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Volcano's magma hit top speed

Volcanologists might need to update their ideas about how molten rock travels from deep within Earth to erupt at the surface.

Magma needed just a week and a half to rise from more than 20 kilometres below Earth's surface to erupt as lava from a now-dormant Icelandic volcano, scientists estimate The finding could prompt volcanologists to revise their methods of predicting future eruptions.

Bárðarbunga Volcano in Iceland. Molten rock flowed from another, now-dormant Icelandic volcano after a blazingly fast rise from near the bottom of Earth's crust. **Arctic Images/Alamy**

Euan Mutch, John Maclennan and their colleagues at the University of Cambridge, UK, studied lava flows from the Borgarhraun eruption, which took place in northern Iceland between 7,000 and 10,500 years ago.

The chemistry of crystals in the lava indicated their depth in Earth's crust when the magma began moving upwards and how the magma cooled as it rose.

The magma zipped from 24 kilometres deep to the surface in about 10 days — the fastest ascent ever recorded for one of the planet's most common types of molten rock.

It rose so quickly that there was no time to release much of the carbon dioxide trapped within it.

This suggests that the common strategy of monitoring the carbon dioxide emissions of active volcanoes might in some cases provide only a day's warning of an imminent eruption.

Nature Geosci. (2019)

http://bit.ly/2FzrkAZ

Discovery of performance-enhancing bacteria in the human microbiome

A single microbe accumulating in the microbiome of elite athletes can enhance exercise performance in mice, paving the way to highly-validated performance-enhancing probiotics

By Benjamin Boettner

BOSTON - The human microbiome, the vast collection of microbes that colonize the surfaces lining many of our organs and our skin - is a critical pillar sustaining our general health. At any one time, 500 to 1,000 different species of bacteria inhabit us, which together contain far more genes than our human genome. Researchers have also come to realize that no two individuals share the same microbiome, and that an individual's microbiome composition can change with diet, lifestyle, treatment with antibiotics and other drugs, and other factors. Whereas various links have been found between individual microbiomes and diseases as diverse as obesity, inflammatory bowel disease, arthritis, cancer, and autism, it remained unknown whether the opposite also could be true with the microbiome actively enhancing health and physical performance.

"At the start of this project, we hypothesized that the microbiomes of elite athletes must have highly adjusted bacterial species in common that could help with their performance and recovery, and that, once identified, these could become the basis of highly validated performance-enhancing probiotics," said co-first author Jonathan Scheiman, Ph.D., a former Postdoctoral Fellow who initiated the project with George Church, Ph.D. Core Faculty member at Harvard's Wyss Institute for Biologically Inspired Engineering and Professor at Harvard Medical School (HMS). Scheiman also is the CEO of FitBiomics Inc., and himself a former professional basketball player.

Now, a highly collaborative team of researchers led by Scheiman and Church at the Wyss Institute and HMS, and Aleksandar Kostic at Joslin Diabetes Center in Boston pinpointed one specific group of bacteria, called *Veillonella*, that they found was enriched in the gut microbiome of Boston Marathon runners after after completing the 26.2 race and in an independent group of 87 elite and Olympic athletes after competitions. *Veillonella* bacteria isolated from marathon athletes and given to mice increased the animals' performances in laboratory treadmill tests by 13% compared to control bacteria.

"We were able to demonstrate that the *Veillonella*-driven performance boost was due to the bacteria's ability to break down lactate, a metabolite known to accumulate with prolonged strenuous exercise, and to produce propionate, a short-chain fatty acid (SCFA), that in turn enhances the body's resilience to exercise stress," said co-corresponding author Kostic, Ph.D., who is Assistant Professor of Microbiology at Joslin Diabetes Center, and pursuing computational and experimental approaches geared at better understanding the relationship between the human microbiome and metabolic diseases such as diabetes.

In their initial analysis of 2015 Boston Marathon runners, the researchers analyzed the runners' microbiome composition by determining the DNA sequences of an omnipresent but highly species-specific cluster of genes from bacteria obtained from athletes' stool samples. "Collecting samples daily throughout the week before the run and the week following the run and analyzing them with the help of Aleksandar's bioinformatics pipeline, enabled us to identify meaningful fluctuations within the entire microbiome with the increase in the *Veillonella* genus as the most prominent one," said Scheiman.

Veillonella's ability to consume lactate as an energy source was known but the team went a crucial step further. They demonstrated that one single species of *Veillonella*, known as *Veillonella atypica*, which they isolated from athletes' microbiomes and added to the intestinal microbiomes of mice, by itself could boost the animals' performance in the treadmill running tests.

Key bioinformatics analysis and animal experiments were carried out by co-first authors Jacob Luber, and Theodore Chavkin who both are graduate students in Kostic's group.

But how? With lactate being produced in working muscles, circulating through the vascular system, and being cleared by the liver, and the bacteria on the other hand residing in the intestinal lumen, there was no obvious connection. Indeed, the team provided the first evidence that lactate can actually cross from the circulation through the intestinal epithelial wall into the gut lumen, where it becomes available to *Veillonella* and possibly other bacteria. Interestingly, the bacteria did not act as a "lactate sink" causing a sizable drop in systemic circulating lactate levels. Rather, it was a product of the bacteria's lactate fermentation, the short-chain fatty acid propionate, that crossed back from the gut lumen into the circulation to enhance performance.

The collaborators indeed showed that propionate, when instilled into the intestinal lumen of mice, can reproduce many of *Veillonella*'s effects, like the increase in treadmill run time to exhaustion, and a decrease in the levels of common inflammatory markers in the intestinal tract that rise during and after extreme athletic performances and treadmill running in the mouse model. "We think that propionate could exhibit its performance benefits by counter-acting inflammation, serving as an energy source for the body, and other as yet unknown effects," speculated Kostic. "Of note, higher exercise capacity strongly correlates with milder progression and greater longevity in diabetes patients, which could potentially make a probiotic *Veillonella* approach therapeutic."

"The study nicely validated our original hypothesis and provides one of the most compelling examples of 'metabolic symbiosis' between the human host and microbiome that could be broadly harnessed as a probiotic strategy not only for athletes but also to improve health in patients," said co-corresponding author Church, who also is Professor of Genetics at HMS and of Health Sciences and Technology at Harvard University and the Massachusetts Institute of Technology (MIT) and the lead of the Wyss Institute's Synthetic Biology Platform. "Now that we have built out a platform for identifying microbes associated with extreme performances, we can explore the microbiomes of other types of extreme athletes or individuals that are highly adapted to environmental challenges, uncover additional beneficial functional links and work towards translating them into probiotic treatments."

Scheiman and Church are co-founders of FitBiomics, Inc., a microbiome biotechnology company targeted at athletes. Scheiman, Church and Kostic hold equity in Fitbiomics, Inc.

"This is a wonderful example of how our Institute provides creative young scientists with the freedom to follow their unconventional ideas wherever they might go. Scheiman's passion for sports and science merged in a such a wonderful way, and by collaborating with other outstanding scientists, each bringing his own expertise, a major discovery resulted that has the potential to change the quality of life of many people around the world using a low-cost probiotic approach," said Wyss Institute Founding Director Donald Ingber who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS).

Other authors on the study are Wyss Institute and HMS researchers Angela Tung, Sukanya Punthambaker, Ph.D., and Mohammad Hattab, Ph.D.; Tara MacDonald, Ph.D., Sarah Lessard, Ph.D., Loc-Duyen Pham, Marsha Wibowo, Braden Tierney, Zhen Yang at Joslin Diabetes Center; Renee Wurth, Ph.D., at FibBiomics Inc.; and Julian Avila Pacheco, Ph.D., and Clary Clish, Ph.D., at the Broad Institute at MIT and Harvard. The study was funded by Harvard's Wyss Institute for Biologically Inspired Engineering, and the National Institutes of Health's National Human Genome Research Institute and National Institute of Diabetes and Digestive and Kidney Diseases.

http://bit.ly/2JdQaYa

Commonly prescribed drugs could increase the risk of dementia, says a new study

Nearly 50% increased risk of dementia among patients aged 55 and over with long-term use of strong anticholinergic medication

The study, carried out by experts from the University of Nottingham and funded by the NIHR School for Primary Care Research, found that there was nearly a 50% increased risk of dementia among patients aged 55 and over who had used strong anticholinergic medication daily for three years or more.

Anticholinergic drugs help to contract and relax muscles. They work by blocking acetylcholine, a chemical that transmits messages in the nervous system.

Doctors prescribe the drugs to treat a variety of conditions, including chronic obstructive pulmonary disease, bladder conditions, allergies, gastrointestinal disorders and symptoms of Parkinson's disease.

These medicines can have short-term side effects, including confusion and memory loss, but it is less certain whether long-term use increases the risk of dementia.

The research, published in the JAMA Internal Medicine journal and led by Professor Carol Coupland from the University's Division of Primary Care, looked at the medical records of 58,769 patients with a diagnosis of dementia and 225,574 patients without a diagnosis of dementia, all aged 55 and over and registered with UK GPs contributing data to the QResearch database, between 1 January 2004 and 31 January 2016.

The study findings showed increased risks of dementia for anticholinergic drugs overall and specifically for the anticholinergic antidepressants, antipsychotic drugs, antiparkinsons drugs, bladder drugs and epilepsy drugs after accounting for other risk factors for dementia.

No increased risks were found for the other types of anticholinergic drug studied such as antihistamines and gastrointestinal drugs.

Professor Tom Dening, Head of the Centre for Dementia at the University of Nottingham and a member of the research study team, said: "This study provides further evidence that doctors should be careful when prescribing certain drugs that have anticholinergic properties. However, it's important that patients taking medications of this kind don't just stop them abruptly as this may be much more harmful. If patients have concerns, then they should discuss them with their doctor to consider the pros and cons of the treatment they are receiving."

The 58,769 patients with dementia had an average age of 82 and 63% were women. Each dementia case was matched to five control patients of the same age, sex, and general practice.

Anticholinergic drug exposure was assessed using prescription information over a complete period of 10 years from 1 to 11 years before diagnosis of dementia or the equivalent dates in control patients, and was compared between the two patient groups. Further analysis looked at prescriptions for anticholinergic drugs up to 20 years before diagnosis of dementia.

This is an observational study so no firm conclusions can be drawn about whether these anticholinergic drugs cause dementia, and it is possible that the drugs were being prescribed for very early symptoms of dementia.

Professor Coupland said: "Our study adds further evidence of the potential risks associated with strong anticholinergic drugs, particularly antidepressants, bladder antimuscarinic drugs, anti-Parkinson drugs and epilepsy drugs.

"The risks of this type of medication should be carefully considered by healthcare professionals alongside the benefits when the drugs are prescribed and alternative treatments should be considered where possible, such as other types of antidepressants or alternative types of treatment for bladder conditions. These findings also highlight the importance of carrying out regular medication reviews.

"We found a greater risk for people diagnosed with dementia before the age of 80 which indicates that anticholinergic drugs should be prescribed with caution in middle-aged people as well as in older people."

These results, along with those of a similar study published in 2018 help to clarify which types of anticholinergic drug are associated with the highest risks of dementia.

In the 1-11 years before the dementia diagnosis date or equivalent in controls, nearly 57% of cases and 51% of controls were prescribed at least one strong anticholinergic drug, with an average of six prescriptions in cases and 4 in controls. The most frequently-prescribed types of drugs were antidepressants, anti-vertigo and bladder antimuscarinic drugs - which are used to treat an overactive bladder.

The increased risk associated with these drugs indicates that if the association is causal around 10% of dementia diagnoses could be attributable to anticholinergic drug exposure, which would equate to around 20,000 of the 209,600 new cases of dementia per year in the UK.

