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Penn team eradicates Hepatitis C in patients after heart transplants from infected donors

Study suggests the use of HCV-infected organs may be viable option for patients awaiting a heart transplant

PHILADELPHIA - Nine patients at Penn Medicine have been cured of the Hepatitis C virus (HCV) following lifesaving heart transplants from deceased donors who were infected with the disease, according to a study published in the *American Journal of Transplantation*. The results highlight the potential for expanding the use of HCV-infected organs, including hearts, to broaden the donor pool for the more than 100,000 Americans currently on a transplant waitlist.

In 2017, Penn Medicine launched a clinical trial to test the effect of transplanting hearts from donors with HCV into patients on the transplant waitlist who do not have the virus. Researchers modeled the clinical trial, known as USHER, after an innovative Penn Medicine-led study that involved transplanting HCV-infected kidneys (known as THINKER), and then treating the recipients with an antiviral therapy to eradicate the virus after transplantation. In both studies, all the patients who completed the antiviral therapy regimen have been cured of their contracted HCV.

"For decades, Hepatitis C-infected hearts were often discarded - and the few people who received these organs were found to have a significantly lower rate of survival," said Peter Reese, MD, MSCE, an associate professor of Medicine and Epidemiology. "Our trial provides fresh evidence to show that new antiviral treatments for HCV work well in immunosuppressed patients, which has the potential to really impact the field of transplantation. These preliminary results suggest that we should make it a priority to expand the use of good-quality HCV-infected organs."

Reese, who co-led the study with Rhondalyn McLean, MD, MHS, medical director of Penn's Heart Transplant program, and David S. Goldberg, MD, MSCE, an assistant professor of Medicine and Epidemiology, enrolled candidates who faced lengthy wait times due to a variety of factors, including a heart failure classification -- often as many as five, seven, even 10 years. During the pre-enrollment phase, the research team conducted a three-step process of education and informed consent to ensure participants and their loved ones understood the potential risks. The team then used specific criteria to evaluate available organs, including a genotype restriction meant to minimize risk.

Between June 2017 and April 2018, 10 patients received transplants using the protocol. At three days after surgery, patients were tested for HCV, and all 10 tested positive for the virus. The research team then treated participants with a 12-week course of elbasvir/grazoprevir, known commonly as Zepatier, a highly effective oral medication approved by the U.S. Food and Drug Administration (FDA) to treat HCV. All 10 patients responded rapidly to the antiviral therapy. While the presence of HCV and use of antiviral therapy did not cause any adverse events, one patient died due to complications of antibody-mediated rejection in the first three months following transplantation. The other nine participants have been cured of their contracted HCV, and have reported good quality of life following their transplants.

The researchers noted that this is the first trial in thoracic surgery to transplant Hepatitis C-infected hearts into Hepatitis-C negative patients with a formal protocol, which enabled detailed prospective data collection from the donor and recipient. In the case of this study, the team was able to identify novel data on the viral replication and clearance in heart recipients in the USHER trial, as well as in the kidney recipients from the team's THINKER trial.

"Unfortunately, every year, hundreds of the nearly 4,000 people on the heart transplant waitlist either die or get too sick for transplant - a tragic problem that stems from a limited donor pool," McLean said. "We started this trial in hopes that we could introduce an entirely new pool of donors that would significantly expand the nation's supply of available organs, enabling us to effectively transplant hundreds more candidates. Our data suggests the use of Hepatitis C-infected hearts - when followed by antiviral therapy - can be viable option for patients who may otherwise never receive a transplant."

The research team recently launched another new clinical trial that will study this same approach in patients who are awaiting a lung transplant. Researchers note there is a need for longer and larger trials to continue evaluating the effectiveness of HCV-positive to HCV-negative transplantation followed by antiviral therapy in a broader population.

Additional Penn Medicine experts on this study span disciplines including cardiovascular medicine, infectious diseases, transplantation surgery, gastroenterology, renal-electrolyte and hypertension and pathology and laboratory medicine. Researchers in these groups include Michael Acker, Pavan Atluri, Christian Bermudez, Lee Goldberg, Peter Abt, Emily Blumberg, Vivianna Van Deerlin, Raj Reddy, Roy Bloom, Anna Sicilia, Muhammad Zahid, Ashley Woodards, Katharine Bar, Paige Porrett, Matthew Levine, Nicole Hornsby, Caren Gentile, and Jennifer Smith. The study is supported by a research grant from Merck, and Merck supplied the antiviral drugs used in the study.

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Why This Man's Blood Turned 'Milky' Colored

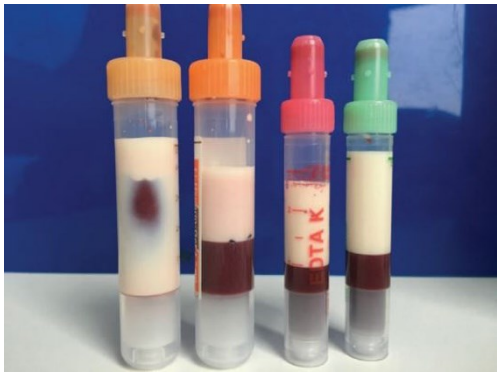
A man's blood was so thick with fat, his doctors needed to manually draw blood to help save his life

By Rachael Rettner, Senior Writer | February 25, 2019 05:09pm ET

A man's blood was so thick with fat, his doctors needed to manually draw blood — a practice known as bloodletting — to help save his life, according to a new report of the unusual case.

The 39-year-old man had gone to the emergency room after experiencing nausea, vomiting, headaches and decreased alertness. He had diabetes, and was on several drugs to treat the condition, but wasn't taking these medications regularly, according to the case report, published today (Feb. 25) in the journal Annals of Internal Medicine.

In the hospital, the man lost consciousness and needed a breathing tube inserted to help him breathe.



A man in Germany had extraordinarily high levels of triglycerides, a type of fat, in his blood. Above, samples of the man's blood about two hours after they were drawn. The white is the fat. **Copyright © 2019 American College of Physicians. Used with permission.**

Tests revealed that the man had extraordinarily high levels of triglycerides, a type of fat, in his blood. Triglyceride levels below 150 milligrams per deciliter (mg/dL) are considered normal, according to the National Institutes of Health (NIH), and levels above 500 mg/dL are considered "very high." The man's triglyceride levels, however, clocked at in at more than 14,000 mg/dL.

The triglycerides levels were so high that the man's blood took on a milky color, said case report co-authors Dr. Philipp Koehler and Dr. Matthias Kochanek, of the University Hospital of Cologne in Germany, who treated the patient.

Such high levels of triglycerides can cause inflammation of the pancreas, or pancreatitis, a potentially serious condition. Indeed, tests showed the man had elevated levels of pancreatic enzymes, which can be a sign of this condition.

Tests also revealed that the man had diabetic ketoacidosis — a potentially life-threatening complication of diabetes that occurs when the body breaks down fat at a rapid rate, which leads to a buildup of acids in the blood called ketones, according to the NIH. Ketoacidosis happens because the body doesn't produce enough

insulin, a hormone that helps sugar, or glucose, get into cells so that the sugar can be used as fuel. (Without glucose, the body turns to fat as fuel.) It's treated, in part, with infusions of insulin into the veins.

Bloodletting

When a patient has extremely high triglyceride levels, doctors can use a machine to filter the fat out of the blood — a process known plasmapheresis. But when the man's doctors attempted plasmapheresis, the machine became clogged due to the extremely high blood fat levels.

His doctors attempted plasmapheresis a second time, but the machine still clogged. That's when they turned to bloodletting. They drew a liter of the man's blood, and replaced it with red blood cells and plasma (the liquid portion of blood) from a donor. This led to a decrease in the man's triglyceride levels, so the doctors withdrew another liter, this time replacing it with fluids.

Two days later, the man's triglyceride levels were low enough for the plasmapheresis machine to work without clogging. Five days later, doctors were able to remove the patient's breathing tube, and he didn't have any lingering neurological symptoms.

"Fascinating and innovative"

Koehler and Kochanek told Live Science that they had never seen a case like this before. The new report suggests that, if plasmapheresis cannot be performed, "conventional bloodletting with [blood and fluid] replacement may be an effective alternative" for patients with extremely high triglycerides," the authors concluded.

Dr. Guy Mintz, the director of cardiovascular health and lipidology at Northwell Health's Sandra Atlas Bass Heart Hospital in Manhasset, New York, who was not involved in the case, said that the case report detailed " a fascinating and innovative treatment adaptation to a life-threatening situation due to high triglycerides in the blood." said "I applaud the doctors for thinking out of the box" to attempt the bloodletting treatment, Mintz told Live Science. The report "gives [doctors] a new treatment option for extremely high triglycerides when standard hospital therapy … fails."

The authors hypothesize that that man's extremely high blood triglyceride levels were caused by a combination of insulin resistance, obesity, inappropriate diet and insufficiently treated diabetes. They noted that both ketoacidosis and very high triglyceride levels are signs of a lack of insulin. Testing also showed the patient had a genetic marker that's associated with higher triglyceride levels, which may have also affected his risk. In addition, the patient was taking a diabetes medication called a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and there is some concern that this medication may increase the risk of ketoacidosis, according to the U.S. Food and Drug Administration.

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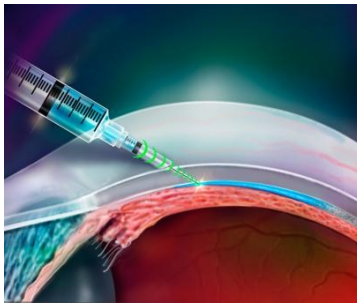
Researchers invent a needle that knows where to go

Resistance-sensing injector allows researchers to more safely and effectively deliver drugs to the body

Boston, MA -- Syringes and hollow needles have been used to deliver medication for more than a century. However, the precise implementation of these devices depends on the operator, and it can be difficult to deliver medication to delicate regions such as the suprachoroidal space at the back of the eye. Investigators from Brigham and Women's Hospital have developed a highly sensitive intelligent-injector for tissue-targeting (i2T2) that detects changes in resistance in order to properly and safely deliver medication in preclinical testing. Their results are published in Nature Biomedical Engineering.

