not to simply make assumptions about the past. "They really take the necessary care and do all this work to say 'this is certainly interpersonal violence.' It's as certain as these things get in these types of sciences." The study was published online today (July 3) in the journal PLOS ONE.

http://bit.ly/2LFsaQi

Low Levels of 'Bad' Cholesterol May Have a Downside

Study suggests it may be possible for cholesterol levels to be too low

By Rachael Rettner, Senior Writer

When it comes to "bad" cholesterol, lower is usually better for heart disease risk. But a new study suggests it may be possible for cholesterol levels to be too low. The study researchers found that low levels of "bad" cholesterol, known as LDL cholesterol, were tied to an increased risk of hemorrhagic stroke, which occurs when a blood vessel bursts in the brain.

The findings suggest that, "as is true with many things in nutrition, moderation and balance is key when deciding the optimal target level of LDL cholesterol," study senior author Dr. Xiang Gao, an associate professor of nutritional sciences at Penn State, said in a statement. "You can't go to either extreme — too high or too low."

The authors said the findings, which were published yesterday (July 2) in the journal Neurology, might help further refine recommendations for healthy cholesterol levels. For example, people who are at high risk for hemorrhagic stroke, because of risk factors such as having a family history of the condition, might be better off aiming for cholesterol targets that aren't quite as stringent as would otherwise be recommended.

Still, the findings will need to be confirmed by further research. Although the new study was large, involving nearly 100,000 people, all of the participants lived in a single city in China, and it's unclear how well the findings apply to other populations.

People should discuss their optimal cholesterol targets with their doctor, Gao told Live Science.

Lower not always better?

Cholesterol is a waxy substance found in the body. There are several types of cholesterol, including LDL (short for low-density lipoprotein), which is sometimes called "bad" cholesterol. That's because high levels of LDL can lead to the buildup of plaque in the arteries, and increase the risk of heart disease and ischemic stroke, which occurs when a clot blocks blood flow to part of the brain.

For healthy adults, LDL cholesterol should stay below 100 milligrams per deciliter (mg/dL), according to the National Institutes of Health. However, recent guidelines recommend that people who are at very high risk of heart problems should aim to get their LDL cholesterol even lower, below 70 mg/dL.

Still, some previous studies have found a link between low LDL cholesterol levels and an increased risk of hemorrhagic stroke. However, most of these studies were small and measured cholesterol levels at a single point in time, which means they couldn't take into account fluctuations in cholesterol levels over time, the authors said.

In the new study, the researchers analyzed information from about 96,000 adults in the industrial city of Tangshan, China, who had no prior history of stroke, heart attack or cancer. The participants had their cholesterol levels measured at the start of the study and again each year for nine years.

During the study period, there were 753 cases of hemorrhagic stroke.

People with LDL cholesterol levels below 70 mg/dL were 65% more likely to have a hemorrhagic stroke during the study period, compared with those who had LDL levels of 70 to 99 mg/dL, the study found. And people with LDL cholesterol levels below 50 mg/dL were more than twice as likely to have a hemorrhagic stroke, compared with those who had LDL levels of 70 to 99 mg/dL.

Still, it's important to note that the overall risk of hemorrhagic stroke was relatively low, occurring in less than 1% of the participants.

Exactly why low LDL cholesterol is linked with an increased risk of hemorrhagic stroke is not known. But cholesterol itself plays a key role in the formation of cell membranes, and it may be that very low LDL levels lead to fragility in red blood cells, making them more prone to rupture, Gao said. LDL is also thought to be involved in the pathway that allows blood to clot, he said, so low LDL levels may increase bleeding risk.

Future research

In terms of preventing ischemic heart disease and stroke — that is, disease caused by the restriction of blood flow to tissues — lower "bad" cholesterol is better, said Dana Hunnes, a senior dietitian at the Ronald Reagan UCLA Medical Center in Los Angeles who wasn't involved with the study. But at the same time, the new findings suggest that "levels of LDL cholesterol that are too low, in this case, less than 70 mg/dL, are also detrimental" in this particular population, by increasing the risk of hemorrhagic stroke, Hunnes

told Live Science. However, the authors acknowledged that it may be challenging to apply these results to people in other countries living under different circumstances, Hunnes said.