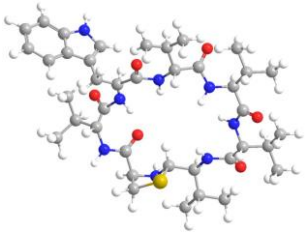
This is a sizeable proportion and is comparable with other modifiable risk factors for dementia, including 5% for midlife hypertension, 3% for diabetes, 14% for later life smoking and 6.5% for physical inactivity.

http://bit.ly/2J6V7lf

Natural antibiotic's multi-level attack strategy prevents resistance

The natural antibiotic lugdunin, discovered three years ago by Tübingen researchers, attacks pathogenic bacteria in several different ways simultaneously.

It also interacts with the defense mechanisms of the human body, according to a recent study published in *Nature Communications*. The study is the work of a research team led by Professor Birgit Schittek from the Department of Dermatology at the Tübingen University Hospital and Professor Andreas Peschel from the Interfaculty Institute of Microbiology and Infection Medicine at the University of Tübingen, and of the German Center for Infection Research (DZIF).



The researchers believe that lugdunin has remained effective over a long period of time because its manifold ability to attack stopped resistance to the antibiotic from developing.

Lugdunin is a 21-membered cyclic peptide that consists of 6 amino acid residues plus a thiazolidine moiety. Five of the amino acids are L-valine and the sixth is L-tryptophan. Credit: American Chemical Society

The development of antibiotics is one of medicine's great success stories; they save the lives of millions of people every year and have made a key contribution to the enormous increase in life expectancy. However, many experts fear that we could soon enter an era without antibiotics, because more and more of the available drugs are losing their effect due to resistance. Yet antibiotics were not invented by the pharmaceutical industry. "Indeed, numerous bacteria produce these active agents naturally, and have probably done so over long periods of evolution, without loss of effectiveness," says Birgit Schittek. Benign bacteria on the human nasal mucosa produce lugdunin to deter the *Staphylococcus aureus* pathogen. "Why lugdunin remains highly effective to the present day was a complete mystery," she says.

Unexpected properties

Only recently, chemists at the University of Tübingen reported in the journal *Angewandte Chemie* that lugdunin can disrupt the energy balance of pathogenic bacteria and kill them. In their current study, the researchers discovered that lugdunin not only has a direct antimicrobial effect on *S. aureus*, but also has two completely unexpected properties: "Firstly, it works in combination with antimicrobial peptides that make up our human cells," says Andreas Peschel. This increases its efficacy and hinders the development of resistance. "Secondly, it binds with a human receptor protein called TLR2," he says. "This stimulates the immune cells and activates the immune response in such a way that *S. aureus* has no chance of becoming established and causing infections. Schittek and Peschel point out that a natural antibiotic such as lugdunin—which attacks on several levels, more or less independent of one another—is better at preventing resistance than a chemically produced substance that has only a single target in the bacterial cell.

Their findings can help researchers to develop new drugs that work with similar effectiveness and which lead to hardly any resistance. The findings were obtained through collaboration within the Transregional Collaborative Research Center "The skin as sensor and effector orchestrating local and systemic immunity" (SFB/TRR 156). Within the framework of the Tübingen Cluster of Excellence "Control of Microorganisms to Combat Infection," which was launched at the start of the year, they are shedding light on the natural defense mechanisms of the microbiome—the entirety of the microorganisms that colonize humans. The German Center for Infection Research (DZIF) is further developing lugdunin, which has been patented by the University, so that it can be used for treatments in the future.

http://bit.ly/2FA1tsB

Monkey tool design changed over millennia

Researchers find first evidence of gradual changes in the design of stone tools used by capuchins.

Dyani Lewis reports.

The satellites humans fling into space and the massive accelerators that smash together subatomic particles are a far cry from the stone tools our ancestors were making three million years ago.

A capuchin monkey using a stone tool to break open a nut. Tool designs have changed in the past 3000 years, researchers have found. **Ben Cranke/Getty Images**

But it turns out we're not the only ones to change our technologies over time. Stone tools used by capuchin monkeys have changed at least twice over the past 3000 years, according to a study in the journal *Nature Ecology & Evolution*.

The finding is based on a capuchin monkey site in the World Heritage listed Serra da Capivara National Park in northeast Brazil.

Today, bearded capuchin monkeys (*Sapajus libidinosus*) at the site mostly use stone tools to pound open cashew nuts. Elsewhere in the park, monkeys wield stone tools to smash apart seeds and fruit, dig for roots and spiders, and bang together as a threat to others.

Several modern-day primates are known to use tools, but few archaeological sites exist showing non-human tool use in prehistory. The oldest example, from chimpanzees in Côte d'Ivoire, dates to 4000 years ago.

The Brazilian site is unique because not all artefacts at the site are the same. The types and sizes of rocks used changed over time. During excavations, more than 1500 stones were dug out of the earth. Of these, 122 had impact marks, crushed surfaces, stuck-on residue or other signs they had been used as tools.

Radiocarbon dating of charcoal excavated alongside the stones indicate that the earliest period of occupation occurred between 2400 and 3000 years ago – roughly 450 capuchin generations away.

Hammer-stones from this time were low-weight rocks, likely used to process foods smaller and less resistant than cashew nuts.

By around 600 years ago, anvils had been added to the capuchin toolkit; by 250 years ago, low-weight rocks had been replaced by sturdier ones, probably for opening harder foods.

A final change, over the last 100 years or so, saw tools revert to a smaller size, similar to the cashew-pounding tools used by modern-day capuchins.

"This discovery presents the first example of long-term tool use variation outside of the human lineage," write Tiago Falótico from the University of São Paulo in Brazil, Tomos Proffitt from University College London in the UK, and colleagues.

The exact reasons behind the technological change for the monkeys is currently unknown, according to the authors.

The region is home to numerous capuchin groups that are able to learn stone tool use from each other. The changes in the archaeological record could mean that different groups of the species – with different favourite foods – occupied the site at different times.

Alternatively, a single group could have occupied the site more or less continuously. Changing tools might reflect a change in the availability of different foods. The abundant cashew trees of today, for instance, might not always have been so common.

Similar explanations – of differing cultural traditions or raw materials – have been used to explain tool changes in the early human record.

http://bit.ly/2NkOcu2

Exercise an effective protection against life-threatening cerebral hemorrhage

A Finnish study demonstrates that as little as half an hour of light exercise per week effectively protects against subarachnoid haemorrhage, the most lethal disorder of the cerebral circulation.

Among disorders of the cerebral circulation, subarachnoid haemorrhage (SAH) is the most lethal kind, with as many as half of those affected dying within three months. As the related mortality rate is high, a feverish search for predisposing factors has been underway across the globe for the past few decades. Previously, smoking and high blood pressure have been observed to heighten the risk of an SAH haemorrhage, but research evidence on the effects of exercise has remained scarce.

In a Finnish follow-up study published in the distinguished Scientific Reports journal, the effects of exercise on SAH risk were investigated in a cohort of roughly 70,000 Finns gained from the FINRISK population survey. The findings indicate that as little as half an hour of light exercise per week reduces the risk of SAH by approximately 5%, with the benefit increasing proportionally to the amount of exercise. This can be achieved, for example, by walking, cycling or, say, skiing to work.

"Even moderate physical exercise, such as a 30-minute walk or bike ride four days a week reduces the risk of SAH by roughly 20%, regardless of age and gender," says physician Joni Lindbohm, the principal author of the research article.

"As such, the finding did not really come as a surprise, as exercise is known to work well in preventing many other cardiovascular diseases. However, the extent and comprehensive nature of the benefit among various groups of people was a positive surprise."

The study also demonstrated the favourable effect of increased exercise in connection with smoking and high blood pressure, the other SAH risk factors. For smokers in particular, exercise reduces the risk as much as twice the amount applicable to the rest of the population.

"However, what must not be overlooked is the fact that smoking remains the number one risk factor for SAH and that quitting smoking is the principal way of preventing the appearance of the disorder," Lindbohm notes.

Most SAH haemorrhages are the result of ruptured cerebral aneurysms, causing blood to flow from the largest cerebral arteries into the space between meninges, the membranes surrounding the brain, which increases intracranial pressure and reduces cerebral circulation.

"Even with no accurate scientific evidence of the biological mechanism of action produced by exercise in terms of SAH, the reduced risk is most likely connected with a reduction in a systemic inflammatory state, which also affects the walls of cerebral arteries," neurosurgeon Miikka Korja explains. According to Lindbohm and Korja, key to minimising the risk of SAH is quitting smoking, balancing one's blood pressure and exercising regularly.

Reference: Lindbohm J, Rautalin I, Jousilahti P, Salomaa V, Kaprio J, Korja M. Physical activity associates with subarachnoid hemorrhage risk- a population-based long-term cohort study. Sci Rep, 2019.

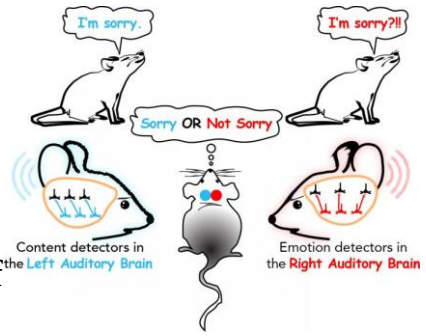
http://bit.ly/2RGz7l4

Scientists closer to unraveling mechanisms of speech processing in the brain

The discovery could aid understanding of neurodevelopmental communication disorders

NEW YORK - In the 1860s, French physician Paul Broca published his findings that the brain's speech production center was located in the left hemisphere. Though scientists have largely accepted since then that the left half of the brain dominates language processing, the reasons behind this lateralization have remained unclear.

"The lateralization of language processing in the auditory cortical areas of the brain has been known for over 150 years, but the function, neural mechanisms, and development of this hemispheric specialization are still unknown," said Hysell V. Oviedo, a biology professor with The Graduate Center, CUNY and the City College of New York.



Understanding differences between the left and right auditory processing centers' wiring diagram and sensitivity to tone sequences in the mouse brain are providing clues to specializations for processing speech. Such mapping could be useful in sorting out the potential miswiring at the root of neurodevelopment communication disorders like autism and schizophrenia.

H. Lebreault

A new study from Oviedo's lab, published in Nature Communications, makes headway into this mystery. Using the mouse as a model system, the researchers observed different specializations between the left and right auditory processing centers of the brain, and found differences in their wiring diagrams that may explain their distinct speech processing functions.

In addition to answering long-standing questions in neuroscience and language processing, the results of Oviedo's study could someday lead to a better understanding of certain mental health problems. Autism spectrum disorder has been linked to a failure of lateralized language processing to develop between the two halves of the brain. And abnormal lateralization is a risk factor for auditory hallucinations in schizophrenia.

One common feature of mouse vocalizations is syllables with downward jumps in pitch. The left auditory cortex in the mouse showed greater activation in response to these tone sequences, whereas the right auditory cortex appeared to be more of a generalist, responding to any tone sequence. Specializations to detect specific tone sequences prevalent in vocalizations could underlie the left auditory center's dominance in processing the content or meaning of speech. While the right auditory center's generalist scheme could underlie its dominance in processing the intonation or prosody of speech.

Notably, the specialized differences between the left and right sides are not innate. Rather, Oviedo says, the differences between their circuitry depend on the acoustic environment in which the mouse was raised.

"Our discovery of the differences in the wiring diagram provides the opportunity to study the molecular phenotypes that shape the development of vocalization processing and how it goes awry in neurodevelopmental communication disorders," Oviedo said.