"Targeting specific tissues using a conventional needle can be difficult and often requires a highly trained individual," said senior corresponding author Jeff Karp, PhD, Professor of Medicine at the

Brigham. "In the past century there has been minimal innovation to the needle itself, and we saw this as an opportunity to develop better, more accurate devices. We sought to achieve improved tissue targeting while keeping the design as simple as possible for ease of use."



In preclinical testing, resistance-sensing injector allows researchers to more safely and effectively deliver drugs to the body **Nature Biomedical Engineering**

One location that is difficult to target with a standard needle is the suprachoroidal space (SCS), which is located between the sclera and choroid in the back of the eye. The SCS has emerged as an important location for medication delivery and is challenging to target because the needle must stop after transitioning through the sclera, which is less than 1 millimeter thick (about half the thickness of a U.S. quarter), to avoid damaging the retina. Additional common tissue targets include the epidural space around the spinal cord (used for epidural anesthesia to ease pain during labor), the peritoneal space in the abdomen, and subcutaneous tissue between the skin and muscles.

The i2T2 device was fabricated using a standard hypodermic needle and parts from commercially available syringes. Body tissues have different densities, and the intelligent injector harnesses differences in pressure to enable needle movement into a target tissue. The driving force, maximal forces and frictional force of the injector were tested using a universal testing machine. The feedback of the injector is instantaneous, which allows for better tissue targeting and minimal overshoot (injecting past the target tissue) into an undesired location.

The i2T2 was tested on tissue from three animal models to examine delivery accuracy in the suprachoroidal, epidural and peritoneal spaces as well as subcutaneously. Using both extracted tissue and an animal model, the researchers found that the i2T2 prevented overshoot injuries and precisely delivered medication to the desired location without any additional training or specialized technique.

In preclinical models, the researchers reported high coverage of contrast agent in the posterior section of the eye, indicating that the payload had been injected into the correct location. The researchers also showed the injector could deliver stem cells to the back of the eye that could be useful for regenerative therapies.

"The stem cells injected into the SCS survived, indicating that the force of injection and the transit through the SCS were gentle on the cells," said Kisuk Yang, a co-author and postdoctoral fellow in Karp's laboratory. "This should open the door to regenerative therapies for patients suffering from conditions of the eye and beyond."

"This intelligent injector is a simple solution that could be rapidly advanced to patients to help increase target tissue precision and decrease overshoot injuries. We have completely transformed needles with a small modification that achieves better tissue targeting," said first author Girish Chitnis, PhD, a former postdoctoral fellow in Karp's laboratory. "This is a platform technology, so the uses could be very widespread."

"The i2T2 will help facilitate injections in difficult-to-target locations in the body," said Miguel González-Andrades, MD, PhD, ophthalmologist co-author of the manuscript and collaborator with Karp's lab. "The next step toward human use is to demonstrate the utility and safety of the technology in relevant pre-clinical disease models."

Funding for this work was provided by the National Institutes of Health (R01HL095722) and Boston- KPro.

Paper cited: Chitnis, G et al. "An Intelligent Injector for Tissue Targeting and its Application for Drug Delivery" Nature Biomedical Engineering *DOI: 10.1038/s41551-019-0350-2*

http://bit.ly/2U9rpQT

Researchers ID gene that may predict pancreatic cancer in people with Type 2 diabetes

"UCP-1" may predict the development of pancreatic cancer in people with Type 2 diabetes

ROCHESTER, Minn. — Mayo Clinic researchers have identified a gene called "UCP-1" that may predict the development of pancreatic cancer in people with Type 2 diabetes. Their findings are published in *Gastroenterology*.

"Developing strategies for the early detection of pancreatic cancer in people without symptoms is critical for improving survival," says Suresh Chari, M.D., a Mayo Clinic gastroenterologist and senior author of the study.

For this study, Dr. Chari and his colleagues studied a population-based cohort of patients with pancreatic cancer and matched controls. Researchers studied changes in patients' fasting blood glucose, body weight and blood lipids over a five-year period prior to their pancreatic cancer diagnosis. They also reviewed serial CT scans completed over time for other indications prior to their diagnosis.

The review of CT these scans helped researchers identify changes in patients' subcutaneous fat, visceral fat and muscle over time. Researchers found that metabolic changes in patients with pancreatic cancer started 36 months prior to their cancer diagnosis, along with a rise in blood glucose. They also found that at 18 months prior to a pancreatic cancer diagnosis, patients experienced weight loss and a decrease in blood lipids, which included triglycerides, total cholesterol and low-density cholesterol.

"We observed [those] subcutaneous fat levels start decreasing approximately 18 months prior to a pancreatic cancer diagnosis, and coincide with a decrease in body weight and lipids," says Dr. Chari. "Visceral fat and muscle decreased in the last six months prior to a pancreatic cancer diagnosis and coincided with the development of advanced cancer symptoms."

Dr. Chari says the decrease in fat and lipids 18 months prior to a pancreatic diagnosis were reminiscent of the effects of browning of white adipose tissue, a phenomenon found in other cancers. "Brown fat generates body heat, a phenomenon especially prominent in newborn babies but much less so in adults," says Dr. Chari.

Dr. Chari says a specific marker of brown fat is an uncoupling protein called UCP-1. "White fat can be turned brown by turning on certain 'browning' genes, including, UCP-1," he says. "We hypothesized that pancreatic cancer causes browning of subcutaneous fat, and we confirmed our hypothesis in animal, experimental and human studies."

Based on their findings Dr. Chari and his colleagues identified three distinct metabolic phases prior to a diagnosis of pancreatic cancer. Each phase is characterized by the onset of a new metabolic change:

- **Phase** I

This phase, at 36 to18 months, is characterized by rise in blood glucose levels.

- **Phase** II

This phase, at eight to six months, is characterized by decreases in lipids and weight, browning of subcutaneous fat and a rise in body temperature.

- **Phase** III

This phase, at six to zero months, is characterized by a further rise in blood glucose levels and body temperature, along with a decrease in lipids; weight; and soft tissues that include subcutaneous fat, visceral fat and muscle.

"Our study has important implications for the early detection of pancreatic cancer," says Dr. Chari. "Along with supporting data from animal and experimental studies, we were able to show that UCP-1 gene levels are markedly increased in patients with pancreatic cancer, compared to controls. We believe UCP-1 can

potentially be used as a biomarker to predict pancreatic cancer in high-risk groups, such as patients with new-onset or long-standing diabetes who are unintentionally losing weight."

Dr. Chari's previous research focused on studying patients with new-onset diabetes as a high-risk group for developing pancreatic cancer. As part of this work, Dr. Chari and his colleagues developed and validated a score called Enriching New-Onset Diabetes for Pancreatic Cancer or ENDPAC that stratifies the risk of developing pancreatic among patients with new-onset diabetes.

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Mini tumors could help identify personalized treatments for people with rare cancers

New technique developed at UCLA can screen hundreds of drugs using patients' own cells

UCLA scientists have developed a new method to quickly screen hundreds of drugs in order to identify treatments that can target specific tumors.

The approach could help scientists understand how a person's tumor would respond to a certain drug or drug combination, and it could help guide treatment decisions for people with rare and hard-to-treat cancers. A paper detailing the new technique was published in *Communications Biology*.

"We always focus on how we need new and better drugs to treat cancer," said Alice Soragni, the senior author of the study and a scientist at the UCLA Jonsson Comprehensive Cancer Center. "While that's true, we also have many drugs currently available -- we just haven't been able to figure out who is going to respond to which ones for most of them."

The screening method uses patients' own cells, collected during surgery, to create miniature tumor organoids.

Organoids are simpler, smaller versions of bodily organs or tumors that scientists can grow in a lab to replicate the full-function structures; researchers create them to study diseases and possible treatments.

"We obtain cancer cells directly from surgery and that same day we can seed them to generate tumor organoids," said Soragni, an assistant professor in the division of hematology/oncology at the David Geffen School of Medicine at UCLA and member of the Molecular Biology Institute at UCLA. "We created a miniaturized system that allows the setup of hundreds of wells for testing with minimal manipulation."

After the tumor organoids are established, typically in three to five days, the lab screens hundreds of drugs to determine which ones are effective. The approach developed by Soragni's lab uses an automated feed -- instead of testing one drug at a time, scientists use robots to simultaneously screen hundreds of different treatments. The method is fast and efficient: The entire process, from surgery to final results, can take as little as one to two weeks.

To test the technique, Soragni's team took cells from four patients -- three with ovarian cancer and one with peritoneal cancer -- to grow tumor organoids. The test enabled the researchers to produce personalized snapshots of which drugs were effective for each patient's organoids.

For example, one of the four participants in the study was a woman with an extremely rare type of ovarian cancer. (The specific subtype of cancer is diagnosed in fewer than 200 U.S. women each year.) The organoids developed from her cancer cells responded to a class of drugs called cyclin-kinase inhibitors, which can target cancer by preventing it from growing. Soragni said there are currently no known biomarkers to predict the effect of the specific cyclin-kinase inhibitors identified by the screening on tumor growth. So without the test, it would have been impossible to know that the drugs would work on that specific subtype of cancer.

For many rare types of cancer, scientists know little about drug susceptibilities. But being able to create models of rare tumors in the lab can help scientists identify patients who could benefit the most from a specific treatment. In addition to identifying personalized treatments, the technique could also help scientists select patients to participate in clinical trials for potential new cancer therapies.

"This could become a powerful tool to help guide therapies for people who really have no known treatment options left," Soragni said.

The study's first author is Nhan Phan, a visiting graduate student researcher through the UCLA-Department of Energy Center for Global Mentoring. The other authors are Jenny Hong, Bobby Tofig, Matthew Mapua, David Elashoff, Neda Moatamed, Jin Huang, Dr. Sanaz Memarzadeh and Robert Damoiseaux, all of UCLA.

The research was supported by a Worldwide Cancer Research grant. Additional support was provided by the Hirshberg Foundation, a National Institutes of Health/National Center for Advancing Translational Science grant, the UCLA Specialized Program of Research Excellence in Prostate Cancer, and an American Association for Cancer Research - Millennium Fellowship in Prostate Cancer.

http://bit.ly/2EzSdV6

You probably don't have a penicillin allergy

Five facts about penicillin allergy

Hamilton, ON - You may think you have an allergy to penicillin, but you probably don't.

Nine out of 10 people who believe they're allergic to the antibiotic either aren't allergic or have only some intolerance, and eight of 10 people who had an allergic reaction to penicillin 10 or more years ago will now be fine.

