https://go.nature.com/2N54qOC

Weaponized cells seek and destroy HIV lurking in the body

Approach could allow people infected with HIV to set aside their medication — without risking a resurgence of the virus.

Custom-designed immune cells can vanquish pockets of HIV hidden in the cells of people infected with the virus.

Antiretroviral therapies keep HIV in check, but virus-laden cells persist in the body — forcing people with the virus to take the drugs for life. Warner Greene at the Gladstone Institute of Virology and Immunology in San Francisco, California, and his colleagues sought a way to reduce and control the amount of this persistent HIV. Such a therapy could allow patients to safely stop taking medication.

The researchers opted to use CAR-T cells — immune cells that are engineered to home in on and destroy specific targets such as cancer cells. The team's CAR-T cells kill HIV-infected cells and are guided to their targets by antibodies that can be easily changed. This confers flexibility on the killer cells, which the team named 'convertible' CAR-T cells. In tests on blood cells taken from people infected with HIV, the convertible CAR-T cells cut the amount of latent virus by more than half in just two days.

Cell (2019)

http://bit.ly/34mif8w

Lush Okavango Delta Pinpointed as Ancestral Homeland of All Living Humans

Genetic evidence traces our origins to a hunter-gatherer community that lived 200,000 years ago, but the study has generated controversy

By Richard Conniff

Anyone lucky enough to have visited the Okavango Delta in the southern African nation of Botswana will recall the comforting and oddly familiar sensation of looking out from the shelter of a stand of trees at the panorama of wildlife—from elephants and African wild dogs to lilac-breasted rollers—moving across the lush surrounding floodplains. That sense of familiarity may run deeper than we imagine, a new study suggests—back to a time when early modern humans also wandered there.

Jul'hoansi hunters /kun /kunta, N‡amce Sao and /kun N‡amce re-creating how our ancestors hunted when the Homeland was once a vast wetland. /kun /kunta, N‡amce Sao and /kun N‡amce today live within the dried Homeland.
Chris Bennett

The study, appearing Monday in the journal *Nature*, uses genetic, archaeological, linguistic and climatic evidence to argue that the ancestral homeland of everyone alive today was in northern Botswana—not in East Africa, as previously thought. Based on mitochondrial DNA, passed down from mother to daughter, the paper's co-authors argue that we are all descended from a small community of Khoisan hunter-gatherers who lived 200,000 years ago in vast wetlands encompassing Botswana's Okavango Delta and the Makgadikgadi regions.

Much of that place is now a dry salt pan—and inhabited by modern Khoisan people, sometimes called Bushmen. But back then, it was a vast wetland covering an area the size of Switzerland. The community that lived there was unusually stable, thriving almost unchanged for 70,000 years in a habitat closely resembling the modern Okavango Delta, according to senior author Vanessa M. Hayes, a geneticist at the Garvan Institute of Medical Research in Australia.

The new study looks at the mitogenomes, or mitochondrial genomes, of 1,217 individuals from multiple southern African

ethnic identities, and focuses on a “rare deep-rooting” lineage called L0, or L zero. It’s the oldest known mitochondrial lineage, passed down intact from mother to daughter across the generations, though mutations can sometimes occur and may be associated with important evolutionary changes. Hayes became interested in that lineage as a result of her work with the South African Genome Project, which found evidence of L0 ancestry distributed across southern Africa. Archbishop Emeritus Desmond Tutu, descended mainly from Bantu groups who migrated into southern Africa 1,500 years ago, was among those identified as having Khoisan ancestry, a connection he said left him feeling “very privileged and blessed."

Tracking the accumulation of mutations in the L0 lineage across the eons provides geneticists with a time stamp for evolutionary changes. The co-authors of the *Nature* paper identify and date changes in the L0 lineage. They also correlate these “branching” events with evidence of climatic shifts, as well as with archaeological evidence of human migrations.

During the initial 70,000 years of stable habitation, says co-author Axel Timmermann, a climate scientist at Pusan National University in South Korea, migration was probably constrained by harsh, dry conditions in the surrounding landscape. But about 130,000 years ago, a period of increased rainfall opened a green corridor for migrations to the northeast. Then, about 110,000 years ago, drying conditions within the homeland and opening of a green corridor to the southwest led to further migrations down to the southern tip of Africa. Evidence of both events survives, according to the study, in subgroups of the L0 lineage found in living descendants of those migrations.

The new research fits with other recent genetic evidence of human origin in southern Africa, including a study earlier this year suggesting that a migration from that region to East Africa, and the resulting mixture with populations there, might have been a key turning point in the evolution of modern humans and their migration out of Africa. Another paper this year also argues that a migration from southern Africa to East Africa immediately preceded a major out-of-Africa migration 100,000 to 70,000 years ago. The alternative pan-African, or “polycentric,” viewpoint holds that multiple interlinked populations evolved across the continent, sometimes in isolation and sometimes together.

James Cole, an archaeologist at the University of Brighton in England, who was not involved in the new study, praises Hayes and her colleagues for their cross-disciplinary approach to understanding mitochondrial evolution. But he also notes that their paper overlooks major archaeological evidence, such as the 315,000-year-old skeletal remains of an anatomically modern human recently found in Morocco. Hayes replies that her study focuses only on the population of direct ancestors of “people walking around today,” and in the absence of genetic evidence from the Morocco specimens, the connection to living humans is unknown.

Milford Wolpoff, a paleoanthropologist at the University of Michigan who also was not involved in the new work, similarly argues that the evidence its authors present is too narrow. Reliance solely on mitochondrial evidence leads to misinterpretation, he says, and risks overlooking important evolutionary information in the separate DNA of the cell nucleus. Our widespread inheritance of Neandertal genes shows up, for instance, only in the nuclear DNA, and it is completely absent from the mitogenome. Likewise, Wolpoff says, “the nuclear genome, with three billion base pairs, might tell an entirely different story about the African origin of modern humans from what the mitogenome’s 16,000 base pairs” suggest.

“We’re dealing with a puzzle of a million pieces,” Cole says, “and we’ve probably got the first 100 in place.” Paleogenetics has

“ramped up the scale of complexity exponentially,” he adds. “From the paleontological and archeological record, it was a 1,000-piece puzzle.” But instead of providing a grand answer to the story of human origin, Cole suggests, so far, genetics is mainly showing us just how complex that story really is.

http://bit.ly/2qZaBSY

Which came first: Brain size or drinking propensity?

New research challenges traditional idea about relationship between alcohol use and brain size

For years, researchers have observed that alcohol consumption is associated with reduced brain volume and concluded that drinking can literally shrink the brain.

But new research turns that theory on its head, suggesting that reduced brain volume may represent a genetically-conferred predispositional risk factor for heavier alcohol consumption.

"Our results suggest that associations between alcohol consumption and reduced brain volume are attributable to shared genetic factors," said senior author Ryan Bogdan, associate professor of psychological and brain sciences in Arts & Sciences and director of the Brain Lab at Washington University in St. Louis, where the research is based. "Lower brain volume in specific regions may predispose a person to greater alcohol consumption.

"The study is impressive because it uses a variety of approaches and data analysis techniques to reach findings that all converge on the same conclusion," he said.

The study, recently published online in the journal *Biological Psychiatry*, is based on longitudinal and family data from three independent brain imaging studies - including the comparison of drinking behaviors in twin and non-twin siblings; longitudinal research within children who were never exposed to alcohol at baseline; and gene expression analyses using postmortem brain tissue.

"Our study provides convergent evidence that there are genetic factors that lead to both lower gray matter volumes and increased alcohol use," said David Baranger, the study's lead author and a former doctoral student in in Bogdan's lab.

"These findings don't discount the hypothesis that alcohol abuse may further reduce gray matter volumes, but it does suggest that brain volumes started out lower to begin with," Baranger said. "As a result, brain volumes may also serve as useful biological markers for gene variations linked to increased vulnerability for alcohol consumption."

Baranger, who is now a postdoctoral scholar at the University of Pittsburgh, led the research project, which included other Arts & Sciences psychology graduate students and faculty from Washington University School of Medicine in St. Louis; Duke University; and the Medical University of South Carolina.

Researchers used data from the Duke Neurogenetics Study, the Human Connectome Project and the Teen Alcohol Outcomes Study to confirm that greater alcohol consumption is associated with lower gray matter volume in two brain regions, the dorsolateral prefrontal cortex and the insula, that feature prominently in emotion, memory, reward, cognitive control and decision making.

Analyses of brain imaging and family data spanning childhood to adulthood revealed genetically-conferred reductions in gray matter volume in the frontal cortex and insula, which were, in turn, predictive of future alcohol use, including the initiation of drinking in adolescence and future drinking in young adulthood.

To further confirm genetic links between lower brain volumes and alcohol consumption, the team examined data from twin and non-twin siblings with differing histories of alcohol consumption. When compared with siblings with a shared history of low alcohol use, siblings who drank more heavily had lower grey matter volumes. Interestingly, the study found no differences in gray matter volume

in brains of same-family siblings where one drank more heavily than the other - both looked like heavy-drinkers. This finding provides additional evidence that lower gray matter volume is a pre-existing vulnerability factor associated with the potential for alcohol use, as opposed to a consequence of alcohol use.

Finally, the research team used data of gene expression in the human brain to explore whether genetic risk for alcohol consumption is enriched for genes expressed in these regions and could be associated with the expression of specific genes.

Baranger and colleagues found that genomic risk for alcohol consumption is enriched for genes that are preferentially expressed in the dorsolateral prefrontal cortex relative to other tissues and brain regions. Further, they found that the expression of specific genes in this region are replicably associated with genomic risk for alcohol consumption. These data provide additional convergent evidence that it is biologically plausible that lower grey matter volume in the frontal cortex may be driven by genetic risk for alcohol consumption.

"Our analyses in three independent samples provides unique convergent evidence that associations between middle/superior frontal gray matter volume and alcohol use are genetically-conferred and predict future use and initiation," the study concludes. "Taken alongside evidence that heavy alcohol consumption induces gray matter volume reductions, our data raise the intriguing possibility that genetically-conferred reductions in regional gray matter volumes may promote alcohol use from adolescence to young adulthood, which may, in turn, lead to accelerated atrophy within these and other regions," the authors wrote

The results might be generalized to other substances, the group concluded, because different substances can all be affected by the same genetic factors.

http://bit.ly/2WxZPyH

Medical alarms may be inaudible to hospital staff

Study shows 'masking' effect of multiple alarms impacts care providers

Thousands of alarms are generated each day in any given hospital, but there are many reasons why humans may fail to respond to medical alarms, including trouble hearing the alarm.

New research from the University of Illinois at Chicago looked at one common issue that affects alarm preceivability -- simultaneous masking.

"We know that our sensory system works as a filter and while that filter, generally, helps us, it can also prevent us from hearing one or more concurrent sounds in certain circumstances," said Andrew Boyd, senior author of the study.

To study this effect among health care professionals, Boyd and his colleagues played standard medical alarm sounds for 28 nursing students. In the experiments, the participants were provided an initial sound -- they were then played additional sounds and asked if the initial sound was present. Students were played sounds under two conditions, a masking condition and a non-masking condition, that each mimicked real-life hospital scenarios.

"Miss rates were significantly higher and sensitivity was significantly lower for the masking condition than for the non-masking one," said Boyd, associate professor of biomedical information sciences at the UIC College of Applied Health Sciences.

Boyd and his colleagues write that "the results show that masking of an alarm's primary harmonic is sufficient to make an alarm sound indistinguishable."

"Considering an average hospital patient may produce hundreds of alarms each day, the presence of masking among standard hospital alarms is dangerous," he said.