Moreover, the study didn't account for people's dietary habits, which Hunnes would like future studies to consider.

"The dietitian in me is dying to know if certain dietary patterns may attenuate or accentuate the risks seen" in this study, Hunnes said.

http://bit.ly/2L8f6nd

The Lancet: Nerve transfer surgery restores hand function and elbow extension in 13 young adults with complete paralysis

13 young adults with tetraplegia are able to feed themselves, hold a drink, brush their teeth, and write as a result of a novel surgical technique which connects functioning nerves with injured nerves to restore power in paralyzed muscles

13 young adults with tetraplegia are able to feed themselves, hold a drink, brush their teeth, and write as a result of a novel surgical technique which connects functioning nerves with injured nerves to restore power in paralysed muscles Nerve transfer surgery has enabled 13 young adults with complete paralysis to regain movement and function in their elbows and hands, according to the largest case series of this technique in people with tetraplegia (paralysis of both the upper and lower limbs), published in *The Lancet*.

During the surgery, Australian surgeons attached functioning nerves above the spinal injury to paralysed nerves below the injury. Two years after surgery, and following intensive physical therapy, participants were able to reach their arm out in front of them and open their hand to pick up and manipulate objects. Restoring elbow extension improved their ability to propel their wheelchair and to transfer into bed or a car.

They can now perform everyday tasks independently such as feeding themselves, brushing teeth and hair, putting on make-up, writing, handling money and credit cards, and using tools and electronic devices.

The findings suggest that nerve transfers can achieve similar functional improvements to traditional tendon transfers, with the benefit of smaller incisions and shorter immobilisation times after surgery.

In 10 participants, nerve transfers were uniquely combined with tendon transfers allowing different styles of reconstruction to be performed in each hand, and enabling participants to benefit from the innate strengths of both tendon and nerve transfers. Nerve transfers restored more natural movement and finer motor control in one hand, and tendon transfers restored more power and heavy lifting ability in the other hand.

While only a small study, researchers say that nerve transfers are a major advance in the restoration of hand and arm function, and offer another safe, reliable surgical option for people living with tetraplegia.

Nevertheless, four nerve transfers failed in three participants and the authors conclude that more research will be needed to determine which people are the best candidates to select for nerve transfer surgery to minimise the incidence of failure.

"For people with tetraplegia, improvement in hand function is the single most important goal. We believe that nerve transfer surgery offers an exciting new option, offering individuals with paralysis the possibility of regaining arm and hand functions to perform everyday tasks, and giving them greater independence and the ability to participate more easily in family and work life", says Dr Natasha van Zyl from Austin Health in Melbourne, Australia who led the research. [1]

"What's more, we have shown that nerve transfers can be successfully combined with traditional tendon transfer techniques to maximise benefits. When grasp and pinch was restored using nerve transfers in one hand and tendon transfers in the other, participants consistently reporting that they liked both hands for different reasons and would not choose to have two hands reconstructed in the same way." [1]

Traditionally, upper limb function has been reconstructed using tendon transfer surgery, during which muscles that still work, but are designed for another function, are surgically re-sited to do the work of muscles that are paralysed. In contrast, nerve transfers allow the direct reanimation of the paralysed muscle itself. Additionally, nerve transfers can re-animate more than one muscle at a time, have a shorter period of immobilisation after surgery (10 days in a sling vs 6-12 weeks in a brace for a nerve transfer for elbow extension), and avoid the technical problems associated with of tendon transfer surgery including tendon tensioning during surgery and mechanical failure (stretch or rupture) after surgery.

Previous single case reports and small retrospective studies have shown nerve transfer surgery to be feasible and safe in people with tetraplegia. But this is the first prospective study to use standardised functional outcome measures and combinations of multiple nerve and tendon transfer surgeries.