Two McMaster University physicians have five facts about penicillin allergy published today in the *Canadian Medical Association Journal* (CMAJ). Derek Chu is a fellow in clinical immunology and allergy and David McCullagh is a fellow in infectious disease in the Department of Medicine.

They say the five things to know about a penicillin allergy are:

- ***Penicillin allergy is commonly reported, but nine times out of 10, a patient can tolerate penicillin.***

About 10 per cent of people report a penicillin allergy, but 90 per cent to 95 per cent are not truly allergic. Reasons for this include mislabelling intolerances as allergies and waning of the allergy over time.

- ***Penicillin allergy is lost over time, with 50 per cent of people over five years, and 80 per cent over 10 years losing their allergy.***

Those who had reactions more than 10 years ago are unlikely to still be allergic and should be tested before given penicillin. If there is an strong indication for antibiotics, an allergist physician should be consulted about therapy.

- ***A penicillin allergy label is bad for patients and the health-care system.***

People labelled with penicillin allergy are offered more costly and less effective second-line and broad-spectrum antibiotics which have a significantly increased risk of infections such as methicillin-resistant* Staphylococcus aureus *(MRSA) and* Clostridium difficile *(C. diff).

- ***Patients who suspect penicillin allergy can be identified to determine if they should be seen by a specialist.***

A side effect of penicillin such as nausea should not be noted as an allergy. As well, people without a personal history of a penicillin allergy or who have tolerated penicillin in the past, do not need to avoid penicillin. Severe allergic drug reactions causing hospitalization due to widespread skin blistering, organ failure, and/or joint swelling are rare and these patients should strictly avoid penicillin until specialist evaluation. True immediate allergic reactions cause rapid-onset hives, lip and face swelling, and anaphylaxis. Patients with these kinds of reactions, or who are unsure if this type occurred or not, should be evaluated by an allergy specialist.

- ***Allergy referral and testing is underused, but is safe, accurate, fast and cost-effective.***

Allergy testing over one to two hours using a combination of skin and challenge testing by trained personnel has been shown to be safe and

effective for children and adults close to 100 per cent of the time. Patients with a possible penicillin allergy should talk to their doctor about whether or not they need penicillin allergy testing.

Read the article here: http://www.cmaj.ca/content/191/8/E231
A CMAJ podcast of an interview with the author may be found here: https://soundcloud.com/cmajpodcasts/181117-five

http://bit.ly/2TmW684

Researchers discover the secret to bats' immunity

Molecular and genetic mechanisms that allow bats to stay healthy while hosting viruses that kill other animals

An international research team led by Duke-NUS Medical School, Singapore, has identified molecular and genetic mechanisms that allow bats to stay healthy while hosting viruses that kill other animals, according to a new study published in the journal *Nature Microbiology*.

Bats live very long and host numerous viruses, such as Ebola virus, Nipah virus, and severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses, that are extremely harmful when they infect humans and other animals. Researchers at Duke-NUS Medical School and colleagues wanted to find out how bats can harbour so many of these pathogens without suffering from diseases.

The key, they found, is in the bat's ability to limit inflammation. Bats do not react to infection with the typical inflammatory response that often leads to pathological damage. In humans, while the inflammatory response helps fight infection when properly controlled, it has also been shown to contribute to the damage caused by infectious diseases, as well as to aging and age-related diseases when it goes into overdrive.

The researchers found that the inflammation sensor that normally triggers the body's response to fight off stress and infection, a protein called NLRP3, barely reacts in bats compared to humans and mice, even in the presence of high viral loads.

"Bats' natural ability to dampen inflammation caused by stress and infection may be a key mechanism underlying their long lifespans and unique viral reservoir status," said Dr. Matae Ahn, first author of the study and an MD-Ph.D. candidate of the Emerging Infectious Diseases (EID) Programme at Duke-NUS Medical School.

The researchers compared the responses of immune cells from bats, mice and humans to three different RNA viruses – influenza A virus, MERS coronavirus, and Melaka virus. The inflammation mediated by NLRP3 was significantly reduced in bats compared to mice and humans.

Digging further, they found that 'transcriptional priming', a key step in the process to make NLRP3 proteins, was reduced in bats compared with mice and humans. They also found unique variants of NLRP3 only present in bats that render the proteins less active in bats than in other species. These variations were observed in two very distinct species of bats – *Pteropus alecto*, a large fruit bat known as the Black Flying Fox, and *Myotis davadii*, a tiny vesper bat from China – indicating that they have been genetically conserved through evolution. Further analysis comparing 10 bat and 17 non-bat mammalian NLRP3 gene sequences confirmed that these adaptations appear to be bat-specific.

What this implies, the researchers explain, is that rather than having a better ability to fight infection, bats have a much higher tolerance for it. The dampening of the inflammatory response actually enables them to survive.

"Bats appear to be capable of limiting excessive or inappropriate virus-induced inflammation, which often leads to severe diseases in other infected animals and people," said Professor Wang Lin-Fa, Director of Duke-NUS' EID Programme and senior author of the study. "Our finding may provide lessons for controlling human infectious diseases by shifting the focus from the traditional specific

anti-pathogen approach to the broader anti-disease approach successfully adopted by bats."

Professor Patrick Casey, Duke-NUS Medical School's Vice Dean for Research, noted of the findings: "With this study, our researchers have advanced our understanding of an area that had long remained a mystery. This is yet another example of the world-class research and global collaboration that is a hallmark of Duke-NUS."

More information: *Ahn M, Anderson DE, Zhang Q, Tan CW, Lim BL, Luko K, Wen M, Chia WN, Mani S, Wang LC, Ng JHJ, Sobota RM, Dutertre CA, Ginhoux F, Shi ZL, Irving AT, Wang LF (2019). Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. Nature https://wb.md/2Xm3Bvj Microbiology. DOI: 10.1038/s41564-019-0371-3*

http://bit.ly/2EA2eSi

At-Home Test for Colorectal Cancer Could Simplify Screening

An at-home screening test for colorectal cancer may be as good an option as a colonoscopy, a new review study finds.

By Cari Nierenberg, Live Science Contributor

The FIT, or fecal immunochemical test, works by determining whether there is blood in a person's stool sample that is not visible to the naked eye. Blood in the stool may be an early sign of a colon polyp (a small growth that's typically not cancerous) or of colorectal cancer.

In the review, published yesterday (Feb. 25) in the journal Annals of Internal Medicine, the researchers looked at data from 31 studies that compared the performance of FIT tests to colonoscopies. [5 Lifestyle Tips that Lower Your Risk of Colorectal Cancer]

The study found that the FIT test had a sensitivity of a 75 to 80 percent, meaning it identified cancer in 75 to 80 percent of individuals who had the disease, said lead author Dr. Thomas Imperiale, a gastroenterologist at the Indiana University School of Medicine and Regenstrief Institute in Indianapolis. In comparison, colonoscopy had a sensitivity of 95 percent.

These findings suggest that a FIT test done every year is a very acceptable alternative to a colonoscopy for people at average risk of colorectal cancer, Imperiale told Live Science. An average risk means the person doesn't have a family history of the disease and does not have inflammatory bowel disease or colon polyps. (Unlike a colonoscopy, which is recommended once every 10 years, the FIT test is recommended yearly.)

The FIT test is done by placing a paper sling in the toilet seat to catch a stool sample before it hits the bowl, Imperiale said. Then, a brush is used to obtain a smaller stool sample, which is sent to a lab for analysis. Results are then sent to physicians, who communicate the findings to their patients. If a patient has a positive result, they would need to have follow-up testing in the form of a colonoscopy.

Some of the benefits of the FIT test are that it is easy to do at home and doesn't require advanced preparation, an invasive procedure or going under sedation, Imperiale said. However, the screening test needs to be carried out more frequently (once a year versus once a decade) and doesn't preclude a person from having a colonoscopy, as a positive FIT-test result would likely necessitate that procedure.

Which test is best?

Regardless of the testing method used, only about 65 percent of U.S. adults ages 50 to 75 get screened for colorectal cancer, according to the review. The disease is the second most common cause of cancer-related deaths in the country.

So, with about one-third of adults not getting screened, more evidence is needed regarding the effectiveness of other colorectal cancer-screening methods.

Dr. James Allison, a gastroenterologist and research scientist emeritus at Kaiser Permanente Northern California Division of Research, noted that although Americans may have been told that colonoscopy is the "gold standard" screening test for colorectal cancer, there's a lack of evidence that any one test is best for

screening. Allison wrote an editorial about the review that was also published in the Annals of Internal Medicine.

What's more, comparing the performance of a single FIT test to a one-time application of colonoscopy as a screening method for colorectal cancer is like comparing apples to oranges, Allison told Live Science. That's because colonoscopy is recommended once every 10 years while FIT testing would be recommended every year, which would allow for the discovery of advanced tumors and early treatable cancers each year, he noted.

https://wb.md/2Xm3Bvj

Noninvasive Stool Test Effective for Colon Cancer Screening

Fecal immunochemical tests (FITs), used annually, are effective for screening for colorectal cancer (CRC) in average-risk, asymptomatic adults, according to a new meta-analysis.

Fran Lowry

"Our results provide the strongest evidence to date to support recommendations that average-risk patients can safely opt for an annual, easy-to-use home stool test instead of a screening colonoscopy," lead author Thomas Imperiale, MD, Lawrence Lumeng Professor in Gastroenterology and Hepatology at Indiana University School of Medicine and the Regenstrief Institute, Indianapolis, told *Medscape Medical News*.

"I would like to see patients be more aware of the options for colorectal cancer screening, the options to colonoscopy, and to be able to bring it up if their primary care providers don't mention FIT as an option," Imperiale added.

The meta-analysis was published online February 25 in the *Annals of Internal Medicine*.

The US Preventive Services Task Force currently recommends screening for CRC for persons aged 50 to 75 years using any of several options: fecal occult blood testing (a category that includes FIT), sigmoidoscopy, colonoscopy, and other tests. It does not recommend one screening modality over another.

Colonoscopy is considered to be the "gold standard" for CRC screening in the United States, but only 60% to 65% of the eligible American population is current with screening, the authors note. Several other countries, especially those in which healthcare finances are limited, use annual or biennial stool blood tests or a combination of stool testing and lower endoscopy for screening, they note.