Through a battery of experiments such as 3D whole-brain imaging, electrophysiology, and optogenetics, the researchers analyzed properties including synaptic connectivity, axonal projections and development of both hemispheres. "Our study is the first to show that there are significant differences in the wiring diagram of the language centers in the brain that could underlie their distinct speech processing capabilities," Oviedo said.

https://go.nature.com/2IV5Zno

Startling China organ claims raise alarm about transplant research

Researchers hope the conclusions of a people's tribunal will pressure journals to reject papers that might include data from unethical transplants.

David Cyranoski

A startling report concluding that prisoners in China are being killed for their organs has renewed concerns about the origins of some organs used in research.

On 17 June, the China Tribunal, a panel established by the non-governmental organization the International Coalition to End

Transplant Abuse in China (ETAC), concluded that prisoners in China, in particular those imprisoned for their political or religious views, have been killed for their organs for years. It said that the practice — which it branded a crime against humanity — probably still continues.

The seven-member panel took evidence in London and was chaired by barrister Geoffrey Nice — but has no legal authority. It looked at many lines of evidence, including analyses of Chinese transplant data and expert testimony from doctors, human-rights workers and former prisoners.

The Chinese government has yet to respond to the tribunal's report, but has previously admitted that in the past, it took organs from prisoners who had been sentenced to death. It says the practice has been banned since it introduced a voluntary donor programme in 2015. The government has denied that it ever killed people for the sole purpose of harvesting their organs.

The report "illustrates the gravity of events transpiring in China", says Wendy Rogers, an ethicist at Macquarie University in Sydney, Australia, who has investigated the extent to which studies in the scientific literature have relied on organs obtained unethically in China, and who chairs the international advisory committee of the ETAC.

"I hope hospitals and journals will take a closer look at their policies," adds Rogers, who testified about her research findings before the panel.

The World Health Organization and the World Medical Association condemn the practice of procuring organs for transplant from executed prisoners. The use of data from such organs for research is also widely criticized, and a number of journals have policies that ban the publication of such data.

Journal action

Some journals took action following the publication in *BMJ Open* in February of a paper[1], co-authored by Rogers, that analysed almost 450 studies of transplants — representing more than 85,000 organs — that took place in China. The studies were published between 2000 and 2017. The analysis found that 86% of the papers failed to follow ethical standards by stating the provenance of the organs or giving a statement about the cause of death of the donors. Only 1% of the papers reported whether consent was sought or granted for the donations and only 7% of papers included a statement that no organs from prisoners were used.

The authors conclude that a large number of the studies conducted before 2015 probably contain data from executed prisoners, given that China says prisoners were a source of organs at this time.

Nature contacted six journals that each published ten or more of the 445 papers in the *BMJ Open* analysis.

Joerg Heber, editor-in-chief of *PLoS ONE,* which published 15 papers without information on the source of organs that were cited in the study, and one without an ethics statement, told *Nature* that the journal has been investigating articles for which the source of organs is unclear.

"I strongly believe that any research involving human participants or organ transplantations must follow the highest ethical standards," says Heber. The journal will retract papers if it becomes clear that ethical standards have not been met, he says.

The journal *Liver Transplantation* published 12 papers cited in the *BMJ Open* study that didn't include details of organ origin, and 3 without ethics statements. A spokesperson says that before the study was published, *Liver Transplantation* already had a policy of asking authors submitting papers to confirm their data do not come from executed prisoners, and it does not require donor identification.

The spokesperson says the journal has not launched an investigation, but will retract a paper if it becomes clear after

publication that it contains data from executed prisoners. The other four journals have yet to respond to *Nature*'s questions.

And the journal *Transplantation*, which is also named in the *BMJ Open* study, has moved to retract papers that lack details of the origin of the organs. In an editorial[2] posted online on 5 June, the journal said that it had investigated nine papers, including five cited in the *BMJ Open* study. In one case, the author was able to provide a satisfactory description of the single transplant described in the paper, and another paper was published before the journal had clear guidelines on donor-reporting requirements. In the other seven cases, neither the authors nor their institutions had offered explanations. Editor-in-chief Jeremy Chapman told *Nature* that the journal will retract the seven papers in its August issue.

Springer Nature, which publishes several of the journals named in the analysis, is concerned by the findings and is investigating the papers reported in the study, says Suzanne Farley, director of research integrity at Springer Nature in London. "We will not hesitate to take editorial action in cases where appropriate," she says. (*Nature*'s news team is editorially independent of its publisher Springer Nature.)

Building a case

As well as examining the extent to which unethically-obtained organs are used in studies, researchers are also using data to understand what is going on in China.

Chinese health administrators announced pilot programmes for voluntary organ donation in 2010. An official system to track and allocate all organs, the China Organ Transplant Response System (COTRS), was launched in 2013. The government stated that all transplants would come from donors from the start of 2015.

In its report, the tribunal referred to a research paper[3] posted on the preprint server SocArXiv in January that examined data on voluntary organ transplants from 2010 to 2016. This found a significant and consistent growth in the number of voluntary organ transplants each year, which the study authors said was hard to believe given the huge amount of co-ordination required in a voluntary organ donation, allocation and transplantation system — and given that it didn't match data trends in other countries.

The report, co-authored by Matthew Robertson, a research fellow in China studies with the Victims of Communism Memorial Foundation in Washington DC, concludes that China's voluntary system probably includes organs from non-voluntary donors, likely to be prisoners, who are misclassified as voluntary.

But Francis Delmonico, a surgeon at Massachusetts General Hospital in Boston, says that although there is evidence that organs were taken from prisoners in the past — which he condemns — he is not convinced by the SocArXiv evidence because it is not direct. Delmonico is chair of the World Health Organization's Task Force on Donation and Transplantation of Human Organs and Tissues and has been supporting organ-donation reform in China for more than a decade, although he made his comments to *Nature* in a personal capacity.

The tribunal commissioned a statistician to review the analysis in the SocArXiv paper, and agrees with the paper's conclusion that the data on voluntary transplants seem unreliable, says Hamid Sabi, counsel to the China Tribunal.

The impact of the tribunal's findings will depend on whether international organ-transplantation groups, human-rights groups and Western governments take action, says Robertson.

Nature ***570***, *425-426 (2019) doi: 10.1038/d41586-019-01890-4*

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http://bit.ly/2xlJDVw

Radioactive tadpoles reveal contamination clues

Tadpoles can be used to measure the amount of radiocesium, a radioactive material, in aquatic environments, according to new research from University of Georgia scientists.

by Vicky L. Sutton-Jackson

Whether from nuclear accidents, global fallout from weapons testing, or production of nuclear energy, tadpoles could be used to determine the extent and severity of radioactive contamination.

James C. Leaphart, lead investigator on the 32-day study, evaluated the rate at which the environmental pollutant radiocesium, a byproduct of nuclear production, accumulated through time in bullfrog tadpoles.

Taken from an uncontaminated wetland, the tadpoles were placed in various locations in a canal on the U.S. Department of Energy's Savannah River Site, a former nuclear production facility. The canal received releases of radiocesium from a nearby reactor from 1954 to 1964.

"Due to the rapid accumulation of radiocesium in these tadpoles, how much they accumulated and their inability to leave aquatic systems before metamorphosis, these tadpoles are excellent indicators of the bioavailability and distribution of radiocesium in the system," said Leaphart, graduate student at the Savannah River Ecology Laboratory and Warnell School of Forestry and Natural Resources.

According to the study results, published in the *Journal of Environmental Radioactivity*, bullfrog tadpoles reached what the researchers describe as maximum threshold, or the point at which their uptake of the contaminant stopped, between 11 and 14 days.

This accumulation rate was significantly faster than rates recorded for waterfowl and fish, species previously studied for uptake of the contaminant, according to Leaphart. Rates in these species varied significantly, with a range of 17 to 175 days.

James Beasley, Leaphart's adviser and associate professor at SREL and Warnell, said how quickly a species reaches the threshold level of accumulation is vital in determining its use as a biomonitor of the contaminant.

"If it takes a long time to achieve the threshold level, factors like animal movement and changes in diet can play a role in influencing the results," he said.

Tadpoles are more likely to reflect local contamination levels, according to Beasley. That's because factors like movement and changes in food availability will not have as much of an impact on an individual's exposure compared to species that may take several weeks or months to achieve maximum levels.

"Isolation is key," Leaphart said. "Tadpoles spend the first portion of their lives in aquatic systems—canals, wetlands and ponds—foraging on plants, algae, insect larvae and sediments where radiocesium has a tendency to bind."

Understanding radiocesium accumulation patterns in amphibians is important, the researchers said, because they have the potential to transfer contaminants within food webs as well as disperse aquatic contaminants into terrestrial ecosystems following metamorphosis.

James C. Leaphart et al. Bioaccumulation of 137Cs in anuran larvae utilizing a contaminated effluent canal on the U.S. Department of Energy's Savannah River Site, Journal of Environmental Radioactivity (2019). DOI: 10.1016/j.jenvrad.2019.02.012

http://bit.ly/2XD8eDX

Is multiple sclerosis linked to childhood viral infections?

UNIGE researchers have discovered a potential link between viral infections in the brain in childhood and the risk to develop auto-immune disease in adulthood

Although the exact causes of multiple sclerosis still remain unknown, it is assumed that the disease is triggered by a combination of genetic and environmental risk factors. But which? In a mouse model of the disease, researchers at the University of Geneva (UNIGE) and the Geneva University Hospitals (HUG) , Switzerland, studied the potential link between transient cerebral viral infections in early childhood and the development of this cerebral autoimmune disease later in life. Indeed, the brain area affected by viral infection during childhood undergoes a change that can call, a long time later, on the immune system to turn against itself at this precise location, triggering autoimmune lesions. These results, which are published in the journal *Science Translational Medicine*, provide a first step in answering one of the possible environmental causes of this serious disease.

Multiple sclerosis affects one in 1,000 people in Switzerland, two-thirds of whom are women. It is the most common auto-immune disease affecting the brain. Up to date, there is still neither a cure available, nor a clear understanding of the factors that trigger this disease at around 30 years of age. "We asked ourselves whether brain viral infections that could be contracted in early childhood were among the possible causes," says Doron Merkler, a professor in the Department of Pathology and Immunology in UNIGE's Faculty of Medicine and senior consultant in the Clinical Pathology Service of the HUG. Such transient brain infections can be controlled quickly by the immune system, without the affected individual even noticing any symptoms. "But these transient infections may, under certain circumstances, leave a local footprint, an inflammatory signature, in the brain," continues the researcher.

The childhood: a pivotal moment influencing disease risk

The scientists induced a transient viral infection in a group of adult mice and in a group of mice at a very young age in order to test this hypothesis. Karin Steinbach, a researcher in the same department, explains: "In both cases, the mice showed no signs of the disease and eliminated the infection within a week with a similar anti-viral immune response."

The scientists then allowed the two groups of mice to grow older before they were transferred with self-reactive cells, which can target the normal brain structure and are also thought to contribute to the illness of patients with multiple sclerosis. "These self-reactive cells are present in most of us, but do not necessarily induce a disease, since they are controlled by different regulatory mechanisms and usually don't have access to the brain," explains Karin Steinbach. Indeed, in the group of mice infected with the virus in adulthood, the transferred self-reactive cells did not gain access to the brain and no brain lesions were observed. However, in those mice that had been infected at a very young age, the self-reactive cells gained access to the brain in adulthood, and migrated to the precise location where the infection had previously occurred. As a result, self-reactive cells started to attack the brain structure in these areas, leading to the development of brain lesions. Why was there such a difference depending on the age at which the mice suffered a prior viral infection?