The results are published in Human Factors, *a journal of the Human Factors and Ergonomics Society.*

Boyd worked with colleagues from the University at Buffalo, the State University of New York, and University of Plymouth on this research. His co-authors are first author Matthew Bolton and Xi Xheng, Meng Li and Judy Reed Edworthy.

The study was supported by the Agency for Healthcare Research and Quality (R18HS024679).

http://bit.ly/2JGJZwv

This Newly Discovered Virus Replicates in a Completely Unknown Way

A newly discovered virus seems to lack the proteins needed to replicate itself. Yet somehow, it's thriving, according to a new study.

By Yasemin Saplakoglu - Staff Writer

To find this mysterious virus, a group of researchers in Japan have spent nearly a decade analyzing pig and cow poop for novel viruses. These dirty environments, where lots of animals constantly interact, are a good place for viruses to quickly evolve, according to a statement from Tokyo University of Agriculture and Technology in Japan.

The researchers have found on farms several novel viruses that have recombined — meaning that two or more viruses have swapped genetic material.

But they were particularly intrigued when they found a new type of enterovirus G (EV-G), which is composed of a single strand of genetic material. This new virus was formed from an enterovirus G and another type, called a torovirus.

Mysteriously, the newly discovered microbe lacks a feature present in all other known viruses — so called “structural proteins” that help the parasite attach to and enter host cells, then replicate. Though the new enterovirus lacks the genes that code for these structural proteins, it does have a couple of "unknown" genes, according to the researchers.

"This is very strange," senior author Tetsuya Mizutani, the director at the Research and Education Center for Prevention of Global Infectious Disease of Animal (TUAT) in Japan, told Live Science in an email.

Without structural proteins, the virus shouldn't be able to infect other cells, he added.

Yet, three years later, the researchers found the same virus in pig poop on the same farm, suggesting that the virus did replicate in pigs. The scientists analyzed poop they gathered from other farms and also found this virus present.

So, how does the virus, which they named type 2 EV-G, survive? Mizutani and his team hypothesize that the virus borrows structural proteins from other nearby viruses, called "helper viruses."

That’s not totally unheard of. Hepatitis D virus needs the hepatitis B virus to replicate in the body, though it does have its own structural proteins, said Dr. Amesh Adalja, an infectious disease specialist and a senior scholar at the Johns Hopkins Center for Health Security in Baltimore, who wasn't involved with the study.

"Understanding how viral recombination occurs and how viruses develop dependencies on helper viruses is an important key to unlocking some of the mysteries of virus evolution," Adalja told Live Science.

There are now over 30 virus families in the world, which likely evolved from one or a few common ancestors, Mizutani said. It's clear that they didn't all evolve from random mutations in their genomes, but rather combined with each other, just as the ancestors of type 2 EV-G did, he added. Now, Mizutani and his team hope to figure out which helper viruses enable 2 EV-G to survive, and exactly what the unknown genes do.

The findings were published on July 22 in the journal Infection, Genetics and Evolution.

http://bit.ly/2WynD5K

Study finds coffee is associated with improved sports performance in men and women

Study finds coffee ingestion improves 5 km cycling time trial performance in recreationally active men and women by similar

A new study, published in Nutrients, of 38 participants (19 men, 19 women) has found that drinking caffeinated coffee improves speed of cycling.

The study, which investigated the effect of coffee ingestion in a 5km cycling trial, found that it had a positive effect on the time trial performance of both sexes. The study's findings suggest that both men and women respond similarly to coffee and that coffee ingestion may be a practical source of caffeine prior to exercise to improve performance.

Participants restricted coffee consumption for 12 hours before drinking either: coffee providing 3mg.kg^{-1} of caffeine, a placebo in water or nothing as a control. In a 5km cycling time trial, following coffee ingestion, the performance of both men and women improved by approximately nine seconds and six seconds compared with placebo and control, respectively. No differences in performance were observed between the placebo and control.

The study contributes to the growing body of research that highlights the ergogenic benefit of coffee ingestion. To date, much of the research on this topic has focused only on anhydrous caffeine and on men.

Study author

Associate Professor Neil Clarke, School of Life Sciences, Faculty of Health and Life Sciences, Coventry University, United Kingdom

References

1. N Clarke et al. (2019). Coffee ingestion improves 5 km cycling performance in men and women by a similar magnitude. Nutrients. *Published online.*

http://bit.ly/33qf8Pq

Can aspirin decrease the rate of intracranial aneurysm growth?

Aspirin associated with decreased rate of intracranial aneurysm growth

Charlottesville, Va. Researchers conducted a database search to investigate whether aspirin can aid in the prevention of intracranial aneurysm rupture by hindering aneurysm growth. The researchers identified 146 patients harboring multiple intracranial aneurysms, five millimeters or less in diameter, that had been observed for at least five years. In this set of patients, the researchers found an association between aspirin use and a decreased rate of aneurysm growth. Growth is important in intracranial aneurysms because it increases the risk of aneurysm rupture. Detailed findings are found in the article, "Aspirin associated with decreased rate of intracranial aneurysm growth," by Mario Zanaty, M.D., and colleagues, published today in the *Journal of Neurosurgery*.

Background

An intracranial aneurysm is a cerebrovascular disorder in which the wall of an artery in the brain has weakened and bulges outward. The worry is that the weakened aneurysm wall might rupture, causing subarachnoid hemorrhage--bleeding in the brain.

According to the Brain Aneurysm Foundation, in the United States an estimated 6.5 million people have an unruptured intracranial artery. It is not unusual to have more than one. Many small aneurysms do not cause symptoms and are unlikely to rupture. We may only know that they exist because they are identified on imaging studies obtained for another reason.

Each year, however, approximately 30,000 people in the United States experience aneurysm rupture. A ruptured aneurysm can result in substantial disability and even death.

Aneurysms larger than 7 mm are more likely to rupture than small ones. Unfortunately, some small aneurysms grow, increasing the risks that they may rupture. It is for this reason that physicians observe small, unruptured aneurysms over time by asking patients to undergo regularly scheduled imaging examinations. When it comes to the brain, intervention carries risks as well, and most neurosurgeons would prefer not to treat a small, unruptured aneurysm unless the risk of rupture meets or exceeds the risk of intervention.

The authors of this paper note, "to date, there is no medical treatment to arrest aneurysm growth and subsequent progression to rupture." If there were, patients could feel assured that the risk of aneurysm rupture would remain steady. The authors do tell us that there has been some evidence that aspirin may reduce the risk of aneurysm rupture due to the drug's anti-inflammatory effect on the weakened aneurysm wall. Their aim in the current study was to discover whether aspirin can protect against aneurysm growth in a population of patients harboring multiple small intracranial aneurysms.

Present Study

The data collected by the researchers came from the medical records of 146 patients with multiple intracranial saccular aneurysms, who had undergone surgical or endovascular treatment by the senior author, David M. Hasan, M.D., initially for one aneurysm that had ruptured or was deemed at risk for rupture. Following treatment of this primary aneurysm, the patients still harbored a total of 229 intracranial aneurysms, all of which measured five millimeters or less. These 229 aneurysms are the focus of this paper. The patients periodically returned for follow-up appointments with Dr. Hasan, during which their remaining aneurysms were assessed for growth. Growth was defined as an increase in aneurysm size of at least one millimeter. If growth was identified, the aneurysm was treated. This occurred with 24 aneurysms.

By the end of the study period (July 2009-January 2019), each patient had been monitored for at least 5 years. None of the 229 aneurysms ruptured during the study period.

To examine what factors might lead to aneurysm growth or protect against aneurysm growth over time, the authors performed univariate and multivariate analyses on a variety of demographic and aneurysm-related information retrieved from the database. These included patient age and sex, family and patient medical history, present comorbidities, aneurysm size and location in the brain, status of the primary aneurysm (ruptured or unruptured) prior to treatment, type of procedure used to treat aneurysms, daily use of at least 81 milligrams aspirin, and use of another anticoagulant medication.

According to the univariate analysis, significant predictors of aneurysm growth included a patient's history of ruptured aneurysm, drug abuse, hypertension, and polycystic kidney disease. There was an association between both aspirin use and one type of treatment, stent-assisted coil embolization, and a lower rate of aneurysm growth. In the multivariate analysis, the independent factors associated with aneurysm growth were again patient's history of ruptured aneurysm, drug abuse, hypertension, and polycystic kidney disease. Only aspirin use proved to be associated with a significant decreased rate of aneurysm growth.

On the basis of the statistical analyses, use of aspirin appears to exert a protective effect against aneurysm growth and very likely against future rupture.

The authors point out that their findings are observational and that future, interventional studies should be conducted.

When asked about the study, Dr. Hasan said, "This study is very promising, as it outlines for the first time the potential therapeutic

effect of aspirin in decreasing aneurysm growth. If proven in a larger study, this could offer the first, cheap, effective over-the-counter therapeutic agent that could halt aneurysm growth and prevent rupture. Many people around the world could benefit from this."

Zanaty M, Roa Jorge A, Nakagawa D, Chalouhi N, Allan L, Al Kasab S. Limaye K, Ishii D, Samaniego EA, Jabbour P, Torner JC, Hasan DM: Aspirin associated with decreased rate of intracranial aneurysm growth. Journal of Neurosurgery, published online, ahead of print, October 29, 2019; DOI: 10.3171/2019.6.JNS191273.

Disclosure: The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Drs. Zanaty, Roa, Allan, Al Kasab, Limaye, Samaniego, Torner, and Hasan are affiliated with the University of Iowa Hospitals and Clinics, Iowa City, Iowa; Dr. Nakagawa with The University of Tokyo Hospital, Tokyo, Japan; Drs. Chalouhi and Jabbour with Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; and Dr. Ishii with Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan.

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https://go.nature.com/2NzXvU3

The declining art of brachytherapy

Brachytherapy is an established treatment for prostate cancer with much to recommend it, but its use is declining as clinicians opt for flashier therapies.

Modern medicine advances so quickly that it might be surprising to learn that a 100-year-old treatment for prostate cancer is still relevant. Brachytherapy, which involves bombarding the tumour with radiation from isotopes positioned around it, has a track record as a safe and effective procedure, and is less costly than other interventions such as robot-assisted surgery. Nevertheless, many oncologists are concerned that the technique could fall out of use.

In the first demonstration of brachytherapy in 1911, French physician Octave Pasteau used a urethral catheter containing radium. The technique evolved, and by the 1980s, a version known as low-dose-rate (LDR) brachytherapy, which is still in use today, had emerged. The therapy involves injecting 'seeds' of radioactive iodine or palladium into the gland, with the help of ultrasound imaging. These seeds are permanently embedded, releasing radiation for several months.

The process poses some problems: implanted seeds can expose patients' sexual partners to radiation, and the seeds can migrate into healthy tissues over time, for example. Another iteration of the treatment, known as high-dose-rate (HDR) brachytherapy, remedies this by temporarily introducing iridium isotopes into the prostate inside catheters.

LDR brachytherapy has long been used to treat people with prostate tumours, and the clinical performance of the HDR variety is promising. Both are delivered alone or alongside other treatments. But the use of both forms is in decline. In 2002, 17% of people in the United States with prostate cancer received the treatment; by 2010, that number had fallen to just 8% (J. M. Martin *et al. Cancer* **120**, 2114–2121; 2014).

In part, this decline can be ascribed to the fact that aggressive treatment by any method has become less common — many clinicians now opt instead to keep a close eye on low-risk tumours. But brachytherapy is also being eclipsed by more technologically sophisticated treatments such as robot-assisted surgery and proton therapy — a shift partly facilitated by hospital-reimbursement policies that favour newer approaches. The fall has alarmed many oncologists and radiotherapists, with some suggesting that it could lead to a decline in cure rates.