Study Details

For the meta-analysis, Imperiale and coauthors reviewed and analyzed the findings of 31 studies that evaluated FIT sensitivity and specificity for CRC. The review included 120,255 asymptomatic participants and 18 FITs.

FITs used in the studies included OC-Sensor (Eiken Chemical), which was used in 14 (58%) of the studies, OC FIT-CHEK (Eiken Chemical), OC-Light (Eiken Chemical), OC-Hemodia (Eiken Chemical), and FOB Gold (Sentinel Diagnostics).

Performance characteristics of FITs depended on the threshold for a positive result.

A threshold of 10 µg/g resulted in a sensitivity of 0.91 (95% confidence interval [CI], 0.84 – 0.95) and a negative likelihood ratio of 0.10 (CI, 0.06 – 0.19) for CRC, whereas a threshold of >20 µg/g resulted in specificity of 0.95 (CI, 0.94 – 0.96) and a positive likelihood ratio of 15.49 (CI, 9.82 – 22.39).

The researchers also evaluated performance characteristics of FITs for advanced adenomas in average-risk individuals who underwent screening colonoscopy.

There, FITs were much less sensitive for advanced adenomas. Sensitivity was 0.40 (CI, 0.33 – 0.47), and the negative likelihood ratio was 0.67 (CI, 0.57 – 0.78) at 10 µg/g. At >20 µg/g, the

specificity was 0.95 (CI, 0.94 – 0.96), and the positive likelihood ratio was 5.86 (CI, 3.77 – 8.97).

Not All FITs Are Created Equal

"Our results suggest a need for a head-to-head comparison of different FITs at various thresholds for both colorectal cancer and advanced adenomas," Imperiale said.

In an accompanying editorial, James Allison, MD, University of California, San Francisco, and emeritus investigator in Kaiser Permanente's Division of Research, writes that the systematic review "may help to reassure physicians and patients about the performance of FITs for CRC detection."

In an interview with *Medscape Medical News*, Allison noted that some primary care physicians in the United States, as well as many of their patients, may be unaware that FITs are similar in effectiveness to colonoscopy when used in a consistent, programmatic way to screen for CRC.

"We've got to get away from the idea that there's only one good test for colon cancer screening. We must increase our national screening for CRC numbers, especially in the vulnerable population — the uninsured, underinsured, poor. Calling a colonoscopy screening test the best, or the gold standard, is not helpful or true. It's a good test, and I'm not saying don't have a colonoscopy. I'm saying don't limit yourself to colonoscopy because it's called the best or gold standard by some," he said.

"There is not one US colorectal cancer screening guideline as of 2019 that says that colonoscopy is the best, gold-standard test. FIT is right up there with colonoscopy," Allison added.

He also cautioned that average-risk individuals who undergo screening with FIT must be sure that the FIT supplied by their physician or healthcare system has been carefully studied and that its advertised performance characteristics have been confirmed.

"The FDA's approval of FITs as simple tests for blood rather than for advanced colorectal neoplasms has allowed for clearance of low-performing tests. There are 120 FDA-cleared FITs on the market. Several of them are produced in foreign countries, China in particular. Many of them are marketed as being as good as the tests that have been well tested, and they are not," he warned.

Addressing physicians, he said, "To make sure you are ordering the best FIT for your patient, go to the latest US Preventive Services Task Force guidelines of 2017."

Allison called for changes to existing laws that charge copays for a colonoscopy performed after a patient receives a positive result on FIT. "We need better and more consistent payment policies that ensure coverage of colonoscopy after an abnormal FIT test," he said.

The study was funded by the Department of Medicine of Indiana University School of Medicine. Imperiale and Allison report no relevant financial relationships.

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http://bit.ly/2Eq1DDV

HeLa Cells from Different Labs Vary in Genetics, Phenotype

This could account for some reproducibility problems in cell line research, according to the authors of a comprehensive analysis of HeLa variants.

Katarina Zimmer

HeLa cells have now been cultured for nearly 70 years in many labs across the world, and were long considered to be an infinite supply of unchanging, identical cells. However, new research published in *Nature* last week (February 18) demonstrates that the cells can vary substantially from lab to lab, raising questions about the reproducibility of research conducted with the cell line.

“I’m glad to see this study, but in a sense, I’m not surprised,” says molecular biologist Prasad Jallepalli from Memorial Sloan Kettering Cancer Center who wasn’t involved in the study.

It's not the first report that the HeLa cell line has diversified since its creation: Over the years, other groups have documented significant differences in genetic sequence and RNA expression between variants.

This latest investigation is the first comprehensive analysis of genetic variation across a wide range of HeLa variants—different batches of HeLa cells that live in various labs around the world—and the first to demonstrate that the genetic heterogeneity results in changes in protein expression and phenotype.

The results suggest that HeLa cells have evolved into something slightly different in each lab, says Jallepalli. "What we're seeing is genetic drift. A starting population is evolving into distinct niches over time."

In the study, researchers gathered 14 HeLa samples from 13 labs across six countries, and cultured them under the same laboratory conditions. They first quantified gene copy number variation—the number of repeats of a given gene—revealing stark differences between their genomes. This was especially notable between the two most widely used strains of HeLa cells, known as HeLa CCL2—considered to be the "original" variant of the cell line—and HeLa Kyoto, an offshoot of the cell line that has properties that make it useful for specific applications such as imaging.

Further analyses showed that many of these genetic differences translated into changes in mRNA production and, to a lesser extent, changes in protein abundance. The transcriptomic and proteomic profiles of HeLa CCL2 and the Kyoto lineages are as different to one another as are cancer cell lines from two different types of tissue, the researchers report.

The HeLa variants also differed in how fast they grow in culture, with some cell populations taking 17.5 hours to double, whereas others took a little more than 32 hours under the same culture conditions. They also differed in their responses to *Salmonella* infection: One variant was less susceptible to infection compared to two others, which the researchers attribute to low levels of a protein complex that plays a role in the bacterium's entry into host cells.

In a separate experiment, the team investigated whether gene expression changed in individual HeLa variants over time by culturing a cell line for three months. The researchers documented a roughly 6 percent difference in gene expression between an early and a later generation of cells.

"It was certainly very dramatic how much these cells differed, and how quickly they changed even in the same lab," remarks coauthor Ruedi Aebersold, a professor at the Institute of Molecular Systems Biology at the ETH Zurich. He estimates that if a graduate student had done an experiment with a HeLa cell line at the beginning of his or her project and were asked to repeat it after six months, "they might have gotten different results."

Much of the discussion around the "reproducibility crisis" in research has centered on flaws in experimental design, data analysis, and contaminated or mislabeled cell lines as major drivers. But Aebersold thinks the biological differences in HeLa cells—and cancer cell lines more generally—could play a significant role. At conferences, he has often observed researchers getting into heated arguments over obtaining different results from the same experiment, he notes. "The implication would be one made a mistake," but another explanation is that "the cells may not be the same cells," he explains.

Stanford University cell biologist Tim Stearns sees several possible reasons for why cell lines change under prolonged culture. For one, HeLa cells are cancer cells with known genomic instability and are therefore likely to mutate randomly over time. In addition, they're subjected to various conditions by growth in the lab that might be pushing the cells to evolve unique characteristics. For instance, he says, culturing mammalian cells involves growing them until they

fill a dish, siphoning off a fraction of the cells, and placing them in another dish to grow anew—a process called splitting. "Every person does it a little bit differently," he says. This "[applies] a selection to the cells in ways that we don't fully understand."

Fetal bovine serum—a main ingredient of the growth factor cocktail used to culture mammalian cells—can also vary between labs. "It is not difficult to imagine that based on the source of that material we would create different transcriptional profiles and different selective pressures," Jallepalli explains. "Even simple, humble things like plastic dishes are likely doing more than we realize."

The variation between HeLa isolates may worry some life scientists more than others, notes Jallepalli. Molecular biologists and biochemists who use HeLa cells to study universal cellular processes such as DNA replication or vesicle trafficking are less likely to be concerned that their results may not be reproducible, because these processes are unlikely to change in the face of such selective pressures. Developmental and cell biologists who study more-complex traits such as *Salmonella* infection might have more reason to worry.

Aebersold and his colleagues propose several specific solutions in their paper. For one, researchers ought to use early passages of cancer cell lines and make sure to repeat experiments from one cell line in different samples of the same cell line. Importantly, biologists should clearly report which cell line variants they are using in a given study. "A lot of people aren't even sure what kind of HeLa cells they have," notes Stearns, who agrees that more transparency would be a positive change.

Aebersold hopes to identify more solutions in a workshop he is planning later this year with the European Molecular Biology Organization. This will include 25 experts from various fields, such as science policy, publishing, and science in order to come up with recommendations on how to address reproducibility issues in cell line research.

Ultimately, he hopes his work will help enlighten science policy on the causes of irreproducible results in scientific research. The notion that scientists can't replicate one another's work is a dangerous one, he says. "The simplistic conclusion is either we don't know what we're doing as life scientists, or worse, that things are made up." This would make it easier for science-averse policymakers to argue that money spent on research is wasted. "I think it is important to provide evidence that it is not so simple, people do not just cheat, people are not incompetent, but it's more complicated."

http://bit.ly/2EAbaXS

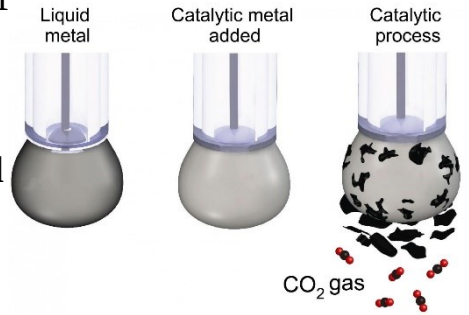
Climate rewind: Scientists turn carbon dioxide back into coal

New technique can efficiently convert CO2 from gas into solid particles of carbon

Researchers have used liquid metals to turn carbon dioxide back into solid coal, in a world-first breakthrough that could transform our approach to carbon capture and storage.

The research team led by RMIT University in Melbourne, Australia, have developed a new technique that can efficiently convert CO2 from a gas into solid particles of carbon.

Published in the journal Nature Communications, the research offers an alternative pathway for safely and permanently removing the greenhouse gas from our atmosphere.