In total the study recruited 16 young adults (average age 27 years) with traumatic, early (less than 18 months post injury) spinal cord injury to the neck (C5-C7), who were referred to Austin Health in Melbourne for restoration of function in the upper limb. Most were the result of motor vehicle accidents or sports injuries.

Participants underwent single or multiple nerve transfers in one or both upper limbs to restore elbow extension, grasp, pinch, and hand opening. This involved taking working nerves to expendable muscles innervated above the spinal injury and attaching them to the nerves of paralysed muscles innervated below the injury to restore voluntary control and reanimate the paralysed muscle.

For example, the surgeons selected the nerve supplying the teres minor muscle in the shoulder as a donor nerve and attached it to the nerve supplying the triceps that activates the muscles that extend (straighten) the elbow. To restore grasp and pinch the nerve to a spare wrist extensor muscle was transferred to the anterior interosseous nerve (figure 1).

In total, 59 nerve transfers were completed in 16 participants (13 men and three women; 27 limbs). In 10 participants (12 limbs), nerve transfers were combined with tendon transfers to improve hand function.

Participants completed assessments on their level of independence related to activities of daily living (e.g., self-care, toilet, upper limb function, muscle power, grasp and pinch strength, and hand opening ability) before surgery, one year after surgery, and again two years later. Two participants were lost to follow up, and there was one death (unrelated to the surgery).

At 24 months, significant improvements were noted in the hands ability to pick up and release several objects within a specified time frame and independence. Prior to surgery, none of the participants were able to score on the grasp or pinch strength tests, but 2 years later pinch and grasp strength were high enough to perform most activities of daily living (table 4).

Three participants had four failed nerve transfers--two had a permanent decrease in sensation, and two had a temporary decrease in wrist strength that resolved by 1 year after surgery. Overall, surgery was well tolerated. Five serious adverse events were recorded (including a fall from a wheelchair with femur fracture), but none were related to the surgery.

Despite these achievements, nerve transfer surgery still has some limitations. For the best results nerve transfers should ideally be

performed within 6-12 months of injury. Additionally, it can take months after nerve transfer for nerve regrowth into the paralysed muscle to occur and for new movement to be seen, and years until full strength is achieved. However, the authors note that one of the benefits of nerve transfers is that most movements not successfully restored by nerve transfers can still be restored using tendon transfers.

Discussing the implications of the findings in a linked comment, Dr Ida Fox from Washington University in the USA writes, "Stem cells and neuroprostheses could change the landscape of regenerative medicine in the future. For now, nerve transfers are a cost-effective way to harness the body's innate capability to restore movement in a paralysed limb. As nerve transfers are adopted and their uses adapted, careful ongoing outcomes research--including comparison of nerve versus tendon transfer outcomes, which nerve transfers produce the greatest functional improvements, and optimal timings for surgery after injury--is paramount to advancing the field. Detailed study of the reasons for nerve transfer failure is also required, as is improving our understanding of the effects of biopsychosocial factors (including access to information and care, psychological readiness, and social support) on patient decision making and outcomes."

NOTES TO EDITORS

This study was funded by the Institute for Safety, Compensation, and Recovery Research (Australia). It was conducted by researchers from Austin Health, Melbourne, VIC, Australia; Epworth Monash Rehabilitation Medicine Unit, Melbourne, VIC, Australia; The University of Melbourne, Melbourne, VIC, Australia.

The labels have been added to this press release as part of a project run by the Academy of Medical Sciences seeking to improve the communication of evidence. For more information, please see: http://www.sciencemediacentre.org/wp-content/uploads/2018/01/AMS-press-release-labelling-system-GUIDANCE.pdf if you have any questions or feedback, please contact The Lancet *press office pressoffice@lancet.com*

[1] Quotes direct from author and cannot be found in text of Article.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31143-2/fulltext

http://bit.ly/328ptg5

Strain of common cold virus could revolutionize treatment of bladder cancer

Strain of the common cold virus has been found to potentially target, infect and destroy cancer cells in patients with bladder cancer

A strain of the common cold virus has been found to potentially target, infect and destroy cancer cells in patients with bladder cancer, a new study in the medical journal Clinical Cancer Research reports. No trace of the cancer was found in one patient following treatment with the virus.