Without action, brachytherapy's decline in use seems set to continue. The drop means fewer opportunities for medical students and residents to see the technique in action — a feedback loop that, according to a survey of US radiation-oncology residents, might already be affecting their familiarity with the technique (N. Nabavizadeh *et al. Int. J. Radiat. Oncol. Biol. Phys.* **94**, 228–234;

2016). But the radiation-oncology community is taking steps to ensure that brachytherapy remains an option. The American Brachytherapy Society in Reston, Virginia, has embarked on an initiative to train 30 practitioners in the technique every year for the next decade. And the American Society for Radiation Oncology is lobbying the US Centers for Medicare and Medicaid Services to re-evaluate how it reimburses hospitals for certain treatments. Brachytherapy has a long history, and many practitioners think that if it disappears, it is patients who will lose out.

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http://bit.ly/2C5dEez

Tumors turn gut 'brain cells' into tumor growth promoters

When enteric glial cells are exposed to secretions from colon tumors, they convert into promoters of tumor growth

Research led by North Carolina State University has found that when enteric glial cells are exposed to secretions from colon tumors, the glial cells convert into promoters of tumor growth. The work demonstrates enteric glial cells' importance in the tumor microenvironment and could lead to new targets for treatment of colon cancer.

The enteric nervous system functions as the gut's "brain," or local nervous system. Neurons and enteric glial cells (EGCs) in the enteric nervous system work together to regulate important intestinal functions like peristalsis and help control the function of the epithelium, or intestinal lining.

When a cancerous tumor grows within the intestine, it creates a tumor microenvironment composed of resident or recruited cells such as the surrounding ECGs, neurons, blood vessels, immune cells, and various signaling molecules. The tumor and the surrounding microenvironment interact constantly.

"Only a fraction of cancer cells - known as colon cancer stem cells, or CSCs - is thought to be able to create tumors," says Laurianne Van Landeghem, assistant professor of neurogastroenterology at NC State and corresponding author of a paper describing the work. "CSCs are constantly exposed to regulatory cues in the form of molecules secreted by neighboring cells in the tumor microenvironment. EGCs are an important part of the tumor microenvironment, but no one had studied whether these cells affect the CSCs' ability to create new tumors."

Van Landeghem and an international team of researchers that included Ph.D. student Simon Valès from the University of Nantes, France, looked at tumors from colon cancer patients in both the U.S. and France. "We isolated CSCs from the tumors and grew them in presence or absence of glial cells to see if the EGCs' secretions affected tumor initiation and growth," Van Landeghem says.

When the team exposed CSCs to secretions of EGCs that were grown alone and independently from the tumor, there wasn't a discernable increase in tumor growth. However, when the team grew EGCs in the same medium in which they had grown tumor cells and then exposed those secretions to CSCs, tumors formed more quickly and were bigger.

"In the tumor microenvironment, the cancer cells secrete a molecule known as IL-1, which, if taken up by nearby EGCs, can change them," Van Landeghem says. "Those changed glia in turn secrete a molecule known as PGE2, which stimulates the CSCs and causes tumor initiation and faster tumor growth. Both of these molecules

are well described, but we didn't know they were involved in the communication between the tumor and glial cells until now.

"The tumor is essentially remodeling the nearby glia with the aim of making itself thrive. We have identified the molecules responsible for this remodeling and EGCs' pro-tumor initiation impact. Hopefully this work can lead to better understanding of the role EGCs play in colon cancer and perhaps help us identify new targets for cancer therapies."

The work appears in EBioMedicine *and was supported by grants from the French National Cancer Institute, La Ligue contre le Cancer, the 'Région des Pays de la Loire', and the UNC Lineberger Comprehensive Cancer Care Center. Simon Vales, from Nantes University, France, is first author. These studies were a collaborative work between the Van Landeghem Lab at NC State and the INSERM groups 1235 and 1232 (Nantes, France), the Cancéropôle Grand Ouest (Nantes, France) as well as clinicians from Nantes Hospital and Jules Verne Clinic (Nantes, France).* ***Note to editors: An abstract follows****. "Tumor Cells Hijack Enteric Glia to Activate Colon Cancer Stem Cells and Stimulate Tumorigenesis" DOI: 10.1016/j.ebiom.2019.09.045Authors: Simon Valès, Nantes University, INSERM 1235, France; Laurianne Van Landeghem, North Carolina State University, et al. Published: Oct. 28, 2019 in* EBioMedicine

http://bit.ly/32bNnWK

Avocados may help manage obesity, prevent diabetes

Your guacamole may hold the key to managing obesity and helping delay or prevent diabetes, according to a new study by a University of Guelph research team.

For the first time, researchers led by Prof. Paul Spagnuolo have shown how a compound found only in avocados can inhibit cellular processes that normally lead to diabetes. In safety testing in humans, the team also found that the substance was absorbed into the blood with no adverse effects in the kidney, liver or muscle.

The study was recently published in the journal *Molecular Nutrition and Food Research*.

About one in four Canadians is obese, a chronic condition that is a leading cause of Type 2 diabetes. Insulin resistance in diabetic patients means their bodies are unable to properly remove glucose from the blood.

Those complications can arise when mitochondria, or the energy powerhouses in the body's cells, are unable to burn fatty acids completely.

Normally, fatty acid oxidation allows the body to burn fats. Obesity or diabetes hinders that process, leading to incomplete oxidation.

The U of G researchers discovered that avocatin B (AvoB), a fat molecule found only in avocados, counters incomplete oxidation in skeletal muscle and the pancreas to reduce insulin resistance.

In their study, the team fed mice high-fat diets for eight weeks to induce obesity and insulin resistance. For the next five weeks, they added AvoB to the high-fat diets of half of the mice.

The treated mice weighed significantly less than those in the control group, showing slower weight gain. More important, said Spagnuolo, the treated mice showed greater insulin sensitivity, meaning that their bodies were able to absorb and burn blood glucose and improve their response to insulin.

In a human clinical study, AvoB given as a dietary supplement to participants eating a typical western diet was absorbed safely into their blood without affecting the kidney, liver or skeletal muscle. The team also saw reductions in weight in human subjects, although Spagnuolo said the result was not statistically significant.

Having demonstrated its safety in humans, they plan to conduct clinical trials to test AvoB's efficacy in treating metabolic ailments in people.

Spagnuolo said the safety trial helped the team to determine just how much AvoB to include in the supplement formulation.

Having received Health Canada approval for the compound as a human supplement, he will begin selling it in powder and pill forms as soon as 2020 through SP Nutraceuticals Inc., a Burlington, Ont.-based natural health products company.

He said eating avocados alone would likely be ineffective, as the amount of natural avocatin B varies widely in the fruit and we still do not fully understand exactly how it is digested and absorbed when we consume a whole avocado.

Although avocados have been touted as a weight-loss food, Spagnuolo said more study is needed. He said a healthy diet and exercise are recommended to prevent metabolic disorders leading to obesity or diabetes.

PhD student Nawaz Ahmed, lead author of the paper, said, "We advocate healthy eating and exercise as solutions to the problem, but that's difficult for some people. We've known this for decades, and obesity and diabetes are still a significant health problem."

In earlier work funded by the Ontario Institute for Cancer Research, Spagnuolo has studied the potential use of avocatin B for treating acute myeloid leukemia.

http://bit.ly/2C6eJ5Q

Profiling the perpetrators of past plagues

The ancient pathogens in old graves are as dead as the people they once infected. Still, they tell a vivid tale.

By Tim Vernimmen

From the Black Death to the Spanish flu, waves of infectious disease have repeatedly laid waste to human populations. Scientists from many disciplines have long been intrigued by the possibility of disclosing the exact identity of the responsible pathogens and figuring out what made them so deadly.

Yet even after sequencing ancient DNA became possible, the omnipresence of microbes made it challenging to pinpoint the historical culprits.

New technology has now made it much easier and cheaper to sequence large amounts of DNA. And by tracking the damage that accumulates in genetic material as it ages, researchers have found ways to distinguish truly old DNA from that of modern contaminants, finally allowing them to identify the pathogens behind infamous scourges.

One of the pioneers of the field of microbial archaeology is geneticist Johannes Krause, founding director of the Max Planck Institute for the Science of Human History in Jena, Germany. Earlier this month, he published a paper in *Nature Communications* tracing the spread of the Black Death, which killed half the European population — 30 million to 50 million people — in less than five years, starting in 1347.

Krause and coauthors examine the challenges and revelations to be had in exploring ancient pathogens in recent issues of the *Annual Review of Microbiology* and the *Annual Review of Genomics and Human Genetics*.

Excavation of the Black Death cemetery in East Smithfield, London. This 14th-century pandemic killed tens of millions of people in Europe and Asia.
Mola / Getty Images

This interview has been edited for length and clarity.

The job of the average archaeologist, to uncover the ancient remains of humans and all of their artifacts, is hard enough. But how do you find microbes that infected people thousands of years ago?

We extract all the DNA we can get from those same human remains, often fossilized teeth or bone, and we sequence it. This allows us to distinguish human DNA from the DNA of the pathogens we're looking for, and then to try and reconstruct their genomes. This way, we are building a molecular fossil record that can tell us how pathogens have changed through time. And that provides important

information about the biology of the microbial villains that have caused major epidemics in the past.

Ancient DNA is often highly fragmented. How do you know which bits of the genome go where?

There are different ways of doing this. You can try to let the computer put the pieces together based on overlaps. But like a jigsaw puzzle, that can be challenging when pieces are missing. So that's when we need to look at the puzzle box, so to speak, and try to fit the fragments to the DNA of a modern relative instead.

Which means it is as good as impossible to discover a new species, or to recognize a species with genes that mutate very fast, as the sequences may have changed so much we have no idea what it is.

The first thing many people might think of when they hear the words "microbial" and "archaeology" in the same sentence is pathogens escaping from ancient graves, "curse of the pharaohs"-style. Is this something you need to take precautions for?

It is certainly something we thought about early on. There have been some studies, in the 1980s, where people tried to grow ancient bacteria or viruses. But nobody has been able to revive a pathogen that is more than a hundred years old, so I think it is very unlikely that this will happen.

There also is not a single case in which anybody got infected from an old skeleton, and there are thousands of archaeologists and anthropologists in the world handling ancient human bones on a daily basis. These people often don't use gloves, and some of them even touch tiny fragments with the tongue to find out whether the fragments are made of stone or bone — bone is a spongy material, so it will take up liquid from your tongue and stick to it.

The pathogens really appear to be as dead as the person is.

So the largest risk, in fact, may be the reverse: Ancient tissues of people who died from a disease you're interested in could be contaminated by other microbes that interfere with the analysis?

Yes. Microbial DNA is everywhere — ancient tissue samples usually contain up to 99 percent microbial DNA, much of it modern. With the older approaches, almost everything used to show up as positive for the bacteria causing tuberculosis, for example — even stones or plants. That is in part because many pathogens have harmless relatives that are not in our databases yet.

***A pamphlet published in 1625 describes the horror that an epidemic of the plague was wreaking on London. Forty thousand Londoners died during that visit by* Yersinia pestis*, and even more — perhaps 100,000 — during the Great Plague of 1665-1666, the last major plague epidemic that Britain saw. Although the 1666 Great Fire of London has been credited with putting an end to the country's plague episodes, the plague was already on the wane before the fire and the fire can't explain disappearance of the plague in other places.* Sheila Terry / Science Source**

So it is extremely important to make sure that DNA is indeed from the past. We have developed several approaches to do so, including one that looks at DNA damage. In 2011, we could show that the damage patterns in ancient bacterial DNA were identical to those we see in human DNA of the same age. That was the first time we could authenticate ancient bacterial DNA, and it changed the field. Now, if DNA does not have this damage, we don't believe it is old.