A schematic illustration showing how liquid metal is used as a catalyst for converting carbon dioxide into solid coal. **RMIT University**

Current technologies for carbon capture and storage focus on compressing CO2 into a liquid form, transporting it to a suitable site and injecting it underground.

But implementation has been hampered by engineering challenges, issues around economic viability and environmental concerns about possible leaks from the storage sites.

RMIT researcher Dr Torben Daeneke said converting CO2 into a solid could be a more sustainable approach.

"While we can't literally turn back time, turning carbon dioxide back into coal and burying it back in the ground is a bit like rewinding the emissions clock," Daeneke, an Australian Research Council DECRA Fellow, said.

"To date, CO2 has only been converted into a solid at extremely high temperatures, making it industrially unviable.

"By using liquid metals as a catalyst, we've shown it's possible to turn the gas back into carbon at room temperature, in a process that's efficient and scalable. "While more research needs to be done, it's a crucial first step to delivering solid storage of carbon."

How the carbon conversion works

Lead author, Dr Dorna Esrafilzadeh, a Vice-Chancellor's Research Fellow in RMIT's School of Engineering, developed the electrochemical technique to capture and convert atmospheric CO2 to storable solid carbon.

To convert CO2, the researchers designed a liquid metal catalyst with specific surface properties that made it extremely efficient at conducting electricity while chemically activating the surface.

The carbon dioxide is dissolved in a beaker filled with an electrolyte liquid and a small amount of the liquid metal, which is then charged with an electrical current.

The CO2 slowly converts into solid flakes of carbon, which are naturally detached from the liquid metal surface, allowing the continuous production of carbonaceous solid.

Esrafilzadeh said the carbon produced could also be used as an electrode. "A side benefit of the process is that the carbon can hold electrical charge, becoming a supercapacitor, so it could potentially be used as a component in future vehicles."

"The process also produces synthetic fuel as a by-product, which could also have industrial applications."

The research was conducted at RMIT's MicroNano Research Facility and the RMIT Microscopy and Microanalysis Facility, with lead investigator, Honorary RMIT and ARC Laureate Fellow, Professor Kourosh Kalantar-Zadeh (now UNSW).

The research is supported by the Australian Research Council Centre for Future Low-Energy Electronics Technologies (FLEET) and the ARC Centre of Excellence for Electromaterials Science (ACES).

The collaboration involved researchers from Germany (University of Munster), China (Nanjing University of Aeronautics and Astronautics), the US (North Carolina State University) and Australia (UNSW, University of Wollongong, Monash University, QUT).

The paper is published in Nature Communications *("Room temperature CO2 reduction to solid carbon species on liquid metals featuring atomically thin ceria interfaces", DOI: 10.1038/s41467-019-08824-8).*

http://bit.ly/2XtmEDN

The Lancet Oncology: Worldwide estimates suggest that nearly 1 in 2 children with cancer are left undiagnosed and untreated

The first ever global estimates of the number of undiagnosed cases of childhood cancer suggest that the true number of new cases each year could be almost double those currently recorded

A modelling study published in The Lancet Oncology journal estimates that there are almost 400,000 new cases of childhood cancer annually, while current records count only around 200,000.

The new model makes predictions for 200 countries and estimates that undiagnosed cases could account for more than half of the total in Africa, South Central Asia and the Pacific Islands. In contrast, in North America and Europe only three per cent of cases remain undiagnosed. If no improvements are made, the study authors

estimate that nearly three million further cases will be missed between 2015 and 2030.

"Our model suggests that nearly one in two children with cancer are never diagnosed and may die untreated," says study author Zachary Ward from the Harvard T.H. Chan School of Public Health, USA. "Accurate estimates of childhood cancer incidence are critical for policy makers to help them set healthcare priorities and to plan for effective diagnosis and treatment of all children with cancer. While under-diagnosis has been acknowledged as a problem, this model provides specific estimates that have been lacking."

Previous estimates for the total incidence of global childhood cancer have been based on data from cancer registries, which identify cases in defined populations. However, 60% of countries worldwide do not have such registries and those that do only cover a small fraction of the overall population. Many patients are not diagnosed and are therefore not recorded. This can occur due to lack of access to primary care, with patients dying undiagnosed at home, or due to misdiagnosis.

The new model developed for this study, the Global Childhood Cancer microsimulation model, incorporates data from cancer registries in countries where they exist, combining it with data from the World Health Organisation's Global Health Observatory, demographic health surveys and household surveys developed by Unicef. The model was calibrated to data from public registries and adjusts for under-diagnosis due to weaknesses in national health systems.

The study authors provide estimates of under-diagnosis for each of the 200 countries. They estimate that in 2015 there were 397,000 childhood cancer cases globally, compared to 224,000 that were recorded as diagnosed. This suggests that 43% (172,000 cases) of global childhood cancer cases were undiagnosed. There was substantial regional variation, ranging from 3% in both Western Europe (120 undiagnosed cases out of 4,300 total new cases) and North America (300 of 10,900 cases) to 57% (43,000 of 76,000 new cases) in Western Africa.

In most regions of the world, the number of new childhood cancer cases is declining or stable. However, the authors estimate that 92% of all new cases occur in low and middle-income countries, a higher proportion than previously thought.

The most common childhood cancer in most regions of the world in 2015 was found to be acute lymphoblastic leukaemia, with the notable exception of sub-Saharan Africa. There were around 75,000 new cases globally, including nearly 700 in North Europe, over 1,500 in West Africa, over 3,500 in East Africa and nearly 30,000 in South Central Asia. In East and West Africa, Burkitt's lymphoma was more common, with over 4,000 cases in East Africa and over 10,000 in West Africa. For example, there were around 1,000 cases in the Democratic Republic of the Congo and Ethiopia, while only around 20 in the UK.

"Health systems in low-income and middle-income countries are clearly failing to meet the needs of children with cancer. Universal health coverage, a target of United Nations Sustainable Development Goals, must include cancer in children as a priority to prevent needless deaths," says senior author Professor Rifat Atun, Harvard University, USA.

Taking population growth into account, the authors estimate that between 2015 and 2030 there will be 6.7 million new cases of childhood cancer worldwide. Of these, 2.9 million cases will be missed if the performance of health systems does not improve. The authors hope that their findings will help guide new policies in health systems to improve diagnosis and management of childhood cancers.

The authors found that barriers to access and referral in health systems result in substantial under-diagnosis of childhood cancer in

many countries. They argue that current healthcare models, which concentrate treatment in a few specialised hospitals, are not enough. By strengthening health systems more widely, well-functioning healthcare delivery networks could develop, reducing the number of undiagnosed children with cancer.

"As the hidden incidence of childhood cancer starts to come to the fore, stronger health systems are needed for timely diagnosis, referral and treatment," says Ward. "Expanding cancer registration will be important so that progress can be tracked."

The authors highlight that their results might be affected by limited data availability in some countries. There were only two countries in West Africa (Mali and Cameroon) with available registry data, so predictions for this region might be influenced by the extent to which these countries are representative of the region as a whole.

The authors also assumed that all diagnosed cases are accurately recorded in cancer registries. In practice, some cases might be diagnosed but not recorded, or might be incorrectly classified because of deficient pathology services. However, as new country-specific data become available, the model can be refined to provide updated estimates.

Writing in a linked Comment, Dr Eva Steliarova-Foucher, WHO's International Agency for Research on Cancer, France, says: "Where national data are available and used in the presented model, the proposed estimates should be robust. Yet the only way to validate these new estimates is for countries to ensure efficient provision of representative data... increasing registration coverage and improving the data quality of existing registries would help to reduce the estimation error, which is equivalent to 21 000 cases globally, based on the 95% uncertainty interval... developing efficient vital statistics systems would help to ensure registration completeness and unveil the magnitude of underdiagnosis of cancer. Currently, some mortality statistics are available in only four of 34 low-income countries and in 21 of 47 lower-middle income countries."

Peer reviewed / Modelling

NOTES TO EDITORS

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http://bit.ly/2GObyEA

Sea Creatures Still Arriving in the U.S. on Plastic Debris From the Japanese Tsunami Eight Years Ago

Marine biologists don't know how long different species can survive adrift in the open ocean, and some may become invasive when they reach new shores

By Rachel Kaufman

The open ocean is essentially a marine desert. So far from shore, starved of nutrients like phosphorus (which enters the ocean as runoff from land), not much lives out on the open sea.

So when living animals started washing up along the coasts of the Pacific Northwest and California, clinging to plastic debris that was swept out to sea by the 2011 Japanese tsunami, 4,300 miles away, it raised a few eyebrows. And when the living animals—mostly shellfish and crustaceans, but also marine worms, sea stars, sponges and even fish—kept arriving year after year, it raised even more.

By February 2017, nearly 300 species of living organisms had made landfall on the shores of Washington, Oregon, California and Hawaii. Jim Carlton, professor of marine sciences at Williams College, and colleagues published a study that year in the journal *Science* documenting the castaways that had made the trip from Japan to North America.

Two years later, the animals are still arriving, Carlton said earlier this month at the American Association for the Advancement of Science annual meeting in Washington, D.C. Debris seems to wash

up on the shore seasonally, and the most recent recorded sighting of a living animal—a tiny crab—was last July.

Somehow, these creatures, adapted for life on the coasts, are surviving at sea for at least seven years—five years longer than previously documented instances of marine rafting.

"What we're waiting for is whether or not the spring 2019 pulse brings to North America the same arrival of Japanese tsunami marine debris and living species that it has for the past seven years," Carlton says. There's no reason to think it wouldn't. Thanks to this research, we now have no upper limit on the length of time coastal animals can survive adrift at sea.

When the Tōhoku tsunami washed boats, plastic docks, buoys, crates, ropes, and propane tanks out to sea, the natural disaster became the first opportunity to track a large debris field over an immense distance—one of the only times scientists had a known origin point and time for marine junk. "It was as if we had done a giant experiment, tossed out millions of objects with a date on them," Carlton says.