Researchers from the University of Surrey and Royal Surrey County Hospital investigated the safety and tolerability of exposure to the oncolytic ('cancer-killing') virus coxsackievirus (CVA21), a naturally occurring strain of the common cold, in fifteen patients with non-muscle invasive bladder cancer (NMIBC). NMIBC is found in the tissue of the inner surface of the bladder and is the tenth most common cancer in the UK with approximately 10,000 people each year diagnosed with the illness.

Current treatments for this cancer are problematic. Transurethral resection, an invasive procedure that removes all visible lesions, has a high tumour recurrence rate ranging from 50 per cent to 70 per cent as well as a high tumour progression rate between 10 per cent and 20 per cent over a period of two to five years. Another common course of treatment, immunotherapy with Bacille Calmette-Guerin, a live bacterium used to treat bladder cancer, has been found to have serious side effects in one third of NMIBC patients while one third do not respond to the treatment at all.

During this pioneering study fifteen NMIBC patients, one week prior to pre scheduled surgery to remove their tumours, received CVA21 via a catheter in the bladder. Examination of tissue samples post-surgery discovered that the virus was highly selective,

targeting only cancerous cells in the organ and leaving all other cells intact. The virus was found to have infected cancerous cells and replicated itself causing the cells to rupture and die. Urine samples taken from patients on alternate days detected 'shedding' from the virus indicating that once virally infected cancer cells had died, the newly replicated virus continued to attack more cancerous cells in the organ.

Typically tumours in the bladder do not have immune cells, preventing a patient's own immune system from eliminating the cancer as it grows. Evidence suggests treatment with CVA21 inflames the tumour causing immune cells to rush into the cancer environment, targeting and killing the cancer cells. These tumours devoid of immune cells are known as 'cold' areas immunologically; however, treatment with the virus causes inflammation and immune cell stimulation to create 'immunological 'heat'. 'Hot' tumours in this way are more likely to be rejected by the immune system.

Following treatment with the virus cell death was identified in the majority of the patients' tumours. In one patient no trace of the cancer was found during surgery.

Hardev Pandha, Principal Investigator of the study and Professor of Medical Oncology at the University of Surrey, said: "Non-muscle invasive bladder cancer is a highly prevalent illness that requires an intrusive and often lengthy treatment plan. Current treatment is ineffective and toxic in a proportion of patients and there is an urgent need for new therapies.

"Coxsackievirus could help revolutionise treatment for this type of cancer. Reduction of tumour burden and increased cancer cell death was observed in all patients and removed all trace of the disease in one patient following just one week of treatment, showing its potential effectiveness. Notably, no significant side effects were observed in any patient."

Dr Nicola Annels, Research Fellow at the University of Surrey, said: "Traditionally viruses have been associated with illness however in the right situation they can improve our overall health and wellbeing by destroying cancerous cells. Oncolytic viruses such as the coxsackievirus could transform the way we treat cancer and could signal a move away from more established treatments such as chemotherapy."

http://bit.ly/30qekYI

Area for restoring trees far greater than imagined and 'best climate change solution available'

Earth could support enough additional trees to reduce carbon levels in the atmosphere by nearly 25%

日本のニュース

In the first study to quantify how many trees the Earth can support, where, and how much carbon they could store, researchers report that Earth could support enough additional trees to cut carbon levels in the atmosphere by nearly 25% - levels not seen for almost a century.

"We all knew restoring forests could play a part in tackling climate change, but we had no scientific understanding of what impact this could make," said study coauthor Thomas Crowther.

"Our study shows clearly that forest restoration is the best climate change solution available today." Because trees capture and remove carbon dioxide (CO2) from the atmosphere, widespread reforestation has been considered one of the most effective weapons against climate change.

According to the most recent Intergovernmental Panel on Climate Change (IPCC) report, an additional 1 billion hectares of forest will be required to limit global warming to 1.5 degrees Celsius by 2050.

However, it remains unclear if these restoration goals are achievable because researchers do not know how much tree cover might be possible under current or future climate conditions.