When deciding on the first pathogen to target using the brand new ancient DNA toolbox you developed, how did you choose, as the saying goes, between plague and cholera?

Our main motivation to study plague was that when we started this research, it wasn't really clear what had caused the Black Death. There was much discussion among historians on whether it was

some sort of virus, or a disease that is unknown today. An important advantage was that we had access to 50 bodies from the famous East Smithfield cemetery in London, which was used only during the Black Death pandemic, leaving little doubt what the people buried there had died from. In about half of these people, we could identify the plague bacterium *Yersinia pestis*. So that likely caused it.

Does your research also reveal where the Black Death may have come from, originally?

The oldest historical records are from a city called Kaffa in Crimea, a region that was often disputed in the past, as it is today. In the first half of the 14th century, it was a Genoese colony, besieged from the east by the Golden Horde. According to historians, the assailants ended up bombarding Kaffa with dead bodies, which may have spread the disease within the city. This forced the Genoese to retreat to Italy, bringing the plague to Europe, where it spread very quickly, killing half the population in only five years.

"The Black Death was sort of the Big Bang for the plague."

Maria Spyrou, now a postdoc in my lab, collected ancient *Yersinia pestis* samples from different parts of Europe, and one of the genomes she looked at was a 14th century strain from the Samara region in Russia, about 1,500 kilometers northeast of Crimea. When she added that strain to the *Yersinia* family tree, it turned out to be ancestral to the Black Death, corroborating the idea that the disease may have come from the east.

All the other genomes she got from the Black Death period, from many different places in Europe, are 100 percent identical, showing how fast it must have spread. And though the bacteria did change later on, the strain from that time appears to be the common ancestor of most of the strains in the world today. So the Black Death was sort of the Big Bang for the plague.

Interestingly, the genomes from that period don't have anything you don't find in daughter strains today, which means the Black Death is still around.

Does that mean these bacteria could still cause a similar epidemic today?

Theoretically, I think they still could, certainly in a context similar to medieval Europe. Even today, there are about 2,500 human cases every year, and most of them are from related strains. The bacteria that infected a few hundred people in Madagascar in 2017 were very similar in their biology to those that caused the Black Death.

Many viewed the Black Death as punishment from God. A sect called the flagellants flourished during this period — they would publicly whip themselves to atone in hopes of repelling the plague, as depicted in this 1493 woodcut. **World History Archive / Alamy Stock Photo**

Fortunately, we now have good antibiotics, because without treatment, 60 percent of people die of plague within seven to 10 days, and plague occurs in rodent populations almost all over the world. In the Grand Canyon, for example, there are signs saying you shouldn't touch the squirrels, because they carry *Yersinia pestis*. It really is a rodent disease — humans get infected only by accident. We don't live with as many rodents as we used to, and the black rat, which was once very common and lived almost like a mouse, inside people's houses, has since largely been replaced by the brown rat, which usually resides underground.

Last but not least, fleas have also nearly disappeared in many places thanks to improved hygiene. So I think these factors are probably more important than any genetic change in the bacteria — or in people.

In one of the reviews, you mention that a very close relative of *Yersinia pestis*, *Yersinia pseudotuberculosis* — which you initially used to piece together some of the early plague genomes — commonly occurs in the environment, including on "improperly washed" vegetables. Can your genetic analysis teach us why *pestis* is so dangerous and *pseudotuberculosis* is as good as harmless?

Yersinia pseudotuberculosis appears to be very bad at escaping the human immune system. There is no known case of it entering the blood, which is how *pestis* causes the tissue death that results in the black hands and feet that gave the Black Death its name.

Y. pseudotuberculosis also does not have the genes that are necessary for flea transmission. After a flea sucks blood from an individual infected with *Y. pestis*, the bacteria produce a biofilm that clogs the flea's gut, preventing it from swallowing any more blood.

So the flea is starving, and it starts biting hundreds of times a day, and every time it bites it brings the blood in contact with the biofilm, then spits it out again, transmitting the bacteria into the new bite mark. As *Yersinia pseudotuberculosis* does not have the genes to make this biofilm, it could not have been transmitted by flea bites.

Interestingly, we have recently found that *Yersinia pestis* bacteria from the Bronze Age and the Late Stone Age were missing some of those genes as well. They may instead have infected the lungs, and spread through the air, as some plague bacteria still do today. This is quite exciting: We are really starting to see how *Yersinia pestis* has emerged to become a dangerous human pathogen.

10.1146/knowable-102919-1

***Tim Vernimmen** (@timvernimmen) is a freelance science writer based near Antwerp, Belgium. He is not afraid of* Yersinia pseudotuberculosis *at all — in fact, he had some for breakfast this morning.*

http://bit.ly/2C6OOv9

Plants' Reaction to Rain is Close to Panic, Study Shows

***Complex chemical signals are triggered when water lands on a plant to help it prepare for the dangers of rain, according to a new study published in the* Proceedings of the National Academy of Sciences.**

In contrast to humans, plants cannot feel pain. However, so-called mechanical stimulation — rain, wind and physical impact from humans and animals — contributes to the activation of a plant's defense system at a biochemical level. This in turn triggers a stress hormone that, among other things, can lead to the strengthening of a plant's immune system.

"As to why plants would need to panic when it rains, strange as it sounds, rain is actually the leading cause of disease spreading between plants," said University of Western Australia's Professor Harvey Millar, co-author of the study. "When a raindrop splashes across a leaf, tiny droplets of water ricochet in all directions. These droplets can contain bacteria, viruses, or fungal spores."

"The sick leaves can act as a catapult and in turn spread smaller droplets with pathogens to plants several feet away. It is possible that the healthy plants close by want to protect themselves," added study lead author Dr. Olivier Van Aken, a biologist at Lund University.

In lab experiments, Dr. Van Aken, Professor Millar and their colleagues used a common plant spray bottle set on a soft spray. *Arabidopsis thaliana* plants were showered once from a distance of 6 inches (15 cm) after which the researchers noticed a chain reaction in the plant caused by a protein called Myc2.

"When Myc2 is activated, thousands of genes spring into action preparing the plant's defenses," Professor Millar explained. "These warning signals travel from leaf to leaf and induce a range of protective effects." "Our results show that plants are very sensitive

and do not need heavy rain to be affected and alerted at a biochemical level," Dr. Van Aken said.

The findings also suggest that when it rains, the same signals spreading across leaves are transmitted to nearby plants through the air. "One of the chemicals produced is a hormone called jasmonic acid that is used to send signals between plants," Professor Millar said.

"If a plant's neighbors have their defense mechanisms turned on, they are less likely to spread disease, so it's in their best interest for plants to spread the warning to nearby plants." "When danger occurs, plants are not able to move out of the way so instead they rely on complex signaling systems to protect themselves."

"It was clear plants had an intriguing relationship with water, with rain a major carrier of disease but also vital for a plant's survival," Professor Millar concluded.

Alex Van Moerkercke et al. *A MYC2/MYC3/MYC4-dependent transcription factor network regulates water spray-responsive gene expression and jasmonate levels.* PNAS, *published online October 29, 2019; doi: 10.1073/pnas.1911758116*

https://go.nature.com/2PHG4Dt

Measles erases immune 'memory' for other diseases

Results from tests of unvaccinated children and monkeys come as measles cases spike around the world.

Giorgia Guglielmi

Measles infections in children can wipe out the immune system's memory of other illnesses such as influenza, according to a pair of studies[1,2]. This can leave kids who recover from measles vulnerable to other pathogens that they might have been protected from before their bout with the virus.

The findings, published on 31 October in *Science* and *Science Immunology*, come at a time when measles cases are spiking around the world. Globally, there were more measles infections in the first six months of 2019 than in any year since 2006, according to the World Health Organization.

The studies highlight the importance of measles vaccinations, says Michael Mina, an infectious-disease immunologist at the Harvard T. H. Chan School of Public Health in Boston, Massachusetts, and a co-author of the *Science* paper.

The measles virus is highly contagious, and can lead to complications including pneumonia. And previous studies have suggested that the virus induces a kind of forgetfulness in the immune system, says Duane Wesemann, an immunologist at Brigham and Women's Hospital in Boston. When people get an infection, their immune system creates antibodies to fight it off. Once the body clears the infection, special immune cells remember that pathogen and help to mount a faster defence if the virus or bacterium invades again.

The *Science* study is the first to show definitive evidence that measles can destroy this immune memory, Mina says.

Inducing amnesia

Mina and his colleagues analysed blood samples from 77 unvaccinated children from 3 schools in the Netherlands, taken before and after a measles outbreak in 2013. The team also collected blood samples from 33 children before and after their first vaccination against measles, mumps and rubella (MMR). The researchers analysed the kids' antibodies using a test that measures the amount, and the strength, of antibodies against thousands of viral and bacterial substances.

Two months after the unvaccinated children recovered from measles, the team found that the virus had erased 11–73% of their antibodies against other bacteria and viruses. Although the reasons behind the high variability in antibody reduction are unclear, the finding shows that the virus alters previously acquired immune memory, Mina says. The kids who received the MMR vaccine showed no reduction in these antibodies.

Mina and his team also infected macaques with measles and monitored the animals' antibodies against other pathogens for five months. The monkeys lost 40–60% of their antibodies against previously-encountered pathogens, suggesting that the measles virus destroys otherwise-long-lived plasma cells in the bone marrow that can produce pathogen-specific antibodies for decades, Mina says.

Measles also seems to wipe out immune cells that 'remember' encounters with specific bacteria and viruses, according to a separate, independent team that published the *Science Immunology* study. When the scientists analysed blood samples from the same group of unvaccinated children in the *Science* study, the researchers found that those 'memory' cells had disappeared in the children who had contracted measles.

Unexpected protection

The findings emphasize how the MMR vaccine protects against more than just measles, says Velislava Petrova, an immunologist at the Wellcome Sanger Institute in Hinxton, UK, who led the *Science Immunology* study. It also prevents longer-term damage to the immune system that can lead to a resurgence of other diseases, she says.

It's possible to rebuild someone's suite of antibodies against specific bacteria and viruses by exposing them to those pathogens again, says Stephen Elledge, a geneticist at Harvard Medical School in Boston, and a co-author of the *Science* study. But some kids could develop life-threatening diseases as a result. "Every time you're infected with a virus, that's rolling the dice," he says.

As immunization rates drop in some countries because of anti-vaccine campaigns and infrastructure problems, the findings from the two studies could help officials to develop more effective vaccination policies, says Akiko Iwasaki, a viral immunologist at Yale University in New Haven, Connecticut. "For me, that would be making sure vaccination is mandatory for children in public schools," she says.

Clinicians could also consider giving people with measles a booster shot of vaccines they have previously received against other diseases, especially in regions where measles outbreaks are common, such as in sub-Saharan Africa, says Mina.

However various governments choose to address vaccinations, it's crucial that countries prevent measles outbreaks by maintaining high vaccination rates against the virus, Mina says. "We have to do our best to ensure that measles remains on the elimination radar."

doi: 10.1038/d41586-019-03324-7

References

1. Mina, M. et al. Science 366, 599–606 (2019). Google Scholar

2. Petrova, V. N. et al. Sci. Immunol. 4, eaay6125 (2019).

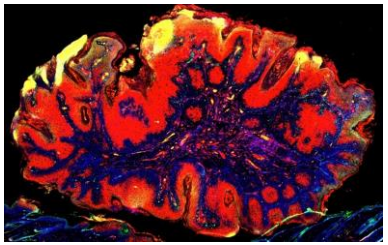
Google Scholar Download references

http://bit.ly/2JQ7ofq

A virus for good, not evil

HPV may protect the skin from some cancers.