The debris from Japan ranged from the small, like buoys, to the very large, like the dock shown in upper right. **(J. W. Chapman/A. Pleus/N. C. Treneman/L. K. Rasmuson/A. Marohl/James T. Carlton et al.)**

Much of the 2011 debris was made of plastic, unlike the last time Japan was hit by a tsunami of this size, in 1933, many years before the widespread emergence of plastic goods. Wooden objects degrade in the ocean in just two or three years as they are munched on by wood-eating worms, Carlton says, so any organisms that might be clinging to a wooden debris raft only have a couple years to make it to shore. Plastic, on the other hand, doesn't degrade, which helps explain how a wood-and-fiberglass fishing boat, the Sai-Shou Maru, washed up on a Washington beach in 2013 with five live fish inside.

The combination of the emergence of plastic, the probability that climate change will intensify hurricanes and typhoons, and the ability of marine species to drift on the open ocean for half a decade or more creates a new vector for invasive species, Carlton says. For now, it's not clear whether any of the species that survived the Pacific crossing have established themselves on the West Coast of the U.S. Determining that a foreign organism has taken root takes time and effort. Carlton says his team is already likely missing some organisms, simply because the number of pieces of debris associated with the tsunami is in the thousands or tens of thousands. "We're only sampling a fraction of the debris field," he says. "It's possible the species that will successfully invade will be a species we will not successfully detect."

If a species establishes itself after floating across the ocean, it won't be the first. Famously, in 1995, a population of 15 iguanas rafted 200 miles on trees ripped from the Caribbean island of Guadeloupe. Enough survived to start a new colony on Anguilla, and they're now considered invasive. Since that first documented journey, scientists have begun to study how animals of all kinds manage to raft across the seas.

Jon Waters, a professor at New Zealand's University of Otago, studies how mollusks, sea stars and other creatures float on natural rafts made of kelp. Waters, who isn't involved in the Japan tsunami research, said that kelp is "amazingly robust" and can last up to two years at sea. In this instance, the creatures bring their own food with them—either the kelp itself or the microbial and algal species that live on the kelp.

But when creatures raft on plastic, the question of what they eat is more complicated. “We had assumed that food is pretty limited out there,” Carlton says.

The Great Pacific Garbage Patch presents a unique opportunity to study the organisms' "pre-landing story," as Carlton calls it. Linsey Haram, a postdoctoral fellow at the Smithsonian Environmental Research Center, is planning to study samples from the Pacific gyre to learn more about the communities that live on the ocean between the coasts. Hopefully the study will shed light on what rafting animals eat. Haram said via email that the hitchhikers might “be living off of algae, animals and detritus present on their singular ‘rafts,’” or they may be surviving off the limited plankton and dissolved minerals in the water.

Knowing that rafting species can survive for years “adds a whole new dimension” to the work, Waters says, emphasizing “how important this type of process can be for marine biodiversity research.”

Animals have been rafting across seas for millennia. Madagascar was probably populated by animals that rafted from mainland Africa 60 million years ago. But our plastic waste has made it possible for organisms to travel farther and longer than we ever thought they could.

http://bit.ly/2GSzGWE

Man's Radioactive Remains Spread Radiation All Over Cremation Chamber

Researchers say it's a problem that may be more common than anyone has yet realized

By Rafi Letzter, Staff Writer

Doctors in Arizona injected a 69-year-old man with a drug designed to shrink tumors growing in his body. The drug was radioactive. Sadly, the medicine didn't save him, and two days later, he died. Five days after that, his body was cremated, spreading radioactive particles all over the crematorium.

That cremation, which occurred without the knowledge of the doctors who had injected the radioactive material into the man's body, posed a danger to crematory workers. And researchers say it's a problem that may be more common than anyone has yet realized.

In a short paper published today (Feb. 26) in the journal JAMA, the researchers reported the results of a thorough investigation of the crematorium and the worker who dealt with the radioactive remains. The researchers found significant radiation left on the crematory equipment, including the "oven, vacuum filter and bone crusher."

A sample of the crematorium worker's urine also turned up trace amounts of radioactive material. The researchers wrote that the worker probably didn't receive a dangerous dose of radiation, but they added that the questions of how often radioactive bodies get incinerated or how frequently crematory workers are exposed remain unanswered. (In other words, a one-time exposure is less dangerous than repeated exposure to radiation.)

The researchers found a maximum Geiger-counter reading of 25,000 counts per minute on the crematory equipment. That translates to an exposure of 7.5 millirem per hour for someone in direct contact with the equipment — much more than is considered safe but very far below the levels that would quickly cause radiation poisoning.

The good news is, the researchers wrote, that lutetium 177 (the radioactive element in the injection) has a short range and short half-life. That means that any dangerous effects wouldn't have spread far or lasted very long.

But in the future, the researchers argued, safety protocols for radioactive medicines should take into account the possibility of death and cremation so as to protect the public. With the exception

of Florida, most states — including Arizona — lack rules to prevent cremation of radioactive remains.

http://bit.ly/2GRepfY

Using 1 Germ to Fight Another When Today's Antibiotics Fail

Pitting one germ against another may sound radical, but it's a sign of a growing global crisis

NEW HAVEN, Conn. (AP) — Bacteria lodged deep in Ella Balasa's lungs were impervious to most antibiotics. At 26, gasping for breath, she sought out a dramatic experiment — deliberately inhaling a virus culled from sewage to attack her superbug.

"I'm really running out of options," said Balasa, who traveled from her Richmond, Virginia, home to Yale University for the last-resort treatment. "I know it might not have an effect. But I am very hopeful."

Pitting one germ against another may sound radical, but it's a sign of a growing global crisis. Increasingly people are dying of infections that once were easy to treat because many common bugs have evolved to withstand multiple antibiotics. Some, dubbed "nightmare bacteria," are untreatable. Now scientists are racing to find novel alternatives to traditional antibiotics, a hunt that is uncovering unusual ways to counter infection, in unusual places.

One possible treatment tricks bacteria out of a nutrient they need to survive. Others rev up the immune system to better fend off germs. And viruses called bacteriophages — discovered a century ago but largely shelved in the West when easier-to-use antibiotics came along — are being tried in a handful of emergency cases.

"People's frustration with antibiotic resistance boiled over," said Yale biologist Benjamin Chan, who travels the world collecting phages and receives calls from desperate patients asking to try them. "We're more appreciative of the fact that we need alternatives."

Nature's bacterial predator, each phage variety targets a different bacterial strain. Originally used to treat dysentery in the early 20th century, today Chan looks in places like ditches, ponds, and, yes, sewage treatment plants for types that attack a variety of human infections.

"The best places are often really dirty places, because we're dirty animals," he said. Chan saw hope for Balasa in a lab dish covered in brownish bacterial goo.

Balasa has a genetic disease called cystic fibrosis that scars her lungs and traps bacteria inside, including a superbug named Pseudomonas aeruginosa. A daily dose of inhaled antibiotics kept the infection in check until last fall, when the drugs quit working. A last-ditch IV antibiotic wasn't helping much either.

Chan grew a sample of Balasa's bacteria from her phlegm. Then came the key test: He dripped several pseudomonas-targeting phages into the grimy dish — and clear circles began appearing as the viruses consumed the bugs around them.

But would what worked in the lab really help Balasa's lungs?

Bugs Outpacing Drugs

At least 23,000 Americans die every year as a direct result of an antibiotic-resistant infection, and many more die from related complications, according to a 2013 report from the Centers for Disease Control and Prevention. The CDC plans an updated count, but other research has estimated the toll could be seven times higher. And while there are no good counts in much of the world, one often-cited British report said unless solutions are found, by 2050 up to 10 million people globally could be dying from drug-resistant infections, slightly more than die from cancer today.

Yet few new antibiotics make it to market, and many major drug companies have ended antibiotic research, seeing little profit in medicines that germs will soon outsmart. A recent report found just 11 traditional antibiotics being studied to treat any of the World

Health Organization's list of worst bugs, with no guarantee they'll work.

And while some people are more at risk — those getting surgery, or cancer chemotherapy, for example — "antibiotic resistance is a problem essentially for everyone," said Dr. Anthony Fauci, infectious diseases chief at the National Institutes of Health.

"Over the next several years, all indicators seem to point to the fact that this is going to get worse and worse," he added.

Looking For Bugs' Weak Spots

Finding alternatives means "figuring out what the vulnerabilities of infecting bacteria are. What do they need to cause an infection?" said Dr. Pradeep Singh of the University of Washington.

Singh and fellow UW lung specialist Dr. Christopher Goss zeroed in on iron, a nutrient vital for bacterial growth. It turns out that bugs can't always tell the difference between iron and a chemically similar metal named gallium. Gallium doesn't nourish and knocks other systems out of whack, Goss said.

For two small studies, the researchers recruited cystic fibrosis patients who had antibiotic-resistant pseudomonas in their lungs but weren't openly sick. The patients received a five-day infusion of a gallium-based drug. Over the next few weeks, their lung function improved, enough that next-step studies are being planned.

"It just seems like a proactive way of destroying bacteria," said study participant Tre LaRosa, 24, of Cincinnati. His sister died of cystic fibrosis and while his own CF is under control, he worries that one day a resistant infection will flare. "I can't do anything to prevent that. Antibiotic resistance I think is one of the least talked about and most significant concerns."

Spurring The Immune System

Fauci envisions doctors one day vaccinating people a few weeks before, say, a planned knee replacement to guard against catching a staph infection in the hospital.

Sixteen experimental vaccines are in development to target various infections, according to a recent presentation to a presidential advisory council on resistant germs.

Particularly promising, Fauci says, are lab-engineered "monoclonal antibodies" designed to home in on specific bugs. In one set of studies, researchers are giving experimental antibodies to ventilator patients who have bacteria building up that could trigger pneumonia.

Harnessing Viruses For The Right Attack

In Virginia, Balasa learned of another cystic fibrosis patient helped by Yale's phage experiments and asked to try, hoping to postpone the last option for CF, a lung transplant.

Phages work very differently than traditional antibiotics. Like a parasite, the virus infiltrates bacterial cells and uses them to copy itself, killing the bug as those copies pop out and search for more bacteria. Once the infection's gone, the virus dies out. Because each phage only recognizes certain bacteria, it shouldn't kill off "good bugs" in the digestive tract like antibiotics do.

Bacteria evolve to escape phages just like they escape antibiotics, but they generally make trade-offs to do so — such as losing some of their antibiotic resistance, said Yale evolutionary biologist Paul Turner.

For example, some phages recognize bacteria by a pump on their surface that deflects antibiotics. As the phages kill those bugs, the bacteria rapidly evolve to get rid of that surface pump — meaning survivors should be susceptible to antibiotics again. "It's reviving an arsenal of drugs that are no longer useful," Turner said.