An accumulation of T cells gives the signal

During their analysis of the brains in the cohort of mice that had overcome the viral infection at a very young age, the researchers observed an accumulation of a sub-type of immune cells: so-called "brain-resident memory T cells". "Under normal circumstances, these cells are distributed throughout the brain, ready to protect it in case of a viral attack. But here, the cells accumulate in surplus at the exact spot of the infantile infection in the brain," says Professor Merkler. The researchers subsequently found that these cells produced a molecule that specifically attracts the self-reactive cells, allowing them to access the brain and to cause auto-immune brain lesions. "In order to verify this observation," continues the

professor, "we blocked the receptor that transmits the signal to the self-reactive cells. Indeed, the mice were then protected from developing brain lesions!"

A similar phenomenon also occurs in humans

"We then looked to see if we could find a similar accumulation of brain-resident memory T cells that produce this molecule in people with multiple sclerosis, and indeed we did", says Karin Steinbach. By analogy, the scientists suggest self-reactive T cells in humans could gain access to the brain by a similar mechanism as observed in mice, something that requires future studies to elaborate on.

"We are continuing our research in this direction. We particularly want to understand why brain-resident memory T cells accumulate in these discrete spots in a child's brain following infection but not in adulthood," concludes Karin Steinbach. In the future, the knowledge gained from these studies may help us understand better the possible causes of multiple sclerosis.

http://bit.ly/2xjD4mr

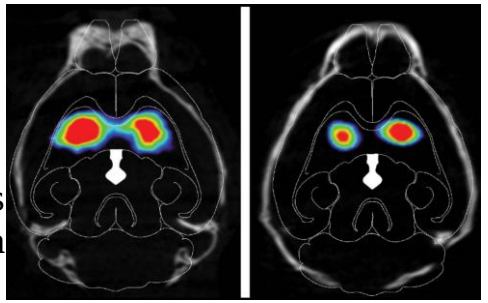
Mouse Model Shows How Parkinson's Disease Begins in the Gut

Johns Hopkins's Ted Dawson discusses his lab's demonstration that misfolded α-synuclein can move from the stomach to the brain and cause physical and cognitive symptoms.

Emma Yasinski

In 2003, Heiko Braak, then a neuroanatomist at the University of Frankfurt, suggested that Parkinson's disease pathology may start in the gut and travel from there to the brain long before a patient shows symptoms. The idea, based on postmortem analyses of samples from parkinson's patients, has been hotly debated ever since.

In a study published today (June 26) in *Neuron*, Ted Dawson, a neurologist at Johns Hopkins School of Medicine, and his team created an animal model of the disease by injecting particular proteins into the stomachs of mice. About a month later, the animals showed symptoms of Parkinson's disease.



The model not only demonstrates how the disease protein can travel up from the gut to the brain, but also presents nonmotor symptoms rarely seen in other animal models *The Scientist* spoke with Dawson about the work.

ABOVE: Scans of the brains of mice show a reduction in dopamine (colored areas) in the striatum of the Parkinson's disease model that was injected with pathogenic α-synuclein (right; control mouse on left).
TED DAWSON ET AL. / *NEURON*, 2019

The Scientist: *Why did you develop this model?*

Ted Dawson: Well, there is this idea that was building that was started by Dr. Braak that Parkinson's disease could start in the gastrointestinal tract, and there was good human data that suggested that possibility.

What was lacking was an animal model that could validate that hypothesis. [The model] validates [the hypothesis] by providing evidence that it's possible that Parkinson's disease could start in the gut.

There's been this very detailed study by Dr. Braak and later by other pathologists that the pathologic alpha-synuclein seemed to progress from the gut up the neuroaxis into the brain, and what our work shows is that this is possible.

TS: *How did you do it?*

TD: We took pathologic alpha-synuclein, . . . and then we injected those preformed fibrils into the pylorus [an area of the stomach close to the small intestine] into one of the mice near where the vagal nerve innervates those regions. Over time, the animals developed Parkinson's disease.

[To clarify], we're injecting exogenous pathologic alpha-synuclein. And that is causing the endogenous synuclein to misfold and transmit up the vagal nerve.

We know that because when we injected the exogenous alpha-synuclein in the alpha-synuclein knock-out, nothing happened. So the exogenous alpha-synuclein is not the synuclein that's transmitting. It's causing the endogenous synuclein to misfold and transmit.

TS: ***What is the importance of the vagus nerve in the pathologic process?***

TD: It's essential for the pathologic alpha-synuclein to get up to the brain. In a subgroup of animals, we performed vagotomies and the pathologic alpha-synuclein did not ascend into the brain. And as a consequence of that, the animals did not develop Parkinson's disease.

TS: ***What else makes this model unique?***

TD: One of the other things that we think is really exciting about this model is that not only do the mice have the motor features of Parkinson's disease, they also have the nonmotor features. They've got cognitive dysfunction, anxiety, depression, problems with smell. And so we now have an animal model to study those problems. We hope that it opens up a whole new set of investigations using those animal models.

This model shows that it's possible for synuclein to ascend from the stomach via the vagal nerve to the brain. What we don't know in humans with Parkinson's disease is how that process starts. That would be the next step, to figure out how it actually starts in humans.

S. Kim et al., "Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease," **Neuron,** ***doi:10.1016/j.neuron.2019.05.035, 2019.***

http://bit.ly/2KOno3e

What made humans 'the fat primate'?

Blame junk food or a lack of exercise. But long before the modern obesity epidemic, evolution made us fat too.

by Robin A. Smith, Duke University

"We're the fat primates," said Devi Swain-Lenz, a postdoctoral associate in biology at Duke University. The fact that humans are chubbier than chimpanzees isn't news to scientists. But new evidence could help explain how we got that way.

Despite having nearly identical DNA sequences, chimps and early humans underwent critical shifts in how DNA is packaged inside their fat cells, Swain-Lenz and her Duke colleagues have found. As a result, the researchers say, this decreased the human body's ability to turn "bad" calorie-storing fat into the "good" calorie-burning kind. The results were published June 24 in the journal *Genome Biology and Evolution*.

Compared to our closest animal relatives, even people with six-pack abs and rippling arms have considerable fat reserves, researchers say. While other primates have less than 9% body fat, a healthy range for humans is anywhere from 14% to 31%.

To understand how humans became the fat primate, a team led by Swain-Lenz and Duke biologist Greg Wray compared fat samples from humans, chimps and a more distantly-related monkey species, rhesus macaques. Using a technique called ATAC-seq, they scanned each species' genome for differences in how their fat cell DNA is packaged.

Normally most of the DNA within a cell is condensed into coils and loops and tightly wound around proteins, such that only certain DNA regions are loosely packed enough to be accessible to the cellular machinery that turns genes on and off.

The researchers identified roughly 780 DNA regions that were accessible in chimps and macaques, but had become more bunched

up in humans. Examining these regions in detail, the team also noticed a recurring snippet of DNA that helps convert fat from one cell type to another.

Not all fat is created equal, Swain-Lenz explained. Most fat is made up of calorie-storing white fat. It's what makes up the marbling in a steak and builds up around our waistlines. Specialized fat cells called beige and brown fat, on the other hand, can burn calories rather than store them to generate heat and keep us warm.

One of the reasons we're so fat, the research suggests, is because the regions of the genome that help turn white fat to brown were essentially locked up—tucked away and closed for business—in humans but not in chimps.

"We've lost some of the ability to shunt fat cells toward beige or brown fat, and we're stuck down the white fat pathway," Swain-Lenz said. It's still possible to activate the body's limited brown fat by doing things like exposing people to cold temperatures, she explained, "but we need to work for it."

Humans, like chimps, need fat to cushion vital organs, insulate us from the cold, and buffer us from starvation. But early humans may have needed to plump up for another reason, the researchers say—as an additional source of energy to fuel our growing, hungry brains. In the six to eight million years since humans and chimps went their separate ways, human brains have roughly tripled in size. Chimpanzee brains haven't budged.

The human brain uses more energy, pound for pound, than any other tissue. Steering fat cells toward calorie-storing white fat rather than calorie-burning brown fat, the thinking goes, would have given our ancestors a survival advantage.

Swain-Lenz said another question she gets a lot is: "Are you going to make me skinny?"

"I wish," she said.

Because of brown fat's calorie-burning abilities, numerous researchers are trying to figure out if boosting our body's ability to convert white fat to beige or brown fat could make it easier to slim down.

Swain-Lenz says the differences they found among primates might one day be used to help patients with obesity—but we're not there yet. "Maybe we could figure out a group of genes that we need to turn on or off, but we're still very far from that," Swain-Lenz said. "I don't think that it's as simple as flipping a switch. If it were, we would have figured this out a long time ago," she explained.

More information: *Devjanee Swain-Lenz et al, Comparative analyses of chromatin landscape in white adipose tissue suggest humans may have less beigeing potential than other primates, Genome Biology and Evolution (2019). DOI: 10.1093/gbe/evz134*

http://bit.ly/2FGTmdB

Higher body weight connected with lower risk of Lou Gehrig's disease

Motor neurons are remarkably vulnerable to energy depletion, research shows.

Natalie Parletta reports.

Carrying excess weight is linked to a plethora of chronic health conditions, but amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is not one of them, according to a Norwegian population study.

The research, published in the journal *Neurology*, found that people who are overweight or obese are up to 37% less likely to develop the rare neurodegenerative disease.

Physicist Stephen Hawking's personal experience with ALS propelled it into global awareness. The disease progressively kills motor neurons (cells that control voluntary muscle movement), ultimately leading to paralysis and death.

Although some cases have genetic variants, the cause is largely unknown and there is no available cure.

However, it has become increasingly evident that motor neurons are remarkably vulnerable to energy depletion, says the lead author of the new study, Ola Nakken from the University of Oslo.

In line with this, a body of research has found that ALS patients burn energy more quickly – and this elevated metabolic rate appears before clinical signs of the disease.

"It is hypothesised that such hypermetabolism and weight loss starts early in ALS patients, possibly many years before diagnosis," Nakken says, adding that extra weight and energy reserves might be protective in these individuals. Several other studies have linked high body mass index (BMI) and weight gain to lower ALS risk, but causality and timing of events have been unclear.

To investigate the temporal relationship in a large, prospective study, Nakken and co-authors mined a population database for health details of nearly 1.5 million people aged 20 to 70 years between 1963 and 1975.

Over an average 33 years' follow-up – during which time 190,500 people completed additional health surveys – they identified 2968 new cases of ALS through death certificates and a national patient registry.

Overall, every five-point increase in BMI from the low to normal range was associated with 17% lower risk of developing ALS. After 50 years, this increased to 31% lower risk.

People whose BMI increased the most had 37% lower risk than those who didn't gain weight or lost weight. Perhaps more surprising, participants who were obese and overweight at the study's inception had, respectively, a 34% and 18% lower chance of developing ALS than those in the low to normal BMI range.

These results remained unchanged when other potential risk factors such as smoking, cholesterol levels and physical activity were factored into analyses. The findings could reflect disease-induced weight loss prior to diagnosis, Nakken says.

But the nature of the relationship – which started slowly during the first few years of follow-up before increasing linearly for 50 years – is not consistent with the hypothesis that hypermetabolism causes ALS. "These results rather point to shared genetic or environmental risk factors between BMI and ALS," the researchers write. It's important to note that, although the study is prospective, it is still observational.

Nakken says it is possible that genetics could make a person more likely to have both a low BMI and a higher risk of ALS without one causing the other. "People must not interpret the results of our study as a suggestion that gaining weight may prevent ALS," she says. "Plus, the health risks of having a high BMI would be greater than any protective effect."

Carmel Armon and Bryan Traynor, from Tel Aviv University in Israel, concur with this statement in a related editorial.