Here, to explore this, Jean-Francois Bastin, Tom Crowther and colleagues leveraged a unique global dataset of forest observations spanning nearly 80,000 forests, combined with the mapping software of Google Earth Engine, which they used to generate a predictive model to map potential tree cover worldwide under current conditions.

Excluding existing trees, agricultural and urban areas, they suggest Earth's ecosystems could support an additional 0.9 billion hectares of tree cover, which, once matured, could sequester more than 200 Gigatons of carbon, or two-thirds of man-made carbon emissions.

The global map of reforestation their study provides is essential for making more effective global-scale restoration targets, and for guiding local-scale restoration projects, the authors say.

In a related Perspective, Robin Chazdon and Pedro Bancalion underscore the need to act quickly within a narrowing window of time, as currently forested areas continue to decline, and as reforestation efforts become more challenging in a warmer world.

http://bit.ly/2XSAouU

DNA Data Storage Is Closer Than You Think

Life's information-storage system is being adapted to handle massive amounts of information

By Sang Yup Lee

Every minute in 2018, Google conducted 3.88 million searches, and people watched 4.33 million videos on YouTube, sent 159,362,760 e-mails, tweeted 473,000 times and posted 49,000 photos on Instagram, according to software company Domo. By 2020 an estimated 1.7 megabytes of data will be created per second per person globally, which translates to about 418 zettabytes in a single year (418 billion one-terabyte hard drive's worth of information), assuming a world population of 7.8 billion. The magnetic or optical data-storage systems that currently hold this volume of 0s and 1s typically cannot last for more than a century, if that. Further, running data centers takes huge amounts of energy. In short, we are about to have a serious data-storage problem that will only become more severe over time.

An alternative to hard drives is progressing: DNA-based data storage. DNA—which consists of long chains of the nucleotides A, T, C and G—is life's information-storage material. Data can be stored in the sequence of these letters, turning DNA into a new form of information technology. It is already routinely sequenced (read), synthesized (written to) and accurately copied with ease. DNA is also incredibly stable, as has been demonstrated by the complete genome sequencing of a fossil horse that lived more than 500,000 years ago. And storing it does not require much energy.

But it is the storage capacity that shines. DNA can accurately stow massive amounts of data at a density far exceeding that of electronic devices. The simple bacterium *Escherichia coli*, for instance, has a storage density of about 10^{19} bits per cubic centimeter, according to calculations published in 2016 in *Nature Materials* by George Church of Harvard University and his colleagues. At that density, all the world's current storage needs for a year could be well met by a cube of DNA measuring about one meter on a side.

The prospect of DNA data storage is not merely theoretical. In 2017, for instance, Church's group at Harvard adopted CRISPR DNA-editing technology to record images of a human hand into the genome of *E. coli*, which were read out with higher than 90 percent accuracy. And researchers at the University of Washington and Microsoft Research have developed a fully automated system for writing, storing and reading data encoded in DNA. A number of companies, including Microsoft and Twist Bioscience, are working to advance DNA-storage technology.

Meanwhile DNA is already being used to manage data in a different way, by researchers who grapple with making sense of tremendous

volumes of data. Recent advancements in next-generation sequencing techniques allow for billions of DNA sequences to be read easily and simultaneously. With this ability, investigators can employ bar coding—use of DNA sequences as molecular identification "tags"—to keep track of experimental results. DNA bar coding is now being used to dramatically accelerate the pace of research in fields such as chemical engineering, materials science and nanotechnology. At the Georgia Institute of Technology, for example, James E. Dahlman's laboratory is rapidly identifying safer gene therapies; others are figuring out how to combat drug resistance and prevent cancer metastasis.

Among the challenges to making DNA data storage commonplace are the costs and speed of reading and writing DNA, which need to drop even further if the approach is to compete with electronic storage. Even if DNA does not become a ubiquitous storage material, it will almost certainly be used for generating information at entirely new scales and preserving certain types of data over the long term.

https://nyti.ms/2XszAsw

Neil Armstrong: First Man on the Moon, and Its First Great Geologist

Had the Apollo program stopped after July 21, 1969, another astronaut says, its lunar samples would have been enough to reshape knowledge of the solar system.