A class of viruses commonly found on human skin – low-risk human papillomaviruses (HPV) – may play a role in protecting us from skin cancer, according to new research. And that would likely explain why multiple studies have failed to find a negative link between HPVs and cancers such as squamous cell carcinoma (SCC).



Early skin cancer that is colonised with a commensal papillomavirus looks like a wart to the immune system and is effectively eliminated. **Jon Messerschmidt**

Writing in the journal *Nature*, a team led by Shawn Demehri from Massachusetts General Hospital, US, reports finding that "commensal" papillomaviruses – low-risk forms of HPV – appear to have an indirect protective rather than harmful effects against SCC. This, they say, suggests a novel method for preventing skin

cancer using a vaccine based on T cells – the essential immune-system cells that identify other cells as abnormal or foreign and mark them for destruction.

http://bit.ly/2NBfObn

Here's what happens when you leave marijuana up your nose for 18 years

The man thought he had swallowed it. But he hadn't.

Beth Mole

Nose pickers are often said to be digging for gold. But a 48-year-old Australian man needed an entirely different kind of nugget mined from his schnoz.

Doctors excavated from the man's right nasal cavity a 19mm×11mm rock-hard mass—the calcified remains of a small amount of marijuana he tried to smuggle into prison a startling 18 years earlier.

The man's nose stone—reported this month in the journal BMJ Case Reports—is a rare example of illicit drugs causing a rhinolith, which are rare on their own. Rhinoliths are stone-like concretions formed by the gradual buildup of salts around things not normally found in the nose. The term rhinolith comes from the Greek *rhino* (meaning nose) and *lithos* (meaning stone). They're estimated to show up in 1 out of 10,000 outpatient visits to an ear, nose, and throat doctor.

Thus, medical records of rhinoliths are sparse but go back as far as 1654. When they have shown up, doctors have found them forming around a wide range of objects. Those include bodily objects (like randomly located teeth, bone fragments, blood clots, and hardened boogers) as well as foreign objects (like seeds, beads, and buttons), which are things often shoved up a nose by a toddler.

The team of doctors reporting the pot smuggler's rhinolith note that there only appears to be one other case of a rhinolith formed from illicit drugs. It was a case from 2007 of a 21-year-old man who came to have a hardened mixture of codeine and opium wrapped in a nylon sheet up his nose for several years.

Chronic pain

In the new case, the small amount of marijuana at the center of it all was a gift to the man from his girlfriend, who presented it to him during a prison visit. To smuggle the dope gift past the guards, the man stuffed the weed—wrapped in a rubber balloon—up his nose. The trick worked, but when he went to retrieve his snotty stash, he accidentally pushed it farther into his nasal cavity. Unable to get it out, he mistakenly came to believe he had swallowed it and eventually forgot about it.

Through the years he suffered recurring sinus infections and had trouble breathing out of the right side of his nose. But he didn't connect the problems to his lost cannabis. It wasn't until 18 years later—when he was struggling with headaches and had a CT scan of his brain—that doctors finally discovered the petrified pot.

Doctors promptly removed the firm wad and dissected it. They reported finding "a 'rubber capsule' containing degenerate vegetable/plant matter" inside. After the doctors asked some obvious follow-up questions, the man finally remembered the nasal smuggling nearly two decades earlier. Three months later, the man reported that his sinus problems had completely resolved.

BMJ Case Reports, 2019. DOI: 10.1136/bcr-2019-231989 (About DOIs).

http://bit.ly/33qW5EC

What Turned This Woman's Pee a Striking Shade of Lilac?

A relatively rare chemical reaction can turn people's pee purple.

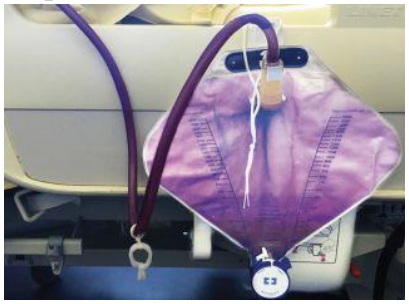
By Nicoletta Lanese - Staff Writer

A woman who was hospitalized after having a stroke surprised doctors when, 10 days after being admitted, her pee turned purple.

Turns out, an unusual chemical reaction can transform urine from its usual yellow to a striking lilac. The bizarre phenomenon,

described in a case report published today (Oct. 30) in the New England Journal of Medicine, may be fairly rare, but doctors have witnessed the anomaly enough times to give it a name, albeit not a very creative one.

"Purple urinary bag syndrome," or PUBS, first appeared in the medical literature back in 1978 and crops up in the occasional patient to this day, according to a 2013 review in the journal Annals of Long-Term Care. The prevalence of PUBS is unknown, but its appearance can be blamed on a combination of bacteria and tryptophan — that sleep-regulating chemical famously found in turkey.



A woman's pee turned purple due to a peculiar chemical reaction. **(Image: © The New England Journal of Medicine 2019)**

PUBS usually manifests as a side effect of using a urinary catheter for an extended period, as a patient might during a hospital stay, according to a 2018 review in the journal BMJ Case Reports. Catheters, constructed from a tube and an attached bag, can be inserted to drain the bladder when patients can't do so themselves. In the case of the woman admitted to the Hôpital de Bicêtre in Le Kremlin Bicêtre, France, she had a catheter placed inserted because a stroke had left half her body weak and stiff.

When the patient's urinary bag took on the color of an eggplant, the doctors tested her pee for signs of suspicious bacteria. They found *Klebsiella pneumoniae*, a type of bacteria normally found in the human gut that can cause infections when relocated to other areas of the body, according to the Centers for Disease Control and Prevention. As these bacteria grew, the woman delivered tryptophan to the gut, as she was eating foods rich in the chemical, according to the report. As its processed by the gut and liver, tryptophan gets broken down into a chemical called "indoxyl sulfate," a key ingredient for purple pee.

Once expelled, the *Klebsiella pneumoniae* and indoxyl sulfate mix in the urinary bag. There, the bacteria split indoxyl sulfate into two new chemicals: One part red, one part blue. Together, the chemicals mix to make purple. Mystery solved!

Usually, purple pee signals that a patient may have a urinary tract infection, according to a 2011 article in the Canadian Urological Association Journal. This was not the case with the French patient, her doctors noted; luckily, the patient's pee returned to its normal color after she was treated with intravenous hydration for a few days. The patient was then transferred to a long-term care facility, where doctors continued to treat the lingering effects of her stroke, her physicians reported.

https://nyti.ms/36tkUiu

How Contaminated Stool Stored in a Freezer Left a Fecal Transplant Patient Dead

Doctors detail the missteps that led to the death of a cancer patient who received a fecal transplant

By Andrew Jacobs

In a frank and public act of self-examination, a group of doctors at Massachusetts General Hospital published an article Wednesday in the New England Journal of Medicine detailing the missteps that led to the death of a cancer patient who received a fecal transplant as part of an experimental trial. The man who died, and another who became severely ill, had received fecal matter from a donor whose stool turned out to contain a type of E. coli bacteria that was resistant to multiple antibiotics.

The death shook the emerging field of fecal microbiota transplants, or F.M.T., a revolutionary procedure that transfers feces from healthy donors to the bowels of sick patients in an effort to restore

their microbiome, the community of beneficial bacteria and other organisms that dwell in the intestines.

Fecal microbiota transplants remain unapproved by the Food and Drug Administration, but the treatment has proved highly effective in combating a deadly bacterial infection known as Clostridium difficile, which kills thousands of Americans annually. Researchers have also been exploring its use for conditions ranging from Alzheimers to autism.

Dr. Elizabeth L. Hohmann, the lead author of the article and an infectious disease specialist who oversees fecal transplant trials at Mass General, expressed remorse over her lab's failure to test stool from a donor that had been stored in a freezer for several months.

"It's been professionally very challenging," she said in an interview. "But this is a cautionary tale about the risks of cutting edge projects."

After doctors reported the incidents to the F.D.A., the agency issued a nationwide alert to health care providers and patients about the risks of the procedure and urged researchers to suspend fecal transplants until labs could safely screen for drug-resistant microbes. Many projects have since resumed.

The patients at Mass General fell ill from E. coli bacteria that produced an enzyme called extended-spectrum beta-lactamase, which made the bacteria resistant to multiple antibiotics. The bacteria are often harmless in healthy people but can wreak havoc on those with compromised immune systems.

The New England Journal article provided a detailed, up-close look at how doctors at Mass General administered encapsulated stool from a donor whose feces had been successfully used to treat scores of patients with C. diff, a debilitating bacterial infection that tends to strike hospitalized patients who have been treated with multiple rounds of antibiotics.

Doctors at Mass General had been testing stool donations for a multitude of infectious bugs, following F.D.A. protocols. In January, the agency tightened the screening standards to include a number of emergent organisms like the drug-resistant strain of E. coli.

The problem, Dr. Hohmann said, was that the F.D.A. did not instruct doctors to test or destroy older material kept in storage. "It wasn't obvious to a lot of smart people here," she said. "We didn't think to go back in time."

The patients sickened by the compromised feces were participating in two separate experimental trials last spring. One patient, a 69-year-old man with end-stage liver disease, received capsules over the course of three weeks. The other, a 73-year-old man with a rare blood cancer, was given the capsules before undergoing a bone marrow transplant. Both men had also been administered antibiotics.

The men turned feverish soon afterward. The liver patient developed pneumonia that tests later determined was caused by the drug-resistant E. coli strain. He was treated with a powerful antibiotic and eventually recovered.

The cancer patient, who had taken drugs to suppress his immune system as part of the bone marrow transplant, declined more precipitously. Eight days after his last F.M.T. dose, he was placed on a ventilator. He died two days later from a severe bloodstream infection.

Genomic sequencing tests later confirmed that the organisms came from the same donor. Looking back at their actions, the doctors acknowledged in the article that the decision to give both men antibiotics before their fecal transplants might have provided an opportunity for the drug-resistant E. coli strain to thrive.

"We've been going through a lot of 20-20 hindsight here," Dr. Hohmann said.

The incident prompted widespread angst among patients and practitioners in the rapidly evolving field of fecal microbiota transplantation.

Dr. Ari Grinspan, a gastroenterologist at Mt. Sinai Hospital in New York who helped pioneer fecal transplants for C. diff, said he received a flood of panicked calls and emails from former patients who thought they might have received compromised stool.

“What happened was horrific, but it’s reminded us that we have to be vigilant about screening protocols,” he said.

The cases have also heightened tensions that have pitted doctors who perform fecal transplants against drug companies that are developing new microbiota therapies derived from human stool. Those companies have been pressing the F.D.A. to more tightly regulate the procedure as a new drug, which some doctors and patient advocates fear would give companies proprietary control over the active ingredients in transplanted feces.

The F.D.A. will hold a public hearing next week in Washington to better understand the risks and benefits of the therapy. For now, the agency allows fecal transplants for C. diff patients who have not responded to standard therapies, an approach known as enforcement discretion.

In a statement yesterday, the agency said: “The F.D.A. would like to clarify that the use of FMT to treat C. difficile remains investigational at this time and the efficacy and safety of this intervention have not yet been established.”

Unlike Mass General, which produces its own fecal transplant material, most of the treatments used by doctors in the United States come from OpenBiome, a nonprofit stool bank in Cambridge, Mass., that has provided 50,000 doses in recent years without any reported serious adverse events related to the material, according to Carolyn Edelstein, the executive director.

OpenBiome has been testing donors for the drug-resistant strain of E. coli since 2016, she said, adding that fewer than three percent of prospective donors make it through the rigorous screening.