"The possibility that elevated BMI per se increases the resistance of the motor neuron super-network to the processes that lead to ALS and its role in shaping the clinical course of patients' needs to be explored further," they write.

https://bbc.in/2X8V5OV

Hopes raised of cervical cancer eradication

The success of the HPV vaccination offers hope of one day eradicating cervical cancer, say scientists who carried out a major review of evidence.

Vaccination against the human papilloma virus, which causes most cervical cancers, began over a decade ago.

A Lancet review of 65 studies covering 60 million people showed a fall in HPV cases and in pre-cancerous growths.

Over decades, this should translate into a significant fall, and possible eradication, of the cancer they said.

Jo's Cervical Cancer Trust said the data should boost faith in the jab.

What is the human papilloma virus (HPV)?

HPV is the name for a common group of viruses; there are more than 100 types of HPV

Many women will be infected with HPV over the course of their lifetime, with no ill effect

Most cervical cancers are caused by infection from a high-risk HPV

Others cause conditions including genital warts and cancers of the head and neck

The vaccine, given as two injections to girls aged 12 and 13, protects against four types of HPV - 16 and 18, which are linked to more than 70% of cervical cancers - and six and 11, which cause about 90% of genital warts

Girls who miss the HPV jab at school can still get it for free on the NHS up to the age of 25

It is also available privately, costing around £150 per dose

Boys aged 12-13 will also be offered the jab from September this year

The vaccine does not protect against all the types of HPV that can cause cervical cancer, so women still need to go for regular screening

Source: NHS Choices

There are 3,200 cases of cervical cancer and 850 deaths from the disease each year.

'Real-world' evidence

The review covered studies in 14 high-income countries, including the UK. They looked at HPV rates, plus cases of genital warts and pre-cancerous cells in the cervix called CIN.

It found that when rates were compared before vaccination started and eight years after:

Cases of HPV 16 and 18 were down 83% in girls aged 15-19 - 66% in women 20-24

Genital warts cases fell 67% in girls 15-19 - 54% in women 20-24

Pre-cancerous growths were down by 51% in girls 15-19 - 31% in women 20-24

It also showed people who were not vaccinated benefited. Cases of genital warts in boys aged 15-19 fell by almost 50%, and also significantly in women over 30.

Rates fell more in countries where a wider age group was vaccinated and where coverage was higher.

Public Health England principal scientist Dr David Mesher said: "We are seeing reductions in HPV strains and in cervical disease as well, so there is every suggestion there will be reductions in cervical cancers too."

Prof Marc Brisson, from Laval University, Canada, who led the review, said: "We will see reductions in women aged 20-30 within the next 10 years."

He said cervical cancer elimination - defined as fewer than four cases per 100,000 - "might be possible if sufficiently high vaccination coverage can be achieved and maintained".

Jo's Cervical Cancer Trust said the findings "clearly showed" the impact of HPV vaccination.

"This study furthers the growing evidence to counteract those who don't believe that this vaccine works, which is now extremely encouraging," said chief executive Robert Music.

"We sincerely hope this will boost public faith in the HPV vaccine, so that more lives can be saved and we get closer to a world where cervical cancer is a thing of the past."

http://bit.ly/2KNiJyN

Infecting healthy people in vaccine research can be ethical and necessary

In challenge studies, people are vaccinated with an experimental vaccine, then deliberately exposed to a pathogen and monitored to see if the vaccine protected them against infection.

Michael Selgelid[*]
Euzebiusz Jamrozik[**]

Medical experiments involving intentionally infecting people with bacteria, viruses, and parasites are surprisingly common. And they are becoming more common worldwide, particularly in developing countries.

The ultimate aim of these "human challenge studies" is usually to test potential new vaccines.

However, because of the risks involved, this kind of research raises difficult ethical questions. For example, who should be infected? And which pathogens would be too dangerous to use?

In many challenge studies, people are first vaccinated with an experimental vaccine, then deliberately exposed to a pathogen and monitored to see if the vaccine protected them against infection.

These studies can be especially valuable from a scientific perspective. They can be significantly faster and less expensive than other kinds of vaccine research. They are also usually much smaller, because fewer people need to be given experimental vaccines (that might not turn out to be safe or effective).

These studies sometimes involve infecting people with deadly diseases such as malaria. In such cases, however, researchers are especially careful to minimise risks by ensuring study participants are provided with treatment.

How can this be ethical?

The very idea of intentionally infecting humans with diseases will likely strike many people as unethical.

The history of human challenge studies is tarnished. Some of the most blatantly unethical medical research ever conducted involved intentional infection. During world war two, for example, German and Japanese researchers infected prisoners with diseases such as tuberculosis and plague, killing them in the process.

According to most bioethicists who have discussed this topic, however, intentionally infecting people in a clinical trials isn't necessarily unethical, at least under certain conditions.

Rather than intentional infection, the problem with the infamous historical cases is they involved cruel and brutal treatment of people against their will.

But human challenge studies can be ethically acceptable so long as we meet basic research ethics requirements.

Among other things, this should involve proper informed consent and minimising risks. There should also be legitimate scientific reasons for performing the study.

Modern human challenge studies are regularly approved by research ethics committees. They have been safely conducted with no deaths or severe lasting harms.

Other types of research with healthy volunteers are sometimes more dangerous. One UK trial of an experimental drug had life-threatening consequences for six volunteers. One reportedly remained in hospital for four months, and all his toes had to be amputated. By comparison, infections in challenge studies are usually much more predictable and easier to treat.

Should this occur in developing countries?

Most recent human challenges studies have taken place in wealthy, developed nations. This might partly reflect the aim of scientists to avoid conducting experiments on especially vulnerable people in developing countries.

But a recent development is the expansion of human challenge studies into low- and middle-income countries – such as Thailand, Colombia, Kenya (and other African countries) – where diseases of interest are more common.

One motivation for this shift is to obtain results more relevant to the populations in these countries. For instance, the diseases and/or vaccines might affect these populations differently to people in developed nations due to variation in immunity, genetics or nutrition.

Beyond being merely permissible, there may be an ethical imperative to conduct more challenge studies in countries where the target disease is endemic or widespread.

The fact that participants from endemic countries are more likely to be partially immune to diseases being studied means that conducting local challenge studies might involve less risk to them.

Studies can also sometimes directly benefit trial participants. That's because infection during a study can lead to immunity against a disease to which they otherwise would have been at risk, or because they receive a vaccine that protects them.

Such benefits do not usually result when challenge studies are conducted in rich countries where the disease does not normally occur.

What ethical issues remain?

Though human challenge studies can be ethical – even in low- and middle-income countries – there are numerous unresolved issues about the conditions under which this kind of research should be conducted.

Who should take part in these studies?

Some studies have aimed to recruit university students because, being more educated, they may be better able to provide adequate informed consent. But students might not provide a good representative sample of the general population, or they might feel pressure to participate in research being conducted at their institutions or by their academic superiors.

How much should participants be paid?

It is generally agreed that subjects should be paid for the costs they incur while taking part in a study. This might include the costs of travel or loss of usual income.

Whether, or the extent to which, they should receive further payments reflecting the risks or other burdens endured, is more controversial.

Some say higher levels of payment reflecting burdens or risks endured would be appropriate, just as some workers receive higher pay for doing dangerous jobs.

Others worry that high levels of payment might be an irresistible lure, especially for poor people. It appears that payment has been a major motivation for people to participate in challenge studies in both high-income and low-income countries.

Should children be involved?

Would it ever be acceptable to involve children in challenge studies?

Because diseases and/or vaccines might affect children differently, conducting research with adults might not always provide reliable enough information about the safety and efficacy of vaccines for children.

But children are widely considered especially vulnerable because, among other reasons, they cannot provide informed consent.

Are there some pathogens that should never be tested?

In general, challenge studies involving high risks that cannot be easily controlled should presumably not be permitted. The use of pathogens like HIV, for example, should be off limits.

In a nutshell

Human challenge studies are sometimes ethically acceptable. And it may be important to conduct them, especially in low- and middle-income countries where neglected diseases are most common.

Yet we still need bioethicists, policymakers and the general public to discuss unresolved ethical questions about where, when and how they should be conducted.

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http://bit.ly/2XdaYns

FEFU scientists likely found way to grow new teeth for patients

Could provide a fundamental basis for development of bioengineering therapies in dentistry and gastroenterology

A group of histologists and dentists from School of Biomedicine, Far Eastern Federal University (FEFU), teamed up with Russian and Japanese colleagues and found cells that are probably responsible for the formation of human dental tissue. Researchers propose to apply the study outcome within the development of bioengineering techniques in dentistry aimed at growing new dental tissue for patients. A related article is published in the International Journal of Applied and Fundamental Research.

FEFU scientists used human prenatal tissues to study the early stage of development of the embryonic oral cavity during the period when the teeth were set up - from the 5th to the 6th week. They have recognized several types of cells that are involved in the formation of one of the teeth rudiments -- the enamel (dental) organ. Among them, chromophobe cells with elongated spindle-shaped form have been identified which are also responsible for the development of human teeth in the first weeks of embryo formation. The data obtained can provide a fundamental basis for the development of bioengineering therapies in dentistry and gastroenterology.

'Numerous attempts to grow teeth from only the stem cells involved in the development of enamel, dentin and pulp, i.e. ameloblasts and odontoblasts, were not successful: there was no enamel on the samples, teeth were covered only by defective dentin. The absence of an easily accessible source of cells for growing dental tissue seriously restricts the development of a bioengineering approach to dental treatment. To develop technologies of tissue engineering and regenerative medicine -- promising methods of treatment in dentistry -- the cells identified by us may become the clue to the new level of quality dental treatment. Natural implants that are completely identical to human teeth will no doubt be better than titanium ones, and their lifespan can be longer than that of artificial ones, which are guaranteed for 10-15 years. Although for a successful experiment, we still have a lack of knowledge about intercellular signaling interactions during the teeth development.' said Ivan Reva, Senior Researcher of the Laboratory for Cell and Molecular Neurobiology, School of Biomedicine, FEFU.

The scientist noted that large chromophobe cells reside not only the place where the teeth of the embryo form, but also exist at the border where the multilayers squamous epithelium of the oral cavity passes into the cylindrical epithelium of the developing digestive tube. This means that the new bio-engineering approach is relevant not only for growing new dental tissue but also for growing organs for subsequent transplantation and likely will be applied in gastroenterology.

The development of new biological approaches for the teeth reconstruction with stem cells is one of the most pressing tasks in dentistry for the upcoming years. There are still a lot of questions challenging the researchers. For example, scientists have yet to figure out how in the earliest stages of human embryo development, from the seemingly homogeneous, and in fact, multilayered ectoderm, which is located in the forming oral cavity, different types and forms of teeth develop. However, it is already clear that more kinds of cells are engaged in the earliest stages of human teeth formation than it was previously supposed. Thanks to the research of FEFU scientists in cooperation with their colleagues from Russia and Japan, it also became clear that the crown of the tooth and its root have different mechanisms of formation.

This work was supported by the FEFU Scientific Foundation, within the framework of the state task 17.5740 / 2017 / 6.7.

http://bit.ly/2FIYrSL

Too many antioxidants may cause lung cancer spread

A new study explains why lung cancer spreads faster in patients with certain genetic changes, and suggests that taking vitamin E, long thought of as preventive, may cause the same spread.

Led by researchers at NYU School of Medicine and Perlmutter Cancer Center, experiments in mice and human tissue revealed how mechanisms that protect cancer cells from the byproducts of their own aggressive growth are connected by the protein BACH1 to cancer cell migration and tissue invasion.

Published online on June 27 in the journal Cell, the study results reflect the nature of cancer cells, which arise in one place, but often spread (metastasize) and take root elsewhere. Lung cancer metastasis is the leading cause of cancer death in the United States.