By Kenneth Chang

At the start of a talk at the Lunar and Planetary Science conference in Houston in March, Harrison Schmitt, one of the two astronauts who walked on the moon during Apollo 17, the last lunar mission, put up a picture of Neil Armstrong.

"Let's pay tribute to this man," said Dr. Schmitt, the only professionally trained scientist among the Apollo astronauts. A ballroom packed with scientists erupted in exuberant applause.

"Neil turned out to be the best field geologist on the moon," he added. "Until Apollo 17, of course. In 20 minutes or so, he collected a fantastic suite of samples."

Dr. E. A. King of the Lunar Receiving Laboratory at NASA's Johnson Space Center in Houston in July 1969, with moon rocks that were collected during the Apollo 11 mission. **NASA, via Associated Press**

Before Apollo 11, even simple questions about the moon confounded scientists. For instance, how old was it, anyway?

Once they started examining the 50 pounds of rocks and soil brought back by Armstrong and Buzz Aldrin, the answer quickly became clear: very, very old.

Dr. Schmitt said that had the Apollo program stopped then, with no additional landings, including his own, those first lunar samples would have been enough to forever reshape knowledge of the solar system.

Armstrong collected two types of rocks: basalts, which are hardened pieces of lava, and breccias, which are fragments of older rocks fused together. The landing site was within a flat lava plain, which was chosen because it appeared to be a safe place to touch down, not because it looked scientifically intriguing.

Nonetheless, the basalts rewrote solar system history. The relative amounts of certain long-lived radioactive elements within the rocks gave a range of ancient ages, unchanged since they cooled and solidified out of lava between 3.6 billion and 3.9 billion years ago. That is far older than almost all of the rocks on Earth, which have been churned, compressed, melted and resolidified over the eons. In fact, the moon rocks were nearly as old as the Earth and the solar system, which formed 4.5 billion years ago.

“Right there, we knew the moon was going to be, at least in part, the record for the early history of the Earth,” Dr. Schmitt said. “That was not clearly understood before Apollo 11. But it is clearly understood afterwards and now.”

Another major discovery lay within soil that Armstrong picked up and dropped into the collection box, because it was not packed full. The soil contained bits of a rock known as anorthosite. Just as ice floats on water, anorthosite, made of the mineral plagioclase, floats on magma.

Within half a year after Apollo 11, two teams of scientists, one at the University of Chicago, the other at Harvard, independently used the presence of anorthosite to come up with what was then a radical notion: The moon, the scientists proposed, had at one point melted into a global ocean of magma.

Buoyant anorthosite would then have risen to the surface while heavier materials, like iron, would have sunk to the core. Speculation of a lunar magma ocean, in turn, led to the hypothesis that the moon formed out of the debris from a collision between Earth and a Mars-size body.

“The concept, the phrase magma ocean, didn’t exist until Apollo 11,” Dr. Schmitt said in an interview. “That’s the way science moves.”

Rocks from later Apollo missions added evidence to the theory.

Armstrong’s soil also contained hydrogen, helium, nitrogen and carbon, much of which had been deposited by the solar wind, the stream of high-speed particles continually flying outward from the sun. A light version of helium, helium-3, is of particular future interest as fuel for fusion reactors, which could generate bountiful, nearly clean energy by combining atoms.

“It told us there were going to be tremendous amounts of potential resources for use in space, and possibly even on Earth,” Dr. Schmitt said.

Another far-reaching scientific legacy of the moon rocks gathered by the Apollo astronauts is how scientists used them to calibrate a technique of using craters to determine the ages of places in the solar system.

The concept is simple. Over time, impacts of asteroids, big and small, pocked the surface of the moon and elsewhere. But a layer of ice or lava can erase the craters and reset the clock. Thus, a heavily cratered surface is older than a smooth one. But while planetary scientists could see which places were older and which were younger, they did not know exactly how old any of them were.