In an era of mounting antimicrobial resistance, many doctors said the incident underscored the challenges presented by organisms that are constantly evolving in their effort to survive the onslaught of antibiotics used in medicine and agriculture. Dr. Alexander Khoruts, a gastroenterologist at the University of Minnesota, said his lab had also been testing for the E. coli strain, but there is always a fear a newly virulent bug will slip through the screening process.

“This is a potential issue that could even be existential and we need to address it head on and always be ahead of the game,” said Dr. Khoruts.

http://bit.ly/36uuSQF

Emotional trauma and fear most likely cause of 'Havana Syndrome'

'Havana Syndrome' is more akin to shell shock

The cause of the mystery illness among US and Canadian diplomats in Havana is most likely to be emotional trauma and fear according to a leading sociologist and an expert in neurodegenerative diseases, writing in the *Journal of the Royal Society of Medicine*.

Concussion-like symptoms, including headaches, dizziness, nausea and fatigue, were initially reported among dozens of US embassy staff between late 2016 and June 2018. They were described by the US State Department as 'medically confirmed symptoms' and government physicians suspected the involvement of a sonic device. Studies on the embassy patients, however, have been inconclusive and contradictory. A similar array of symptoms was reported in over two dozen Canadian diplomats during this same period.

The paper's lead author, Dr Robert Bartholomew, concludes that 'Havana Syndrome' is more akin to shell shock, with the symptoms paralleling those associated with war trauma. "A characteristic

feature of combat syndromes over the past century is the appearance of an array of neurological complaints from an overstimulated nervous system that are commonly misdiagnosed as concussions and brain damage", he writes. He adds: "A signature feature of shell shock was concussion-like symptoms. Like today, their appearance initially baffled physicians until a more careful review of the data determined that what they were seeing was an epidemic of psychogenic illness. In fact, some of the descriptions from 100 years ago are virtually identical, right down to the use of the phrase 'concussion-like symptoms'."

Dr Bartholomew is a medical sociologist based in Auckland, New Zealand. The report was co-authored by Dr Robert W. Baloh, Director of the Neurotology Laboratory at the UCLA Medical Center. The authors describe the diplomats who became sick as participants in a continuation of the Cold War, living in a hostile foreign country where they were under constant surveillance. Between late 2016 and 2017, staff in Havana were living in a cauldron of stress and uncertainty, amid rumours of an enigmatic sonic weapon.

"The political and scientific evidence for the perpetration of an attack on US embassy staff in Cuba is inconclusive," they write. "What is the more likely, that the diplomats were the target of a mysterious new weapon for which there is no concrete evidence, or they were suffering from psychogenic symptoms generated by stress? The evidence overwhelmingly points to the latter."

They add: "There have been four separate studies of 'Havana Syndrome' to date. Each have critical design flaws including the use of inappropriate controls, inflated conclusions, and a lack of evidence for exposure to an energy source or toxin. None adequately test the hypotheses they propose, while promoting exotic explanations that are not supported by the facts. Our conclusions are grounded in the prosaic and known science. There is no need to resort to exotic explanations. Claims that the patients were suffering from brain and auditory damage are not borne out by the data."

Notes to editors

Challenging the diagnosis of 'Havana Syndrome' as a novel clinical entity

(DOI: 10.1177/0141076819877553), by Robert E Bartholomew and Robert W Baloh, will be published by the Journal of the Royal Society of Medicine *at 00:05 hrs (UK time) on Friday 1 November 2019.*

https://journals.sagepub.com/doi/full/10.1177/0141076819877553

http://bit.ly/2NhuwWd

Fishery in Lake Shinji, Japan, collapsed 1 year after neonicotinoid use

Neonicotinoid pesticide use may have caused the abrupt collapse of two commercial fisheries on Lake Shinji, Japan, in 1993, according to a new study.

日本のニュース

While the negative impacts of the world's most widely used insecticide on pollinator species are well known, these results highlight new and potential indirect effects on other organisms, including vertebrates.

Using more than two decades of data on lake chemistry, biology and fishery yields, Masumi Yamamuro and colleagues tracked the impacts of neonicotinoids through the aquatic food chain of Lake Shinji - from zooplankton to the commercially harvested species of smelt and eel.

Yamamuro et al.'s analysis revealed that the very first application of neonicotinoid pesticides in 1993 coincided with an 83% decrease in average springtime zooplankton biomass, which was shortly followed by a complete collapse of the fisheries of the species that feed on them. The smelt harvest alone collapsed from 240 tons per year to 22 tons in a single year after the first use of neonicotinoids.

According to the authors, neonicotinoid pesticides indirectly reduced Lake Shinji's fishery yields by decreasing the abundance of

invertebrates that serve as food for smelt and eels. What's more, the results show that the precipitous decline in zooplankton could not be explained by other confounding factors, such as nutrient depletion or changes in salinity or oxygen concentration.

Yamamuro et al. argue that nationwide decreases in fishery yields in other lakes of Japan during this time were likely also due to food web disruption from pesticide use. Since neonicotinoids are the most widely used pesticide, similar dynamics are likely playing out in bodies of water around the world, the authors say.

"Yamamuro et al.'s study, though observational, presents compelling evidence from more than a decade of data both before and after neonicotinoid insecticides were introduced to this region," writes Olaf Jensen in a related Perspective.

http://bit.ly/2qg3q8P

Common early sign of cardiovascular disease also may indicate cancer risk, study finds

Microvascular endothelial dysfunction, a common early sign of cardiovascular disease, is associated with a greater risk of cancer

ROCHESTER, Minn. -- A Mayo Clinic-led study involving 488 cardiac patients whose cases were followed for up to 12 years finds that microvascular endothelial dysfunction, a common early sign of cardiovascular disease, is associated with a greater than twofold risk of cancer.

The study, published in the European Journal of Preventive Cardiology, finds that microvascular endothelial dysfunction may be a useful marker for predicting risk of solid-tumor cancer, in addition to its known ability to predict more advanced cardiovascular disease, says Amir Lerman, M.D., a Mayo Clinic cardiologist and the study's senior author.

"The study demonstrated that noninvasive vascular function assessment may predict the future development of cancer," says Dr. Lerman, who is director of cardiovascular research at Mayo Clinic. "More studies are needed, but assessment of vascular function potentially may predict individuals at risk."

Microvascular endothelial dysfunction involves damage to the walls of small arteries in the heart, which affects their ability to expand and limits the flow of oxygen-rich blood. Hypertension, high cholesterol, obesity and diabetes are among the causes, and symptoms of dysfunction include chest pain. The condition is treatable but difficult to detect.

The study reviewed the cases of 488 patients who underwent microvascular endothelial function assessment at Mayo Clinic between 2006 and 2014. The noninvasive procedure, called reactive hyperemia peripheral arterial tonometry, measures blood flow to the fingers during blood pressure inflation and release.

Dysfunction was defined as a tonometry index at or below 2, and the median follow-up period was six years. Of 221 patients identified as having dysfunction, 9.5% were diagnosed with solid-tumor cancer during the follow-up period. This compared with 3.7% of patients who had a tonometry index above 2. The findings were consistent after adjusting for age, gender, coronary artery disease and other factors.

The association between microvascular endothelial dysfunction and cancer was independent but more prominent among men and in patients with factors such as hypertension, significant coronary artery disease, smoking and obesity.

"This abnormal vasoreactivity should alert clinicians not only to the risk of cardiovascular disease but to malignancy, as well," Dr. Lerman says. "This risk prediction appears to precede the development of disease by more than five years."

Patients with microvascular endothelial dysfunction tend to have other health issues, as well, and that may have drawn more medical attention to these patients, resulting in higher levels of incidental detection of cancer, according to the study. Whether improvement

in dysfunction translates into a reduced risk of cardiovascular disease and cancer remains to be determined.

"Similarly, the mechanism underlying the association between microvascular endothelial dysfunction and cancer needs to be defined in future studies," Dr. Lerman says.

http://bit.ly/2PLssr4

We Owe Our Pumpkins to Pooping Megafauna

The pumpkin's ancestor was an incredibly bitter, tennis-ball-sized squash—but it was apparently a common snack for mastodons.

Christopher Intagliata reports.

Listen Here

This Halloween, as you carve jack-o-lanterns and make pumpkin pie, take a moment to appreciate just how far the humble pumpkin has come. "The wild form of a pumpkin looks like a tennis ball and it tastes like one. It's incredibly bitter, it's got a really hard rind, and it's incredibly unpalatable to humans."

Logan Kistler, an archaeologist at the Smithsonian's National Museum of Natural History. He says, as unpalatable as those early squashes were, they made a tasty tidbit for *mastodons*. "And we know that because there are deposits of mastodon dung in Florida that are over 30 thousand years old. And so in those mastodon dung deposits, sure enough what we can find are wild squash seeds."

Kistler says mastodons probably weren't put off by the gourds' bitter taste. Because a few years back, his team analyzed the genomes of more than 40 mammals. And they found that the *larger* the animal, the *fewer* copies of a bitter-taste-perception gene they tended to have.

"Turns out there's this absolutely beautiful correlation between body size and the ability to taste bitter compounds. So what we think is going on, is that these are really plants adapted to a landscape with large herbivores. They evolved this bitter toxicity in order to deter small mammals who would destroy the seeds, but they've evolved it at just the right level where large mammals are not put off by the bitterness and they can disperse the seeds."

Through their poop.

Kistler reported those findings in the *Proceedings of the National Academy of Sciences* in 2015. [Logan Kistler et al, Gourds and squashes (Cucurbita spp.) adapted to megafaunal extinction and ecological anachronism through domestication]

Along with dispersing seeds, mastodons, like modern elephants, probably stomped around a lot and vacuumed up vegetation—creating the sort of disturbed environments where squash plants thrive. So it was a beneficial match.

But then, of course, the mastodons died out. And humans, Kistler says, which also tend to disturb the environments around them, creating great squash habitat—may have taken the mastodon's place.

The details are murky. "The way that the domestication of squashes started is still a little bit of a mystery. Because they're bitter and toxic in the wild and they get to this place of palatability."

Perhaps, he says, humans grew the gourds first to use them as storage vessels…and later tamed the bitterness. Either way, squash seeds, stems and rinds discovered in a cave in Oaxaca, Mexico provide evidence that, at least 10,000 years ago, ancient people had already begun domesticating a squash that would, eventually, carve a place for itself as our modern pumpkin.

https://wb.md/2NCjYj7

Bedtime Dosing of Hypertension Meds Reduces CV Events

Taking antihypertensive medication at bedtime led to an almost halving of cardiovascular events in a new study.

Sue Hughes

The Hygia Chronotherapy Trial is the largest ever study to investigate the effect of the time of day when people take their antihypertensive medication on the risk of cardiovascular events.

The trial randomly assigned 19,084 patients to take their medication on waking or at bedtime and followed them for an average of 6 years.

Results showed that patients who took their pills at bedtime had a 45% reduction in overall cardiovascular events. This included a 56% reduction in cardiovascular death, a 34% reduction in myocardial infarction (MI), a 40% reduction in coronary revascularization, a 42% reduction in heart failure, and a 49% reduction in stroke, all of which were statistically significant.

"Our recommendations are that guidelines should consider including sleep-time blood pressure for the diagnosis of hypertension, and antihypertensive treatment should be taken at night," lead author, Ramon C. Hermida, PhD, University of Vigo, Spain, told *Medscape Medical News*.

"This appears to be particularly important for patients taking ACE inhibitors and ARBs [angiotensin receptor blockers] for which we found a larger benefit with bedtime dosing." The study was published online in the *European Heart Journal* on October 22.

Hermida and colleagues have been working on chronobiology — using biological rhythms to increase the diagnosis, treatment response, and prevention of diseases — for the last three decades.