About 40 percent of lung cancers are adenocarcinomas, which form from mucous-producing cells, and which have already spread beyond lung tissue in 22 percent of cases by the time they are diagnosed.

"Our results finally clarify the web of mechanisms surrounding the BACH 1 signal, and suggest that an already approved drug class may counter cancer spread in about 30 percent of lung adenocarcinoma patients," says senior study author Michele Pagano, MD, chair of the Department of Biochemistry and Molecular Pharmacology at NYU School of Medicine.

The Price of Fuel

The newly published work revolves around random changes, called mutations, which occur continually throughout the DNA code. While many are weeded out, some persist to either make no difference, cause disease, or help cells to better survive changing conditions as part of evolution.

Such changes are known to, for instance, help lung adenocarcinoma cells survive oxidative stress, a process where highly-reactive, cell-damaging molecules (oxidants) are made as a side effect of "burning" fuel to make energy. Cancer cells need extra fuel to support aggressive growth, produce more oxidants, and depend more on naturally occurring antioxidants to neutralize them.

Along these lines, past studies have shown that about 30 percent of non-small cell lung cancers (which include adenocarcinomas) thrive by acquiring mutations that ether increase levels of the protein NRF2 - known to turn on genes that increase antioxidant production - or that disable KEAP1, which targets NRF2 for destruction.

Complicating matters, oxidative stress is known to cause the release a chemical compound called heme. Best known for its role in hemoglobin - the oxygen-carrying red blood cell pigment - heme, in its free form, also amplifies oxidative stress. Cells protect themselves from the heme-driven wave of oxidants by making more of the enzyme heme oxygenase-1 (HO1), which neutralizes heme.

By engineering mice with lung adenocarcinoma cells that lacked Keap1 gene (and thereby increasing levels of NRF2), the study authors were able to show that too high NRF2 levels, and the related overproduction of antioxidants, encourages HO1 production. More HO1 activity means lower amounts of active heme.

This became even more important when the researchers discovered that heme partners with the protein FBOX22 to cause the breakdown of BACH1, explaining how increased NRF2 activity increases BACH1 levels.

Normally, say the authors, NRF2-driven, antioxidant-dependent increases in BACH1 levels are short-lived, activated only during brief blasts of oxidative stress, and possibly not rising to levels that trigger cell migration through BACH1. But the new data suggest that big enough increases override mechanisms that would otherwise limit BACH1 levels.

Furthermore, analyses of human tumor tissue revealed that HO1 and BACH1 are found in significantly higher levels in human lung cancer cells that have spread, and in lung cancers of advanced stage and grade. One theory holds that oxidative stress defenses and migration evolved to overlap so that cells faced with extreme stress locally could migrate in search of a better home.

Moving forward, the team seeks to explore whether HO1 inhibitors - already FDA approved the treatment of inherited disorders called porphyrias - could be tested in a clinical trial to slow or prevent lung cancer spread.

Importantly, a second paper publishing in the same edition of Cell, and led by Martin Bergo of the Department of Biosciences and Nutrition at Karolinska Institutet in Sweden, suggests that vitamin E taken as part of a dietary supplement also increases the chances of lung cancer spread through its effect on BACH1.

"For lung cancer patients, taking vitamin E may cause the same increases in cancer's ability to spread as the NRF2 and KEAP1 mutations that our team has linked to shorter survival," says study author Thales Papagiannakopoulos, PhD, assistant professor in the Department of Pathology at NYU School of Medicine. "We hope these findings help to dispel the myth that antioxidants like vitamin E help to prevent every type of cancer."

Along with Pagano and Papagiannakopoulos, study authors from the department of Pathology, and Biochemistry and Molecular Pharmacology, at NYU School of Medicine; as well as the Perlmutter Cancer Center at NYU Langone Health; were Luca Lignitto, Sarah LeBoeuf, Harrison Homer, Shaowen Jiang, Manor Askenazi, Triantafyllia Karakousi, Harvey Pass, Aristotelis Tsirigos, Beatrix Ueberheide and Volkan Sayin. Also a study author was Arjun Bhutkar of the Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology. Pagano is an investigator with the Howard Hughes Medical Institute.

The work was supported by Perlmutter Cancer Center grant P30CA016087; National Institutes of Health grants T32HL007151, NMSF S10OD010582, NCBRD S10OD01058, S10OD018338, K22CA201088. R37CA222504, and R01CA227649; and by American Cancer Society Research Scholar Grant RSG-17-200-01-TBE. The study was also supported by the Italian Cancer Foundation (AICF) and by Associazione Italiana per la Ricerca sul Cancro, which is co-funded by the European Union (AIRC/Marie Curie).

http://bit.ly/2XjPzhd

Pathway discovered that prevents buildup of Alzheimer's protein

St. Jude Children's Research Hospital scientists studying the immune response to brain tumors have identified a pathway that clears a toxic protein that is a hallmark of Alzheimer's disease

St. Jude Children's Research Hospital scientists have discovered a pathway that functions like a car wash to prevent the buildup of a toxic protein associated with Alzheimer's disease. The report appeared online today in the journal Cell.

The findings in a mouse model of Alzheimer's offer a possible new approach to treatment of the chronic neurodegenerative disorder, which is the sixth leading cause of death in the U.S. The newly identified pathway also helps regulate inflammation, so the discovery could yield strategies for unleashing the immune response against malignant brain tumors.

Researchers called the pathway LC3-associated endocytosis or LANDO. They found the pathway in microglial cells, the primary immune cells of the brain and central nervous system. However, preliminary evidence suggests LANDO is a fundamental process that functions in cells throughout the body.

Investigators showed that LANDO protected against deposits of neurotoxic β-amyloid protein in mice. Activation of the pathway also guarded against toxic neuroinflammation and neurodegeneration, including memory problems.

"In the context of neurodegenerative diseases such as Alzheimer's, activating LANDO in microglial cells could prove to be therapeutically beneficial through increased clearance of β-amyloid and mitigation of neuroinflammation," said corresponding author

Douglas Green, Ph.D., chair of the St. Jude Department of Immunology.

While activation of LANDO appears to protect against neurodegenerative disease, first author Bradlee Heckmann, Ph.D., a postdoctoral fellow in Green's laboratory, said inhibiting the pathway might boost the effectiveness of cancer immunotherapy. "Although in its infancy, preliminary data using a primary brain tumor model suggests that inhibition of LANDO might provide a mechanism to activate inflammation within the tumor microenvironment to generate an anti-tumor response," Heckmann said.

Car wash

β-amyloid protein accumulation in neurons is a hallmark of Alzheimer's. Scientists knew microglial cells take up β-amyloid proteins. Discovery of the LANDO pathway answers questions about what comes next.

Heckmann compared LANDO to the operator of an automatic carwash. In this case, the cars are the receptors on the microglial cells that bind to neurotoxic β-amyloid proteins and bring the protein into the car wash. And, just as cars return to the streets after the dirt is gone, when the β-amyloid is disposed of, the receptor returns to the microglial surface where it can pick up additional β-amyloid.

An automatic car wash depends on hardware to attach the car to a track that moves it through the machine. Similarly, several proteins are required for LANDO functioning. The proteins--Rubicon, Beclin 1, ATG5 and ATG7--are better known for their roles in a related cell pathway used to recycle unneeded and unwanted cell components. These proteins decline with age as their expression decreases.

Follow the data

"You never know where science will lead," Green said. "This project started because we were studying immune responses against cancer. Brad recognized the findings had relevance to a disease not of children but of older people.

"That's how science works. When you follow the data, you never know where it will lead."

The other authors are Brett Teubner, Bart Tummers, Emilio Boada-Romero, Lacie Harris, Mao Yang, Clifford Guy and Stanislav Zakharenko, all of St. Jude.

The research was funded in part by grants (AI40646, CA231620, AI138492, CA231423) from the National Institutes of Health; the Lupus Research Alliance; the John H. Sununu Endowed Fellowship; the Paul Barrett Endowed Fellowship; and ALSAC, the fundraising and awareness organization of St. Jude.

http://bit.ly/2ZSIQaM

'Mystical' psychedelic compound found in normal brains

A study in rats has revealed the presence of naturally occurring DMT, an increasingly popular hallucinogen

In the past few years, thrill-seekers from Hollywood, Silicon Valley and beyond have been travelling to South America to take part in so-called Ayahuasca retreats. Their goal: to partake in a brewed concoction made from a vine plant Banisteriopsis caapi, traditionally used by indigenous people for sacred religious ceremonies. Drinkers of Ayahuasca experience short-term hallucinogenic episodes many describe as life-changing.

The active ingredient responsible for these psychedelic visions is a molecule called dimethyltryptamine (DMT). For the first time, a team led by Michigan Medicine has discovered the widespread presence of naturally-occurring DMT in the mammalian brain. The finding is the first step toward studying DMT-- and figuring out its role -- within the brains of humans.

"DMT is not just in plants, but also can be detected in mammals," says Jimo Borjigin, Ph.D., of the Department of Molecular and Integrative Physiology. Her interest in DMT came about

accidentally. Before studying the psychedelic, her research focused on melatonin production in the pineal gland.

In the seventeenth century, the philosopher Rene Descartes claimed that the pineal gland, a small pinecone-shaped organ located deep in the center of the brain, was the seat of the soul. Since its discovery, the pineal gland, known by some as the third eye, has been shrouded in mystery. Scientists now know it controls the production of melatonin, playing an important role in modulating circadian rhythms, or the body's internal clock. However, an online search for notes to include in a course she was teaching opened Borjigin's eyes to a thriving community still convinced of the pineal gland's mystical power.

The core idea seems to come from a documentary featuring the work of researcher Rick Strassman, Ph.D. with the University of New Mexico School of Medicine. In the mid-1990s, he conducted an experiment in which human subjects were given DMT by IV injection and interviewed after its effects wore off. In a documentary about the experiment, Strassman claims that he believed the pineal gland makes and secretes DMT.

"I said to myself, 'wait, I've worked on the pineal gland for years and have never heard of this,'" she said. She contacted Strassman, requesting the source of his statement. When Strassman admitted that it was just a hypothesis, Borjigin suggested they work together to test it. "I thought if DMT is an endogenous monoamine, it should be very easy to detect using a fluorescence detector."

Using a process in which microdialysis tubing is inserted into a rat brain through the pineal gland, the researchers collected a sample that was analyzed for -- and confirmed -- the presence of DMT. That experiment resulted in a paper published in 2013.

However, Borjigin was not satisfied. Next, she sought to discover how and where DMT was synthesized. Her graduate student, Jon Dean, lead author of the paper, set up an experiment using a process called in situ hybridization, which uses a labeled complementary strand of DNA to localize a specific RNA sequence in a tissue section.

"With this technique, we found brain neurons with the two enzymes required to make DMT," says Borjigin. And they were not just in the pineal gland.

"They are also found in other parts of the brain, including the neocortex and hippocampus that are important for higher-order brain functions including learning and memory."

The results are published in the journal Scientific Reports.

Her team's work has also revealed that the levels of DMT increase in some rats experiencing cardiac arrest. A paper published in 2018 by researchers in the U.K. purported that DMT simulates the near death experience, wherein people report the sensation of transcending their bodies and entering another realm. Borjigin hopes to probe further to discover the function of naturally occurring levels of DMT in the brain -- and what if any role it plays in normal brain functions.