With the dating of the rocks taken from Apollo 11’s landing site, scientists then knew the age of that patch of the lunar surface. Rocks from the other five Apollo landings set the ages of those corresponding regions, which then correlated with the different numbers of craters in each place.

The calibrated crater counts are now used to determine ages of bodies throughout the inner solar system.

The dating record still contains a huge two-billion-year gap, from one billion years ago to three billion years ago, because all of the Apollo missions touched down on older swaths of the moon. Scientists have tried to extrapolate the ages of younger regions, but different guesses provide a wide range of age estimates.

“Which is the correct chronology?” David Draper, NASA’s deputy chief scientist, asked. “That part of the curve is unconstrained. We desperately need new samples.”

Dr. Draper is part of a team that has proposed a small robotic mission called the Inner Solar System Chronology, or Isochron, which would grab five ounces of rock from a younger, smoother part of the moon and whisk it back to Earth, where scientists would determine the age of the sample.

Future robotic explorers may one day accomplish much more on the lunar surface than Armstrong could in 1969 with his space-

suited hands holding a sampling stick. But it took the humanity in that test pilot who moonlighted as a field geologist to pause from his collecting and take in the lunar landscape.

"It has a stark beauty all its own," Armstrong said not long after taking his first steps on the moon. "It's like much of the high desert of the United States. It's different, but it's very pretty out here."

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http://bit.ly/32qWhDG

Scientists Discover Vortex Around Black Hole Spinning at 70 Percent the Speed of Light

Astronomers have measured the spin of five supermassive black holes located around 10-11 billion light-years from Earth—and the results reveal that they are moving at staggering speeds.

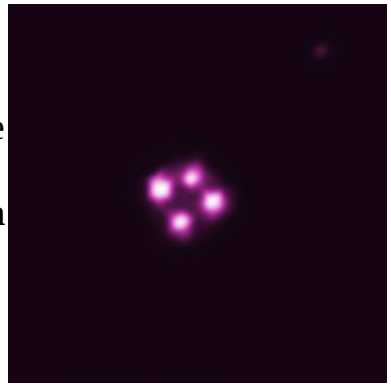
By Aristos Georgiou

According to a study published in the *Astrophysical Journal*, the event horizon of one of these stellar objects is spinning close to or at the speed of light—around 670 million miles per hour. (The event horizon is the point of no return around a black hole past which not even light can escape.)

The four other black holes that the team of astronomers studied appear to be spinning at about half that rate. Furthermore, the scientists found that the vortex of material circling around one of the five black holes is spinning at around 70 percent of the speed of light.

The collection of dust and gas around a black hole—known as an accretion disk—becomes superheated to many millions of degrees as it gradually gets sucked it, generating X-ray light that astronomers can detect using specialized observatories.

The five black holes the team investigated for the latest study have masses between 160 and 500 million times that of our sun. They all are consuming matter from their accretion disk, causing them to grow rapidly.



These types of supermassive black holes that rapidly ingest matter from swirling disks of material—known as quasars—are some of the brightest objects in the universe. However, because the quasars in question are so far away, astronomers made use of a peculiar natural phenomenon known as "gravitational lensing" in order to study them.

Astronomers have used Chandra to measure the spin of five quasars, each consisting of a supermassive black hole rapidly consuming matter from a surrounding accretion disk. **NASA/CXC/Univ. of Oklahoma/X. Dai et al.**

Essentially, we can think of gravitational lensing as nature's magnifying glass. With just the right alignment, the immense mass of large objects, such as galaxies, in the intervening space can bend and distort the light coming from even more distant objects directly behind them. This can magnify or produce multiple images of these more distant objects, making them easier to study.

With the help of NASA's Chandra X-ray Observatory, the astronomers used this technique to work out the spin rate of the distant black holes. The astronomers found that the X-rays these quasars are generating are coming from a region of the accretion disk that is only slightly larger than the event horizon itself. As a result, they concluded that the black holes must be spinning extremely rapidly.

These observations are significant because while we have been able to measure the mass of black holes with relative ease in the past, determining their spin rate has proven to be far harder. Such results can help scientists to understand how black holes grow and evolve over time.