"In hypertension, it is logical to think about when patients take medication as blood pressure changes around the clock in symmetry with the rest/activity cycle," Hermida explained. "Many factors are involved with this variability including the renin angiotensin system being most active in the second half of sleep leading to a peak of aldosterone before waking. This led to us to believe that antihypertensive medication may be more effective when taken at night before sleep."

The group published a study last year showing that blood pressure (BP) during sleep was the major determinant of cardiovascular morbidity and mortality.

"We showed that if blood pressure is elevated during sleep then patients have increased cardiovascular risk regardless of daytime pressure, and if blood pressure during sleep is normal then cardiovascular risk is low even if the [doctor's] office pressure is elevated," Hermida said.

The current study was conducted in primary care, with all patients having hypertension confirmed by 48-hour ambulatory BP measurement on recruitment. Doctors then assigned patients to take their medication in the evening at bedtime or in the morning upon waking.

The trial was a multicenter, controlled PROBE (prospective, randomized, open-label, blinded end point) study. Patients were allocated in a 1:1 ratio into two parallel arms defined according to the circadian time of treatment, the researchers note.

Individual doctors could choose which specific medication or combinations to use from the major therapeutic classes — ARB, ACE inhibitor, calcium blocker, beta-blocker, or diuretic. Ambulatory BP was checked over 48 hours at least once a year throughout the study and more often if medication was altered.

The two groups were well balanced at baseline in terms of comorbidities, other cardiovascular medications, and all evaluated anthropometric and clinical laboratory test variables. BP measurements were also similar in the two groups.

At the conclusion of the study, the number of prescribed hypertension medications (usually each at maximum doses) was slightly but significantly lower in the bedtime-treatment regimen. The most frequently prescribed monotherapies were ARBs or ACE inhibitors (69% of participants).

At the final evaluation, BP values were significantly lower during sleep but not during awake time in the bedtime medication group.

Results showed that during the 6.3-year median patient follow-up, 1752 participants experienced the primary cardiovascular disease

(CVD) outcome (a composite of CVD death, MI, coronary revascularization, heart failure, or stroke).

After adjusting for age, sex, type 2 diabetes, chronic kidney disease, smoking, HDL cholesterol, mean asleep systolic BP, sleep-time relative systolic BP decline, and previous CVD event, patients taking their medication at bedtime showed a significantly lower risk of having primary CVD outcome (hazard ratio, 0.55; $P < .001$).

Hazard ratios for the individual components were CVD death 0.44; MI 0.66; coronary revascularization 0.60; heart failure 0.58; and stroke 0.51 (all $P < .001$).

Hermida noted that the reductions on cardiovascular events with bedtime dosing were seen with all the different classes of antihypertensive drugs used but a larger effect occurred with ACE inhibitors and ARBs. "This is relevant because of the activation of the renin angiotensin system at night," he said.

Did Ambulatory Monitoring Play a Role?

Hermida believes that in addition to the bedtime dosing, the impressive reductions in cardiovascular events may have been brought about by selection of patients with "true" hypertension detected by ambulatory monitoring.

"Ambulatory blood pressure measurement is another key part of our study," he said. "Patients who have elevated blood pressure at night may be missed if we just rely on office blood pressures. And we required periodic reevaluation by ambulatory BP monitoring to ensure that patients were not developing hypotension at night, which can be a risk factor for stroke."

The researchers report that only 39 patients in the waking group and 26 patients in the bedtime group (0.3% of all participants; $P = .114$ between groups) experienced sleep-time hypotension, defined by current ABPM criteria, at any time during follow-up.

In addition, there were no differences in the prevalence of patients reporting any type of adverse effects at any visit during follow-up (6.7% vs 6.0% for the awakening and bedtime-treatment regimen, respectively; $P = .061$).

While acknowledging that most primary care doctors do not currently have access to ambulatory BP monitoring, Hermida said: "We conducted this study in general practice and showed that with proper collaboration we can introduce ambulatory monitoring as the primary method of measuring blood pressure."

"However even in the absence of ambulatory monitoring I would say the benefits of bedtime administration would outweigh the potential adverse effects."

"While it is not my place to make clinical practice recommendations, and every individual doctor needs to make their own decision for each patient, our results suggest that changing the timing of antihypertensive medication to bedtime administration should translate into a significant reduction in cardiovascular events," he concluded.

Findings Very Clear

Commenting on the study for *Medscape Medical News*, Michael A. Weber, MD, professor of medicine at the State University of New York and editor-in-chief of the *Journal of Clinical Hypertension*, pointed out that the trial was open label, "so not as influential as a true blinded trial, but its patient numbers are large and its findings very clear."

Weber noted that previously two influential outcomes studies — HOPE and Syst Eur — showed strong cardiovascular outcomes benefits when patients were treated with nighttime dosing, but this dosing was not compared with daytime dosing. And a meta-analysis by Roush and colleagues showed significantly better outcomes with nighttime dosing than with morning dosing of hypertensive patients, "which adds further credibility to this new report," he said.

Weber added that guidelines or drug labeling have not shown a preference for morning or nighttime dosing, but some physicians

may advise nighttime dosing because drugs might be better tolerated when taken in the evening since the maximum blood concentrations of the drugs would occur while patients are asleep.

"Since nocturnal blood pressure is more closely associated with cardiovascular outcomes than daytime blood pressure, it does appear reasonable that nighttime administration leading to better nighttime blood pressure control might optimize outcomes," Weber commented. "This appears to have been the case in this new study because the nighttime blood pressures were definitely reduced more than the daytime blood pressures."

"Another explanation for the advantage of nighttime drug administration is that patients might be better adherent to their therapy when taking it at night. We need more information to better explore this possibility," he added.

The Hygia Project is an independent investigator-promoted research network supported by unrestricted grants from the Spanish and Galician regional governments, and the University of Vigo. The researchers have disclosed no relevant financial relationships.

Eur Heart J. 2019;ehz754. Full text

http://bit.ly/2oPxtDW

Low blood oxygen strongly increases sick children's risk of death

Low blood oxygen is more common in sick children than previously thought, and strongly increases children's risk of death, Australian-led research has found.

Murdoch Children's Research Institute paediatrician Dr Hamish Graham led the international research project, published in the Lancet's EClinicalMedicine.

Dr Graham said he hoped the findings would encourage policy makers and health care workers in other low and middle income countries, especially in Africa, to increase the use of oxygen measuring tools and oxygen therapy. Dr Graham worked with colleagues in Nigeria to record the blood oxygen levels of more than 23,000 children admitted to 12 medium-sized hospitals.

"Your blood oxygen level is the amount of oxygen carried by red blood cells from the lungs to rest of the body - low blood oxygen damages cells and can lead to death," Dr Graham said.

"Our study found that one in four newborns and one in 10 children in hospital had low blood oxygen, and these children were eight times more likely to die than those with normal blood oxygen."

Dr Graham's study is the largest report of low blood oxygen levels in children and shows that it is common not only in pneumonia, but also in many other conditions. "Low blood oxygen is particularly common in newborn infants, especially those who are premature or have very difficult births," he said.

Dr Graham said pulse oximeters, which accurately measure blood oxygen levels, are widely used in Australia. But hospitals in low- and middle-income countries are not often equipped with good quality devices, which cost about USD250.

"Our modellings suggest that better use of oxygen monitoring and therapy in the 12 highest mortality countries in the world could prevent up to 148,000 child pneumonia deaths annually," he said. "Our study also suggests there are thousands more children and neonates with illnesses besides pneumonia that could also benefit."

University of Melbourne's Centre for International Child Health is leading the implementation of solar powered oxygen delivery systems in district hospitals in Papua New Guinea and Nigeria.

Dr Graham said that training nurses to measure and supply oxygen were simple technologies that could save hundreds of thousands of children's lives. "In sub-Sahara Nigeria, one in 10 children dies before their fifth birthday and the biggest killer of Nigerian children is pneumonia. Nigerian children make up one sixth of under-five pneumonia deaths globally. The first step to preventing these deaths is detecting low blood oxygen," Dr Graham said.

Researchers from the University College Hospital in Nigeria, University of Melbourne, The Royal Children's Hospital, University of Ibadan in Nigeria, Ashdown Consultants in

the UK, World Health Organization in Switzerland and the Bill and Melinda Gates Foundation in the US also contributed to the findings.
Publication: Hamish Graham, Ayobami A. Bakare, Adejumoke I. Ayede, Oladapo B. Oyewole, Amy Gray, David Peel, Barbara McPake, Eleanor Neal, Shamim A. Qazi, Rasa Izadnegahdar, Trevor Duke and Adegoke G. Falade. 'Hypoxaemia in hospitalised children and neonates: A prospective cohort study in Nigerian secondary-level hospitals,' ECLINICALMEDICINE. *DOI: 10.1016/j.eclinm.2019.10.009*

http://bit.ly/2C9q8IX

Quality over quantity! Interval walking training improves fitness and health in elderly individuals

It's not how much you walk, but how intensely you do so for a minimum amount of time to get positive results

In Japan, health-conscious folks have been known to carry around pedometers to track the number of steps they walk everyday. The target number: 10,000 steps, as a foundation for a healthy lifestyle. Conscientious walkers can now update their device from a pedometer to a smartphone and forget about ten thousand steps with the latest study from Dr. Shizue Masuki of Shinshu University who found an effective way to increase overall fitness and decrease lifestyle-related disease (LSD) through Interval Walking Training (IWT). It's not how much you walk, but how intensely you do so for a minimum amount of time to get positive results. This finding may be welcome news for those who want to save time and get the most out of their workout.

Interval Walking Training is the method of walking at 70% of the walker's maximum capacity for 3 minutes, then at 40% of their capacity for the next 3 minutes. This is continued for 5 or more sets. Dr. Masuki studied a group of 679 participants with a medium age of 65 over the course of 5 months. Every two weeks data was collected from participants at a local community office and via the internet through the data measuring device (triaxial accelerometer). The triaxial accelerometer is a device that beeped to let the walker know when they were at least 70% of their peak aerobic capacity (VO_2peak), and at 3 minutes to switch. It recorded their walking data to the central server at the administrative center for automatic analysis.

VO_2peak is the amount (volume) of oxygen (O_2) the body is able to use during physical activity. It is the milliliters of oxygen used by kilogram of body weight per minute. It is determined by measuring the concentration of oxygen and carbon dioxide in the participants breath. When the VO_2 number reaches a figure and plateaus during intense exercise, that is the maximum amount of oxygen the person is able to utilize, and is an indicator of fitness. The higher the number, the more they are able to use, and the more intensely they can exert their body. Endurance athletes such as cyclists can have VO_2peak in the 70s.

Dr Masuki found that her method outperformed the recommendation of the American Heart Association that to achieve peak oxygen capacity 75 minutes a week of high-intensity workout is needed for improvement. Participants in Dr Masuki's study had significant improvements in their aerobic capacity (VO_2peak), with 50 minutes of IWT a week. Improvements to their VO_2peak were plateaued above 50 minutes a week.

With the study published in the Mayo Clinic Proceedings, Dr. Masuki's participants achieved a 14% increase in VO_2peak and a 17% decrease in lifestyle-related disease (LSD) through IWT. This method is highly desirable due to an ease of maintenance. Many participants remained highly motivated and went beyond their prescribed regimen and does not require expensive equipment to administer.

Dr Masuki developed an app to help with the IWT with the PR firm, Gram3.
Dr Masuki was interviewed by SBC television regarding her research.
https://www.shinshu-u.ac.jp/guidance/media/movie/2019/10/22019.html
What a great way to decrease healthcare costs of the elderly through simple, no-cost training activities with a motivating app.

http://bit.ly/2rdlWPB

Secrets in the Brains of People Who Have Committed Murder

MRI scans from more than 800 incarcerated men pinpoint distinct structural features of people who have committed homicide, compared with those who carried out other crimes.