"We don't know what it's doing in the brain. All we're saying is we discovered the neurons that make this chemical in the brain, and they do so at levels similar to other monoamine neurotransmitters."

http://bit.ly/2NkPaXn

Gut Bacteria Consume Parkinson's Drug Levodopa, Often with Harmful Side Effects

If gut microbiota metabolize levodopa before it crosses the blood-brain barrier, medication is ineffective

by News Staff / Source

Parkinson's disease is a debilitating neurological condition affecting more than 1% of the global population aged 60 and above. The primary medication used to treat this disease is levodopa. The efficacy of the treatment is hugely variable between individuals, depending on the composition of their microbiota. Levodopa is converted into active

dopamine, but if the gut microbiota metabolize levodopa before it crosses the blood-brain barrier, medication is ineffective. A research team led by Harvard University scientists has found that different species of bacteria are involved in levodopa metabolism.

"Gut microbes can chew up medications, too, often with hazardous side effects," said study first author Vayu Maini Rekdal, a graduate student at Harvard University.

"Maybe the drug is not going to reach its target in the body, maybe it's going to be toxic all of a sudden, maybe it's going to be less helpful."

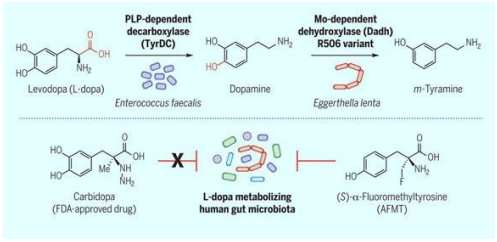
Few bacterial enzymes can perform this conversion. But, a good number bind to tyrosine, an amino acid similar to levodopa. And one, from *Lactobacillus brevis* — a food microbe often found in milk and pickles — can accept both tyrosine and levodopa.

Using the Human Microbiome Project as a reference, Maini Rekdal and his colleagues hunted through bacterial DNA to identify which gut microbes had genes to encode a similar enzyme.

Several fit their criteria; but only one strain, *Enterococcus faecalis* ate all the levodopa, every time.

With this discovery, the researchers provided the first strong evidence connecting *Enterococcus faecalis* and the bacteria's enzyme (PLP-dependent tyrosine decarboxylase, or TyrDC) to levodopa metabolism.

And yet, a human enzyme can and does convert levodopa to dopamine in the gut, the same reaction carbidopa is designed to stop.



When gut microbes metabolize the Parkinson's drug levodopa, they produce dopamine; a second microbe then metabolizes dopamine, producing meta-tyramine. While levodopa metabolism likely limits drug availability and contributes to side effects, the potential ramifications of transforming dopamine into meta-tyramine are unknown. **Harvard University.**

Then why, the team wondered, does the *Enterococcus faecalis* enzyme escape carbidopa's reach?

Even though the human and bacterial enzymes perform the exact same chemical reaction, the bacterial one looks just a little different.

"Carbidopa may not be able to penetrate the microbial cells or the slight structural variance could prevent the drug from interacting with the bacterial enzyme," Maini Rekdal said.

"If true, other host-targeted treatments may be just as ineffective as carbidopa against similar microbial machinations."

But the cause may not matter. The study authors already discovered a molecule capable of inhibiting the bacterial enzyme.

"The molecule turns off this unwanted bacterial metabolism without killing the bacteria; it's just targeting a non-essential enzyme. This and similar compounds could provide a starting place for the development of new drugs to improve levodopa therapy for Parkinson's patients," Maini Rekdal said.

The scientists might have stopped there. But instead, they pushed further to unravel a second step in the microbial metabolism of levodopa.

After *Enterococcus faecalis* converts the drug into dopamine, a second organism — *Eggerthella lenta* — converts dopamine into another compound, meta-tyramine, they found.

"*Eggerthella lenta* consumes dopamine, producing meta-tyramine as a by-product. This kind of reaction is challenging, even for chemists," they said. "There's no way to do it on the bench top, and previously no enzymes were known that did this exact reaction," Maini Rekdal added.

The meta-tyramine by-product may contribute to some of the noxious levodopa side effects; more research needs to be done.

But, apart from the implications for Parkinson's patients, *Eggerthella lenta*'s novel chemistry raises more questions: why would bacteria adapt to use dopamine, which is typically associated

with the brain? what else can gut microbes do? and does this chemistry impact our health?

"All of this suggests that gut microbes may contribute to the dramatic variability that is observed in side effects and efficacy between different patients taking levodopa," said Harvard University's Professor Emily Balskus, senior author of the study.

The findings were published in the journal *Science*.

Vayu Maini Rekdal et al. *2019. Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism.* Science *364 (6445): eaau6323; doi: 10.1126/science.aau6323*

http://bit.ly/2XBEZSd

Vaccine No Match Against Flu Bug That Popped Up Near End

The flu shot was working well early in the season with effectiveness put at 47% in February. But it was virtually worthless during a second wave driven by a tougher strain, at just 9%.

Associated Press

ATLANTA (AP) — The flu vaccine turned out to be a big disappointment again. The vaccine didn't work against a flu bug that popped up halfway through the past flu season, dragging down overall effectiveness to 29%, the U.S. Centers for Disease Control and Prevention reported Thursday.

The flu shot was working well early in the season with effectiveness put at 47% in February. But it was virtually worthless during a second wave driven by a tougher strain, at just 9%.

There was "no significant protection" against that strain, said the CDC's Brendan Flannery.

Flu vaccines are made each year to protect against three or four different kinds of flu virus. The ingredients are based on predictions of what strains will make people sick the following winter.

This season's shot turned out to be a mismatch against the bug that showed up late. That pushed down the overall effectiveness to one of the lowest in recent years. Since 2011, the only season with a lower estimate was the winter of 2014-2015, when effectiveness was 19%. A mismatch was also blamed then.

Vaccines against some other infectious diseases are not considered successful unless they are at least 90% effective. But flu is particularly challenging, partly because the virus can so quickly change. Overall, flu vaccine has averaged around 40%.

Flu shots are recommended for virtually all Americans age 6 months or older. Officials say the vaccine is still worthwhile since it works against some strains, and it likely prevented 40,000 to 90,000 hospitalizations over the winter flu season.

The CDC bases vaccine effectiveness on preventing cases bad enough to send someone to the doctor.

http://bit.ly/2xoAaN6

A deadly, drug-resistant fungus has swept the globe—here's how it spreads

With a 30-60% fatality rate, researchers are trying to stem its mysterious spread.

Beth Mole

Patients infected with a deadly, drug-resistant fungus are dripping with the dangerous germ, which pours into their surroundings where it lies in wait for weeks to find a new victim. That's according to fresh data reported from the annual meeting of the American Society for Microbiology recently in San Francisco.

The data fills in critical unknowns about how the fungus, *Candida auris*, actually spreads. The germ is a relatively new threat, considered an emerging pathogen by experts—and it's emerging quickly with an unusual ability to lurk and kill in healthcare settings.

It was first identified in 2009 in Japan. Studies since have tracked the globetrotting fungus backward and forward in time, from South

Korea in 1996 to an outbreak in New York health facilities that began in 2013 and lasted until 2017. In all, *C. auris* has made an appearance in more than 30 countries, usually leaving a body count wherever it goes.

The fungus mostly sticks to healthcare settings, stealing into the blood of vulnerable patients where it causes invasive infections marked by nondescript fever and chills. It's commonly resistant to multiple drugs, and some isolates have been found to resist all three classes of antifungal drugs, making it extremely difficult if not impossible to cure. Experts estimate that *C. auris* infections have a fatality rate somewhere between 30% and 60%. It's hard to say for sure because many of its victims are seriously ill before they get infected, making it tricky to determine an individual cause afterward.

While the threat is clear, much about *C. auris* infections has been murky—including how it spreads from one victim to another. Researchers have found it loitering on hospital mattresses, furniture, sinks, and medical equipment, but they haven't determined how it got there. Once it is present, however, it's a tough bug to annihilate. The fungal cells can form tight, hardy clumps that can live on plastics for at least two weeks and can go into a metabolically dormant phase for a month.

Torrential terror

For the new study, researchers at the Centers for Disease Control and Prevention and the City of Chicago Public Health Department tried to pin down how it gets onto those surfaces, which they hope can lead to a way to prevent its dispersal. They conducted their work in a ventilator-capable skilled nursing facility currently battling an outbreak, which started with a single case in March of 2017. Despite rigorous decontamination efforts, including bleaching surfaces and wiping down patients, 71 percent of residents have now tested positive for the fungus.

The researchers hypothesized that the fungus spreads by sloughing off of infected patients' skin. Although the *C. auris* usually presents in a bloodstream infection, researchers have found it on the skin of healthy people. And such skin shedding would be a relatively easy explanation for how it scatters in healthcare facilities.

The researchers swabbed the skin of 28 residents and their rooms, fishing for living fungal cells and the strain's genetic fingerprints. They found plenty of both. Residents' skin was loaded with the fungus, with some skin swab concentrations measuring in at an equivalent of more than 10 million fungal cells per milliliter. Importantly, the researchers found that the amount of fungal contamination in each resident's room strongly and positively correlated with the amount festering on the resident's skin. That is, the more skin fungus, the more room contamination.

The finding supports the hypothesis that skin shedding is the primary means by which *C. auris* gets around. The researchers are hopeful that the data link can help direct better decontamination and infection control efforts.

As of April 30, the CDC reports 654 confirmed cases in 2019 across a dozen states, with 30 additional probable cases. Screening in nine states has identified another 1,207 patients carrying the fungus without an infection.

https://bbc.in/2RHAJes

Select batches of Parkinson's and epilepsy medicines recalled

Certain batches of three medicines for Parkinson's, epilepsy and blood clots are being recalled in the UK, and patients are being asked to arrange a new prescription via their GP.

The affected prescription-only medicines are Neupro, Vimpat and Clexane with a B & S Healthcare label, the UK's medicine regulator said.

The drugs may not have been stored correctly before reaching patients.

But the risk of the drugs not working properly is very low, it added.

The Medicines and Healthcare products Regulatory Agency (MHRA) said the recall was precautionary and patients should continue taking their medicine.

Once they have a new prescription, patients should then return the affected batches to their pharmacist.

The medicines are:

- ***Clexane 8000iu Injection 0.8ml***
- ***Neupro 4mg/24 hr patches***
- ***Vimpat 100mg tablets***

The batches of medicines affected are listed on the MHRA website.

There is no evidence that the medicines, which are in Italian packaging, were tampered with, en route from Italy to the UK.

More drugs recalled from pharmacies

A number of other medicines are being recalled from pharmacies as a precaution. They include certain drugs for psoriasis, high cholesterol and chronic obstructive pulmonary disease - also listed online by the MHRA.

Pharmacies are being asked to check for affected packs in B & S Healthcare labelling, and return them to their supplier.

If patients have any questions, they should speak to their GP or pharmacist, the MHRA said.

Dr Samantha Atkinson, director of the MHRA's Inspection, Enforcement and Standards Division, said: "Making sure the medicines people and their families take are acceptably safe and effective is the primary role of the MHRA and is our highest priority. "When we are made aware of potential risks to the security of the supply chain, the MHRA takes action to protect the public."

The recall is taking place as part of a continuing MHRA investigation.

http://bit.ly/2Yw8YIc

Moments of clarity in dementia patients at end of life: Glimmers of hope?

Scientists consider how unexpected awakenings in dementia patients might shed new light on the disease

It happens unexpectedly: a person long thought lost to the ravages of dementia, unable to recall the events of their lives or even recognize those closest to them, will suddenly wake up and exhibit surprisingly normal behavior, only to pass away shortly thereafter. This phenomenon, which experts refer to as terminal or paradoxical lucidity, has been reported since antiquity, yet there have been very few scientific studies of it. That may be about to change.

In an article published in the August issue of Alzheimer's & Dementia , an interdisciplinary workgroup convened by the National Institutes of Health's (NIH) National Institute on Aging and led by Michigan Medicine's George A. Mashour, M.D., Ph.D., outlines what is known and unknown about paradoxical lucidity, considers its potential mechanisms, and details how a thorough scientific analysis could help shed light on the pathophysiology of dementia.