Yale's first test case was an 82-year-old man near death from a heart implant teeming with untreatable pseudomonas. Chan purified a phage from a Connecticut lake that he'd matched to the patient's germs, and with emergency permission from the Food and Drug Administration, doctors squirted it into the wound. The man's infection disappeared.

Then doctors at the University of California, San Diego, saved a colleague who'd been in a months-long coma, using an IV mixture of several phages that target a superbug named Acinetobacter baumannii. Doctors and families began calling both centers seeking emergency care, even as formal studies are being planned to try to prove phages' value.

"There's an incredible opportunity here," said Yale pulmonologist Dr. Jon Koff. "But with that you have to have the appropriate amount of skepticism," with careful testing to tell when it might help.

Last month, Balasa became Yale's eighth patient, inhaling billions of phages over seven days.

Almost immediately, she was coughing up fewer bacteria. It took a few weeks for her to feel better, though, and during that time she switched briefly to some antibiotics she'd previously given up. Without a formal study it's hard to know, but Chan's tests suggest phages killed much of her predominant pseudomonas strain and made the survivors sensitive again to a course of those antibiotics.

Balasa called that "a very big success for me," and was able to quit her antibiotics. She didn't notice additional improvement after a second round of phages, aimed at different strains.

"The true test," Balasa said, "is how long I can go without using any antibiotics again."

https://bbc.in/2Sy23L6

'Tiniest baby boy' ever sent home leaves Tokyo hospital

A baby boy who weighed just 268g (9.45oz) at birth has been released from hospital in Japan, and is believed to be the smallest boy in the world to have been successfully treated.

The baby was born by emergency C-section in August, and was so small he could fit into a pair of cupped hands.

The infant was nurtured in intensive care until he was released last week, two months after his due date.

He had grown to a weight of 3.2kg, and is now feeding normally.

Born at 24 weeks, the tiny boy spent five months in hospital.

"I can only say I'm happy that he has grown this big because honestly, I wasn't sure he could survive," the boy's mother said, according to Tokyo's Keio University Hospital.

Doctor Takeshi Arimitsu, who treated the extraordinary baby, told the BBC he was the smallest infant born (on record) to be discharged from a hospital, according to a database of the world's littlest babies held by the University of Iowa.

He said he wanted to show that "there is a possibility that babies will be able to leave the hospital in good health, even though they are born small".

The previous record-holder was a boy born in Germany, weighing 274g. The smallest surviving baby girl in that same database was also born in Germany, in 2015, and reportedly weighed 252g.

Keio University Hospital said the survival rate of babies born weighing less than a kilogram is about 90% in Japan. But for those born under 300g, that falls to around 50%.

Among the very smallest babies, the survival rate is much lower for boys than girls. Medical experts are unsure why, though some believe it could be linked to the slower development of male babies' lungs.

https://wb.md/2BZjezu

Germ Theory Extended to Alzheimer Disease, Atherosclerosis, Diabetes

Could our whole theory about the most common causes of death be wrong?

Laird Harrison

Over the past few decades, the focus of public health has shifted from infectious diseases to lifestyle. Now that we have tamed such

scourges as tuberculosis, pneumonia, and cholera, the story goes, we need to focus on exercise and diet. With a bit more self-discipline, we could avoid heart disease, cancer, diabetes, and perhaps even Alzheimer disease.

But what if those killers turn out to be like the old ones—caused, at least in part, by pathogens? It's not a new idea, and it remains outside the mainstream. But proponents argue that recent findings merit much more attention than they have received.

"The evidence is accumulating steadily that these conditions are linked to infection, and yet government agencies, such as the US National Institutes of Health, award almost no funding [to research this topic]," says Richard Lathe, PhD, DSc, an honorary professor of biology at the University of Edinburgh, Scotland.

If borne out, the pathogen paradigm could lead to new treatments, perhaps revolutionizing the way the most common diseases are managed. And it could help to explain why seemingly unrelated diseases appear more similar as their causes are investigated.

Alzheimer disease, diabetes, and atherosclerosis all notably involve the buildup of apparently deleterious proteins. Inflammation plays a role in all of them. Insulin resistance figures in both type 2 diabetes and Alzheimer disease. All three diseases become more common with age, and someone with one of these diseases has an increased risk for the others.

The idea that germs might cause senile dementia dates back at least to 1907.[1] But the notion of pathogens as an important factor in Alzheimer disease, type 2 diabetes, cancer, peptic ulcers, or atherosclerosis took a backseat to other apparently more convincing theories—until startling exceptions started cropping up.

In 1989, Michael Bishop and Harold Varmus received the Nobel Prize for the discovery that some retroviruses can cause cancer. In 2005, Barry Marshall and Robin Warren were awarded the same prize for their finding that a bacterium causes gastritis and peptic ulceration. And in 2008, it went to Harald zur Hausen for the discovery that human papillomaviruses can cause cervical cancer.

Could a similar event be in store for Alzheimer disease, diabetes, and atherosclerosis?

The Emerging Link Between Viruses and Alzheimer Disease

For Alzheimer disease particularly, the evidence is tantalizing. Researchers of this disease have long focused on the formation of amyloid plaques and tau tangles. Without quite knowing why these molecules were created, they concentrated on eliminating them. But experimental treatments don't seem to ameliorate the dementia that is the primary symptom of the disease.

"I believe the amyloid theory is more or less on the way out, that amyloid is a by-product," says Jørgen Rungby, MD, PhD, a professor of endocrinology and the University of Copenhagen, Denmark, who is investigating the relationship of Alzheimer disease to type 2 diabetes.

But a by-product of what, exactly? Ruth F. Itzhaki, PhD, thinks she knows. A professor emeritus of neuroscience and experimental psychology at the University of Manchester, United Kingdom, Itzhaki noted back in 1997 that 60% of people with Alzheimer disease had both herpes simplex virus type 1 (HSV1) in their brains and the apolipoprotein E gene (APOE-ε4).[2]

Although the virus is present in the brains of most of people older than 70 years, those who developed Alzheimer disease usually also have the gene. She and others postulated that the gene weakens resistance to the virus. Researchers have found that the gene's carriers are also more vulnerable to cold sores and genital ulcers caused by herpes viruses.[3] After an initial infection, the virus may remain dormant until the immune system further weakens with age. Other researchers found viral DNA in amyloid plaques and tau protein in cell cultures infected with HSV1, leading them to conclude that these proteins serve as a defense mechanism against

the virus.[3] In one study, amyloid beta reduced the growth of *Escherichia coli* by up to 200-fold in vitro, and was also active against *Candida albicans*.[4]

"First the antimicrobial proteins cause destruction of the membrane, effectively killing the pathogen," says Lathe. "Then there is increasing evidence that the aggregation by these proteins causes agglutination; the microbe becomes trapped in these insoluble matrices."

Will This Open Up New Treatment Opportunities?

If Alzheimer disease is caused by a virus, then suppressing the virus should help, a theory that is supported by some emerging evidence. In Taiwan, where data on infections are carefully maintained, researchers found that HSV-infected patients treated with antiherpes agents had a 5.8% risk of developing senile dementia, whereas HSV-infected patients who were not treated had a 28.3% risk for senile dementia. (The researchers focused on senile dementia because not all the patients had been definitively diagnosed with Alzheimer disease.)[5]

The finding is enough to convince Lathe of clinical implications. "If you have a patient with overt herpes simplex, don't wait for it to go away, but if you can possibly do so, intervene with aggressive antiviral medication," he says. "It's a very good idea, because that patient may not get Alzheimer disease later on."

The approach has not been tested in a prospective trial, however, nor have antivirals been studied as a treatment for patients who have already developed dementia. One possibility is that they keep the virus from reaching the brain, but can't undo the damage once the virus is there.[3]

Extending the Viral Link to Other Conditions

Similar, though less dramatic, findings have associated viral infections with schizophrenia,[6] epilepsy,[3] Parkinson disease,[7] and depression.[8] Lathe is working on the theory that prions are antimicrobial as well.

Lathe also believes that similar mechanisms may explain atherosclerosis, which, like Alzheimer disease, is associated with vascular occlusion and decreased cerebral blood flow. The same allelic variants in genes, including *APOE*, increase the risk for both diseases, and also hyperlipidemia. Moreover, atherosclerotic lesions contain amyloid beta.[9]

Scrutinizing the biochemistry of the two conditions, Lathe theorizes that infection leads to inflammation, including the production of 25-hydroxycholesterol to defend against viruses. The resulting cascade ends in "intracellular accumulation of cholesteryl esters and lipid droplets, vascular occlusion, and overt disease."[9]

For type 1 diabetes, the theories of infection are less controversial. Although no one knows exactly what sets off the process, most researchers believe that a pathogen triggers an immune response that somehow goes awry, turning into an autoimmune attack on the pancreas.

Genetic predisposition is key, but the prevalence varies among genetically similar populations, and even among identical twins. Sudden onset of type 1 diabetes has been reported in conjunction with mumps, parainfluenza, human herpesvirus, and enteroviruses, among other pathogens.[10]

"The protein deposited in diabetes, called amylin, is also an antimicrobial protein," Lathe says.

Evidence in Type 2 Diabetes

Could such infections play a role in type 2 diabetes as well? The increase in prevalence has so closely paralleled the introduction of the Western lifestyle and the rise of obesity that questions about infection have not gained much traction. Still, some researchers believe in a role for infection here as well.

For example, they note that periodontitis is a common risk factor for several chronic inflammatory disorders, including atherosclerosis, stroke, diabetes, and Alzheimer disease.[11]

Infections with *Helicobacter pylori* and *Borrelia* are also associated with diabetes. And amyloid beta and amylin deposits, similar to those found in Alzheimer disease, are present in more than 95% of patients with type 2 diabetes. These findings have prompted speculation that a common process unfolds in these diseases, once again entailing an immune response in which amyloid beta and amylin act as antimicrobials but are either unable to completely contain the infections or themselves do damage to healthy tissue.[11]

"If you're an antimicrobial protein produced by a human, you have a tough time to be 100% toxic to microbes and 0% toxic to human cells," says Lathe. "There will always be a little bit of toxicity."