Nicoletta Lanese

Kent Kiehl and his research team regularly park their long, white trailer just outside the doors of maximum-security prisons across the US. Inside the vehicle sits the bulky body of a mobile MRI machine. During each visit, people from the prison make their way to and from the vehicle in hourly shifts to have their brains scanned and help to answer an age-old question: What makes a murderer?

"It's not an uncommon thing for [incarcerated people], while they're getting a scan, to be like, 'I've always been different. Can you tell me why I've always been so different?'" says Kiehl, a neuroscientist at the University of New Mexico and the Albuquerque-based nonprofit Mind Research Network (MRN) who helped design the mobile MRI system back in the early 2000s.

The author of *The Psychopath Whisperer: The Science of Those Without a Conscience*, Kiehl has been fascinated by the criminal mind since he was an undergraduate at the University of California, Davis. Now, as director of mobile imaging at MRN, he oversees efforts to gather brain scans from thousands of people held in US prisons to learn what features, if any, might differ from scans of the general population.

This massive dataset recently allowed Kiehl to examine the brain structures of more than 800 men held in state prisons in New Mexico and Wisconsin in an attempt to distinguish incarcerated people who have committed homicide from those who have committed other crimes.

First, Kiehl and his colleagues laboriously sorted the pool of people who had volunteered for the study into three categories based on their crimes: homicide, violent offenses that were not homicide, or non-violent or minimally violent transgressions. The team relied on official convictions, self-reported homicides, and confidential interviews with participants to determine who attempted or committed murder—both offenses that got a "homicide" label in their dataset.

People charged with felony murder—meaning that they had committed a serious felony that was in some way connected to a person's death, even though they hadn't intended to kill the victim—and people whose cases indicated considerable doubt about a judgment of homicide were not counted among murderers. And occasionally, people were moved from another category into the homicide group, Kiehl says. The researchers excluded people with abnormal radiology reports, traumatic brain injury, or diagnosed psychotic disorders from the study.

Controlling for substance use severity, time in prison, age, and IQ, the team analyzed the MRI data to look for differences among the study participants. Compared with the other two groups, the 200 men who had committed homicide showed significantly reduced gray matter in several brain regions that play important roles in behavioral control and social cognition.

Men who had committed homicide showed significantly reduced gray matter in several brain regions.

"I think that the intriguing thing was, first, that they found a difference," says Hannes Vogel, a neuropathologist at Stanford University Medical Center who was not involved in the work. "And second of all, that it correlates with some of the brain centers that deal with behavior and social interaction."

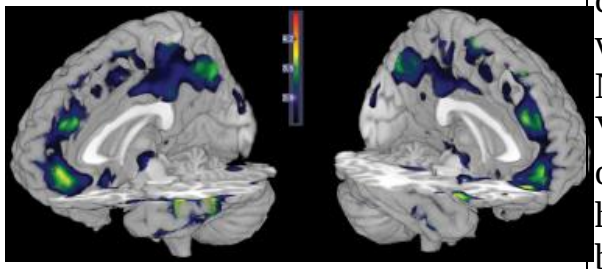
Lora Cope, a neuroscientist who studies substance disorders at the University of Michigan, notes in an email to *The Scientist* that the

team's mobile MRI system has now been used in correctional facilities all over New Mexico and Wisconsin, and "has really revolutionized this area of research." Indeed, the MRN has now used the equipment to collect roughly 6,500 scans from more than 3,000 research participants since its first outing in 2007.

Although Cope wasn't involved in the current project, she worked with Kiehl a few years ago while earning her doctorate at the University of New Mexico. After speaking with members of the Avielle Foundation, named for a six-year-old victim of the 2012 Sandy Hook Elementary School shooting, the two researchers spearheaded a study of more than 150 incarcerated young males, 20 of whom had been convicted of homicide, held at a maximum-security detention facility within the state. "Jeremy, [Avielle's] father, really wanted to know if there was anything neuroscience could tell us about boys who commit homicide," says Kiehl.

As in the current study, Cope and Kiehl deployed the mobile scanner to collect MRI scans of the incarcerated teens in New Mexico and discovered differences between those who had committed homicide and their imprisoned peers. The homicide offenders "had significantly less gray matter volume in parts of their temporal lobes," Cope says.When Kiel compared the data from that study with the results of his latest project, he found a high degree of overlap.

"Lo and behold . . . we found and replicated every region that was different in the boys and was different in the adult males, and in the same way," he says.



ANATOMY OF A MURDERER: Homicide offenders exhibited reduced gray matter density compared with other violent offenders in the regions of the brain highlighted blue and green above. **A. Sajous-Turner Et Al. (2019)**

The latest study's finding that MRI data can distinguish homicide offenders not only from people who committed non-violent crimes, but also from those who performed other violent crimes, is particularly interesting, says Harold Koenigsberg, a psychiatrist at Icahn School of Medicine at Mount Sinai. "I would have thought there would be more of an overlap between [homicide and violent non-homicide offenders]," he says. "I'm surprised that it was so specific to homicide."

Koenigsberg notes that homicidal violence can itself be split into two categories: impulsive and instrumental. Impulsive violence is born of unbridled emotions and overblown reactions, a brand of behavior linked to poor frontal lobe functioning and abnormal serotonin levels. Instrumental violence, on the other hand, is premeditated and is associated with other brain changes, such as reduced amygdala activation during emotion processing. "These two groups, we think that they have different biologies," says Koenigsberg. Kiehl's dataset could be enriched by adding measures of neurotransmitter release and electrical activity, along with related behavioral assessments, he suggests, and with both functional and structural data, psychologists might learn more about what gives rise to these distinct behavioral phenotypes.

Koenigsberg, Vogel, and Kiehl all note that the structural data collected in the current study cannot on its own be used to predict who has committed homicide, let alone who might in the future. Nonetheless, the paper may find its way into the courtroom, says Vogel. If lawyers felt so inclined, they could try to "find an expert on one side who will quote this [paper]" in defense of someone who has committed a homicide, by arguing a client's actions were due to brain abnormalities and thus out of his or her control. Or, a prosecutor could potentially use the paper to argue that MRI findings should be admissible as evidence that a defendant has committed a homicide, says Vogel, who has served as a consultant

for court cases in California and Nevada, and helped investigate the brain of the Route 91 Harvest music festival shooter in 2017. “But then you’re [also] going to find an expert that will tear that [testimony] to pieces.”

Kiehl notes that his MRI study could also someday contribute to new evidence-based measures of homicidal risk. These measures could supplement current measures of violent behavior, such as psychological questionnaires, if future studies demonstrated they carried predictive weight, he says. Beyond courts of law, he also suggests that understanding how violent behavior arises could pave the way to better psychological treatment aimed at both rehabilitation and prevention.

https://wb.md/2qhBu4i

Smell Test, Brief Cognitive Screen Combo May Help Rule Out Dementia

Performance on two quick tests — a cognitive screen and an olfactory test — may rule out future dementia, including Alzheimer disease (AD), for patients with mild memory problems, results of a large follow-up study show.

Damian McNamara

Investigators found that of those participants whose scores on both the Brief Smell Identification Test (B-SIT) and the Blessed Orientation Memory Concentration Test (BOMC) indicated that they were unimpaired, 96.5% did not develop dementia during an average follow-up of 4 years.

"The take-home message for neurologists and other physicians is that if a brief cognitive test is supplemented by a brief olfaction test like the B-SIT, and if a patient with memory complaints scores well on both tests, it is not necessary to investigate further," lead author D. P. Devanand, MD, professor of psychiatry and neurology and director of geriatric psychiatry at Columbia University Medical Center in New York City, told *Medscape Medical News*.

This approach could reduce the need for position-emission tomographic imaging or lumbar puncture to identify for biomarkers of AD, he said.

The study was published online October 29 in *Alzheimer's and Dementia.*

Five-Minute Smell Test

In previous cross-sectional studies, researchers demonstrated that an inability to identify odors helped distinguish older adults who were cognitively intact from others who had mild cognitive impairment (MCI) or AD. In addition, prior work examined how combining odor identification with a brief cognitive test can help differentiate people with MCI or AD from control persons.

However, the researchers note that the "utility of intact performance on brief odor identification and global cognitive tests in predicting lack of cognitive decline or conversion to AD has not been examined explicitly."

To investigate this, the investigators assessed 749 participants with MCI from the Washington Heights/Inwood Columbia Aging Project. The cohort did not have dementia at baseline.

Participants completed the University of Pennsylvania Smell Identification Test (UPSIT) and the BOMC. The B-SIT smell test is a 12-item component of UPSIT. The B-SIT score ranges from 0 (no odor correctly identified) to 12 (a perfect score). The B-SIT and the BOMC each take approximately 5 minutes to administer.

During the follow-up, 15% of the 749 participants who completed at least one subsequent assessment transitioned to dementia. The majority of these 109 patients, 101 people, developed AD dementia. The remaining eight participants developed other cognitive impairments, including Lewy body dementia and vascular dementia.

In terms of predictors, a lower B-SIT score at baseline was significantly associated with transition to dementia when researchers controlled for age, sex, language, and education (hazard

ratio [HR], 2.25; 95% confidence interval [CI], 1.12 – 4.49; *P* = .02). Worse performance on the BOMC was likewise a significant predictor (HR, 5.64; 95% CI, 3.49 – 9.12; *P* < .0001).

When the investigators combined both BOMC and B-SIT results and controlled for the same factors, they found that worse BOMC performance (HR, 5.60; 95% CI, 3.47 – 9.05) and worse B-SIT scores (HR, 2.25; 95% CI, 1.10 – 4.60) each predicted a greater likelihood that a person would transition to dementia. Both these factors were significant (*P* < .0001 and *P* = .03, respectively).

Interestingly, there was no significant interaction between the two predictors.

For the prediction of AD, "very similar results were found to those for dementia," the researchers note. "The need to assess both olfaction and global cognition is highlighted by the weaker predictions for only one of these two measures."

After a patient passes both tests, "the clinician can choose to inform the patient that, at this time, the likelihood of Alzheimer's disease is extremely low based on the test results," said Devanand, who is also a research psychiatrist at the New York State Psychiatric Institute, New York City.

"The patient can be asked to come back for repeat evaluation in a year only if they feel that their memory or other cognitive ability is worsening further," he said.

The findings, the investigators note, "confirm that olfactory sensory impairment, particularly early in the course of dementia, is a salient marker of cognitive decline and future dementia."

Future studies to confirm the results are warranted, Devanand said. "From a research perspective, the results need to be confirmed in other community-based cohorts.

"From a clinical perspective, we need to administer these brief tests to patients in broader clinical settings, particularly primary care, to evaluate if the results remain valid in that setting. We are currently in the process of doing such a study that is funded by the National Institute of Aging," he said

One Piece of the Puzzle?

Commenting on the study for *Medscape Medical News*, Rebecca Edelmayer, PhD, director of scientific engagement at the Alzheimer's Association, described the findings as "very interesting" but cautioned against relying on performance on these two tests in clinical practice until further validation studies have been conducted.

"At this point, it's too preliminary. It's one research study in one population. These are early days for using odor to indicate cognitive decline." However, she added, "the study is still very exciting."

The research is part of a bigger picture of a "blossoming field" regarding the detection of early disease, she added.

In the future, predicting who will progress to dementia or AD could become more sensitive by combining sensory markers such as olfaction and vision, functional indicators, including gait and cadence, and speech, language, and cognitive changes, she said.

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