"We've assumed that advanced dementia is an irreversible neurodegenerative process with irreversible functional limitations," says Mashour, professor in the department of anesthesiology, faculty in the neuroscience graduate program, and director of the Center for Consciousness Science. "But if the brain is able to access some sort of functional network configuration during paradoxical lucidity, even in severe dementia, this suggests a reversible component of the disease."

The paper describes earlier work documenting case studies of individuals with advanced dementia, including Alzheimer's disease, appearing to be able to communicate and recall in a seemingly

normal fashion at the end of life, to the astonishment of their caregivers.

"The accumulation of anecdotal reports about paradoxical lucidity in the scientific literature prompts several important research questions," says NIA medical officer Basil Eldadah, M.D., Ph.D. "We look forward to additional research in this area, such as better characterization of lucidity in its varying presentations, new instruments or methods to assess episodes of lucidity retrospectively or in real-time, tools to analyze speech patterns or other behavioral manifestations of lucidity, and evidence to inform decision-making challenges and opportunities prompted by unexpected lucidity."

One precedent for investigating such events exists in the study of so-called near-death experiences. In 2013, Mashour and his collaborators at Michigan Medicine published a basic science study showing evidence of electrical brain features indicative of a conscious state following cardiac arrest. "We don't know that the same thing is occurring with paradoxical lucidity, but the fact that this is usually happening around the time of death suggests there could be some common neural network mechanism," he says.

Mashour admits that studying paradoxical lucidity will be a challenge, given the fleeting nature of the event. Case studies report episodes lasting from mere seconds to at most several days for a small minority of cases. The workgroup also outlines important ethical implications of this work, including the ability of vulnerable patients to participate in research and how the observation of paradoxical lucidity might change the way caregivers interact with people with dementia.

"Would research that might identify a systematically observable paradoxical lucidity provide comfort, for example, by offering loved ones a potential channel for closure, or might it induce worry if loved ones are left to wonder if a reversible cause of the dementia could have been found? We do not know the answers but these could be important research questions in their own right," says co-first author Lori Frank, Ph.D., of the RAND Corporation and former Health and Aging Congressional fellow with the National Institute on Aging.

The workgroup hopes their paper will help raise awareness within the scientific community to advance paradoxical lucidity research, and help validate the experiences of a multitude of caregivers.

Says Mashour, "Science is now trying to be thoughtful and attentive to something that has long been reported."

http://bit.ly/2LseoQR

An improved vaccine for bacterial meningitis and bloodstream infections

New vaccine will allow younger people to be vaccinated and address several limitations of the current vaccinations

Washington, DC - Researchers have now developed a new vaccine, a native outer membrane vesicle (NOMV) vaccine, for meningitis and bloodstream infections caused by "meningococcal group B" bacteria. This will allow younger people to be vaccinated and will address several limitations of the current vaccinations. The research is published this week in mBio, a journal of the American Society for Microbiology.

"We developed the improved version of the vaccine by making several genetic changes to the strain of bacteria used to produce the vaccine, resulting in a broadly protective vaccine rather than a strain-specific vaccine," said Peter Beernink, Ph.D., Scientist at the Center for Immunobiology and Vaccine Development, Benioff Children's Hospital Oakland.

There are currently only two licensed vaccines for prevention of meningitis and bloodstream infections caused by "meningococcal group B" bacteria, which are only licensed for use in people age 10 years and older. Both vaccines contain a bacterial protein known as

Factor H binding protein (FHbp), which can bind to a host protein known as Factor H (FH). The licensed vaccines have several limitations, which include lack of effectiveness against some bacterial strains and low immune responses of infant humans.

The researchers immunized infant rhesus monkeys with the NOMV-FHbp vaccine, which induced higher levels of protective serum antibodies than a licensed vaccine against five of six bacterial strains tested. Two macaques immunized with the licensed vaccine, which contains FHbp that binds macaque FH, developed antibodies to the host FH protein whereas none of the animals given the NOMV-FHbp vaccine or a negative control vaccine developed such antibodies.

The monkey antibody responses to the vaccines were measured in the laboratory based on the ability of serum antibodies to kill the bacteria in a test that is widely considered to predict protection in humans. The sample sizes of animals were chosen such that the results are highly statistically significant.

"The experimental NOMV vaccine extends the approach of using outer membrane vesicle vaccines, which previously have been given to millions of persons during meningitis B epidemics in Norway, Cuba and New Zealand," said Beernink.

Thus, in a relevant infant non-human primate model, the NOMV-FHbp vaccine elicited higher levels of protective antibodies than the licensed vaccine and anti-FH antibodies in fewer animals. "This shows that the vaccine has the potential to be developed into a more broadly protective vaccine for humans, to extend coverage to infants and toddlers, which are the age groups among the highest risk of developing meningococcal disease, and to increase vaccine safety," said Beernink.

The work was performed by Peter Beernink, Dan Granoff and colleagues at UCSF Benioff Children's Hospital Oakland (California). The work was funded by a research grant from the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

http://bit.ly/2Jd7LiU

New solar technology could produce clean drinking water for millions in need

New material speeds the process of evaporation, enabling a small solar still to provide all the drinking water one family needs

By Robert F. Service

Tanklike devices called solar stills use the sun to evaporate dirty or salty water and condense the vapor into safe drinking water.

But large, expensive stills can only produce enough water for a small family. Now, researchers have developed a new material that speeds the process of evaporation, enabling a small solar still to provide all the drinking water one family needs. If the technology proves cheap enough, it could provide millions of impoverished people access to clean drinking water.

A gel at the heart of this solar still produces a record amount of fresh water.
Xingyi Zhou and Youhong Guo/UT Austin

Today 783 million, or nearly one in 10, people around the world lack such access, according to UNICEF. These people spend a collective 200 million hours a day fetching water from distant sources. And even though technologies exist for purifying contaminated water and desalinating seawater, these typically require expensive infrastructure and lots of energy, putting them beyond the reach of many communities.

Recently, researchers have been working to upgrade solar stills as a cheap, low-tech alternative. The traditional still is little more than a black-bottomed vessel filled with water and topped with clear glass or plastic. The black bottom absorbs sunlight, heating water so that it evaporates and leaves the contaminants behind. The water vapor then condenses on the clear covering and trickles into a collector.

But the output is low because the sun's rays must heat the entire volume of water before evaporation begins. Commercially available versions produce about 0.3 liters of water per hour per square meter (L/h/m2) of the covered water's surface area. The average person requires about 3 liters of water a day for drinking. Providing enough drinking water for a small family requires a still around 5 square meters in size. Operating at their theoretical best, such devices can only produce 1.6 L/h/m2.

Guihua Yu, a materials scientist at the University of Texas in Austin, and colleagues recently reported a way around this limit. It involves hydrogels, polymer mixtures that form a 3D porous, water—absorbent network. Yu and colleagues fashioned a gellike sponge of two polymers—one a water-binding polymer called polyvinyl alcohol (PVA), the other a light absorber called polypyrrole (PPy)—which they then placed atop the water's surface in a solar still.

Inside the gel, a layer of water molecules bonded tightly to the PVA, each forming multiple chemical links known as hydrogen bonds. But with so much of their bonding ability tied up with the PVA, the bound water molecules bind only loosely to other nearby water molecules, creating what Yu calls "intermediate water." Because intermediate water molecules share fewer bonds with their neighbors, they evaporate more readily than regular water. And when they do, they're immediately replaced by other water molecules in the still. Using this technology, Yu's solar still produced 3.2 L/h/m2 of water, double the theoretical limit, his team reported last year in *Nature Nanotechnology*.

Now, Yu and his colleagues have created an even better hydrogel. They mixed in a third polymer, called chitosan, which also strongly attracts water. Adding chitosan to the mix created a gel that could hold more water—and increased the amount of intermediate water as a result. A still using the new hydrogel distilled water at a rate of 3.6 L/h/m2, the highest rate ever reported and about 12 times the amount produced by today's commercially available versions, the researchers report today in *Science Advances*.

"This is a fantastic starting point," says Peng Wang, an environmental engineer at King Abdullah University of Science and Technology in Thuwal, Saudi Arabia. Wang notes that at this higher water production rate, a solar still 1 square meter in size could produce about 30 liters of clean drinking water per day, enough for a small family. Even better, he says, all three polymers in the hydrogel are both commercially available and cheap. That means that if the stills using them are rugged enough, they could help provide clean water for those who need it most.

http://bit.ly/2Nqqi7j

Cockroach 'Superbugs' Becoming Near-Impossible to Kill

In the ongoing evolutionary arms race between hardy cockroach pests and the humans creating poisons to kill them, it looks like the roaches may be winning.

By Mindy Weisberger, Senior Writer | June 28, 2019 11:15am ET

German cockroaches — small, swift, prolific insects that live only around people — are quickly evolving resistance to a range of pesticides at the same time and may soon be nearly impossible to kill with chemicals alone.

A German cockroach (Blattella germanica) samples a gel blob of insecticide.
Credit: John Obermeyer/Purdue Entomology

Exterminators typically rely on different classes of toxic chemicals to eliminate roaches; if the insects happen to be resistant to one class, they'll usually succumb to another. However, researchers recently discovered that German roaches (*Blattella germanica*) are developing cross-resistance to a range of insecticides, which means

that the roaches' offspring are born already impervious to toxins that they haven't directly encountered.

And this sometimes takes place within a single generation, the scientists reported in a new study.

"We didn't have a clue that something like that could happen this fast," said study co-author Michael Scharf, a professor and chair with the Department of Entomology at Purdue University in Indiana.

"Cockroaches developing resistance to multiple classes of insecticides at once will make controlling these pests almost impossible with chemicals alone." Scharf said in a statement.

For the study, the researchers tested the effects of three different courses of insecticides on roach populations in apartment buildings in Danville, Illinois, and in Indianapolis, Indiana, over six months. They exposed one group of roaches to a single insecticide. A second roach population received two insecticides from different classes. And a third was dosed with rotations of three insecticides — one per month, for two three-month cycles.

The scientists also tracked roaches' resistance to insecticides across multiple generations, trapping live roaches to take back to the lab in greased baby food jars baited with beer-soaked bread.

In most cases, roach populations either remained stable or increased, and rotating pesticides was found to be "mostly ineffective" at reducing their numbers, "due to cross-resistance," the study authors reported. Offspring were not only resistant to the pesticide that their parents encountered but also unexpectedly showed signs of resistance to other classes of insecticides as well, according to the study.

The only experiment that worked at all was the single pesticide; it was highly successful in a population that happened to have almost no resistance to the toxin. However, in another experiment the researchers tested a group of insects that had slightly more resistance. In that group, the number of roaches actually increased, with generations born to resistant survivors. A single female roach can produce dozens of offspring every few months, which quickly replenishes depleted communities.

The fast-breeding German cockroach lives throughout the world wherever humans live, and is "the species that gives all other cockroaches a bad name," according to the University of Florida's Department of Entomology and Nematology. Roaches spread bacteria that can cause disease; their feces and shed body parts carry allergens that can trigger asthma; and the mere sight of them can cause psychological distress in some people, the study authors reported.

Ridding urban homes of these pests will require strategies more complex than chemical treatment alone, Scharf said in the statement. A combination of approaches — such as improved sanitation, traps and even vacuums to suck them up — will likely be far more effective than relying on pesticides to do the job, he explained.

"Some of these methods are more expensive than using only insecticides, but if those insecticides aren't going to control or eliminate a population, you're just throwing money away," Scharf said.

The findings were published online June 5 in the journal Scientific Reports.