Remaining Questions

Lathe acknowledges that many details need to be worked out, and some evidence is contrary. To cite just one example, knocking out the *APOE* gene delays Alzheimer disease but accelerates atherosclerosis in a mouse model of that disease.[9]

But perhaps the biggest problem is that no microbe has been definitively proven to cause any of these diseases. Apart from herpes simplex in Alzheimer disease, researchers haven't even found a prime suspect. So many experts remain skeptical.

"We do know that there is inflammation involved in these diseases," says Rungby. "But whether that inflammation is caused by a virus or bacterium is, to my mind, very unlikely." If it were, the pathogens would have been identified by now, he argues.

He does see connections between the diseases, though he doesn't necessarily condone the classification of Alzheimer diabetes as "type 3 diabetes." Both conditions involve insulin resistance and poor glucose metabolism, he points out.

Rungby worked on a study of the type 2 diabetes medication liraglutide in Alzheimer disease. Glucose metabolism improved in the patients' brains.[12] Although the study was not big enough to detect cognitive effects, a larger trial is under way.

A variety of other diabetes drugs have been tried in Alzheimer disease. Insulin administered intranasally had promising results.[13]

The exploration of atherosclerosis drugs for Alzheimer disease and vice versa has not proceeded as far. But trials in mice suggest that both acyl-CoA cholesterol acyltransferase inhibitors and acetylcholinesterase inhibitors might work in both diseases. The findings suggest numerous possibilities for trying treatments for one disease out in another.[9]

Do such findings relieve us of the injunction to eat, exercise, and sleep better? No such luck, says Lathe. Antimicrobials in plants—curcumin and resveratrol are only two of hundreds of possible examples—may attack the microbes behind diabetes, atherosclerosis, and Alzheimer disease, so it's still worthwhile eating lots of fruits and vegetables, Lathe says. And exercise boosts the immune system.

For the time being, a healthy lifestyle remains the best defense against the biggest killers of the 21st century.

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http://bit.ly/2Taj3Mv

Typhoid vaccine may protect against other infections

Vaccination with weakened strains of Salmonella *may also protect against other infections*

New research by the University of Liverpool and Liverpool School of Tropical Medicine shows that vaccination with weakened strains of *Salmonella* may also protect against other infections.

The researchers hope that the findings could impact vaccination strategy in the developing world, where infectious diseases are common and where broader protection could potentially save many lives.

Typhoid fever is a bacterial bloodstream infection caused by *Salmonella Typhi* that is estimated to affect between 11-18 million people and cause between than 128,000-190,000 deaths annually worldwide.

Published in the journal Science Advances, a new experimental study presents promising first data on the 'non-specific' immune response triggered by the live oral typhoid vaccine Ty21a.

"Live-attenuated *Salmonella* vaccines are low-cost, well-tolerated and easily administered. These vaccines could potentially be included in global vaccination programmes, not just for their impact on *Salmonella*, but also for their off-target, non-specific beneficial effects," says lead author Dr Shaun Pennington from the Liverpool School of Tropical Medicine.

Previous evidence has suggested that some live-attenuated vaccines, such as those for measles and polio, can stimulate the human immune system to generate a wider protective response and lower all-cause mortality. In order to investigate whether *Salmonella* vaccines might offer similar protection, the researchers vaccinated a small group 16 healthy adults in the UK with the Ty21a vaccine and studied its impact on their immune system over the course of six months.

They looked at immune responses targeting *Salmonella* as well as those targeting a range of other pathogens. The changes they observed to levels of infection-fighting white blood cells (monocytes) and immune system messengers (cytokines) suggest that Ty21a can strengthen the immune response against subsequent, unrelated infections.

"The next step is to observe whether these responses also occur in children in low-income settings where their impact would be greatest. We'd like to conduct further clinical studies, where we will be able to assess the wider impact of our observations in conferring protection against other common infections, not just *Salmonella*,"

says Professor Melita Gordon from the University of Liverpool and Malawi-Liverpool-Wellcome Trust Clinical Research Programme, who was the study's principal investigator.

The researchers add that the ability to manipulate live-attenuated *Salmonella* so that they express components of other pathogens could make their findings particularly exciting for future 'vector vaccine' design.

"*Salmonella* vector vaccines could provide *Salmonella*-specific protection, vectored-pathogen protection and non-specific protection, making live-attenuated *Salmonella* a hugely powerful 'triple threat' tool for global vaccine development," adds Professor Gordon.

The paper 'Nonspecific effects of oral vaccination with live-attenuated Salmonella Typhi strain Ty21a' is published in Science Advances.

http://bit.ly/2BV6UR1

First semi-identical twins identified in pregnancy

Young Brisbane twins, a boy and a girl, have been identified as only the second set of semi-identical, or sesquizygotic, twins in the world - and the first to be identified by doctors during pregnancy.

- ***The now four-year-old boy and girl are identical (monozygotic) on their mother's side sharing 100 per cent of their mother's DNA, but are like siblings on their father's side, sharing only a proportion of their father's DNA.***
- ***The case, the first worldwide to identify semi-identical twins on genetic testing while in the womb, has been reported today in* The New England Journal of Medicine *(NEJM) by fetal medicine specialist and Deputy Vice-Chancellor (Research) at UNSW Professor Nicholas Fisk and Queensland University of Technology (QUT) clinical geneticist and Diagnostic Genomics course coordinator Dr Michael Gabbett.***
- ***Sesquizygotic represents a third type of 'twinning' between identical and fraternal (dizygotic).***

"It is likely the mother's egg was fertilised simultaneously by two of the father's sperm before dividing," said Professor Fisk, who led the fetal medicine team that cared for the mother and twins while based at Royal Brisbane and Women's Hospital in 2014. Professor Fisk, a past President of the International Fetal Medicine and Surgery Society, worked alongside Dr Gabbett.

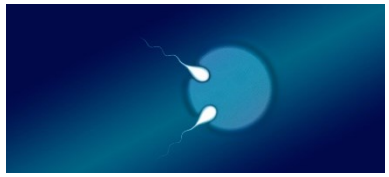


Illustration shows two sperm fertilizing an egg. **QUT**

"The mother's ultrasound at six weeks showed a single placenta and positioning of amniotic sacs that indicated she was expecting identical twins. However, an ultrasound at 14 weeks showed the twins were male and female, which is not possible for identical twins."

Identical twins result when cells from a single egg fertilised by a single sperm divide into two, so identical twins are the same gender and share identical DNA. Fraternal twins occur when each twin develops from a separate egg and the egg is fertilised by its own sperm.

Dr Gabbett said if one egg is fertilised by two sperm it results in three sets of chromosomes, one from the mother and two from the father.

"Three sets of chromosomes are typically incompatible with life and embryos do not usually survive," he said.

"In the case of the Brisbane sesquizygotic twins, the fertilised egg appears to have equally divided up the three sets of chromosomes into groups of cells which then split into two, creating the twins.

"Some of the cells contain the chromosomes from the first sperm while the remaining cells contain chromosomes from the second sperm, resulting in the twins sharing only a proportion rather 100 per cent of the same paternal DNA."

Sesquizygotic twins were first reported in the US in 2007. Those twins came to doctors' attention in infancy after one was identified with ambiguous genitalia. On investigation of mixed chromosomes, doctors found the boy and girl were identical on their mother's side but shared around half of their paternal DNA.

Professor Fisk said an analysis of worldwide twin databases pointed to just how rare sesquizygotic twins are.

"We at first questioned whether there were perhaps other cases which had been wrongly classified or not reported, so examined genetic data from 968 fraternal twins and their parents," he said.

"However we found no other sesquizygotic twins in these data, nor any case of semi-identical twins in large global twin studies.

"We know this is an exceptional case of semi-identical twins. While doctors may keep this in mind in apparently identical twins, its rarity means there is no case for routine genetic testing."

The paper, Molecular Support for Heterogonesis Resulting in Sesquizygotic Twinning, is published in *The New England Journal of Medicine* on February 28.

http://bit.ly/2GUUcFV

Yeast Engineered to Make Cannabinoids

Genes inserted into the yeast genome produce the compounds CBD and THC in the microbes.

Kerry Grens

Genetically engineered yeast produce the cannabinoids THC and CBD, researchers reported today (February 27) in *Nature*. Much like in their typical application of brewing beer, the microbes ferment sugar into the compounds.

The authors say the protocol offers a way to produce a desired cannabinoid without contamination from other plant products. For instance, CBD has been developed into therapeutic products that don't cause the high of THC. "Being able to produce [CBD] in a way that's uncontaminated with THC is a pretty valuable thing," coauthor Jay Keasling of the University of California, Berkeley, tells *Wired*.

To engineer their yeast, Keasling and his colleagues introduced a number of genes for enzymes that convert the sugar galactose to a cannabinoid called CBGA. Then each strain of yeast used its particular suite of introduced genes to make inactivated forms of THC and CBD. Heating the microbes switched the cannabinoids into their active forms.

Yeast have been induced to take steps toward cannabinoid production previously, but Keasling's work has "put it all together and shown that it actually works inside one cell, which is cool," Kevin Chen, the chief executive of Hyasynth Bio in Montreal, Canada, which is working to produce cannabinoids in engineered yeast, bacteria, and algae, tells *Nature*.

One source tells *Nature* that the output of the engineered yeast would need to be boosted 100-fold for it to compete with the cost of plant-derived cannabinoid production.

The scientists also applied their technique to produce cannabinoids not found in nature. "This work lays the foundation for the large-scale fermentation of cannabinoids, independent of *Cannabis* cultivation, which will enable the pharmacological study of these highly promising compounds and could ultimately lead to new and better medicines," they write in their paper.

https://wb.md/2Tr0IKh

More Evidence Prenatal Vitamins Reduce Risk for Autism

May reduce the risk of autism spectrum disorder (ASD) in siblings of affected children by half

Ricki Lewis, PhD

Taking vitamins during the first month of pregnancy may reduce the risk of autism spectrum disorder (ASD) in siblings of affected

children by half, according to findings published online today in *JAMA Psychiatry*.

Although some investigations have associated maternal use of folic acid supplements during early pregnancy with reduced risk for ASD in the child, studies have not probed an association in younger siblings of children diagnosed with ASD.

Rebecca J. Schmidt, PhD, of the University of California, Davis, and co-workers examined recurrence in families considered high risk because an older child has ASD. Focusing on high-risk families avoids the need to recruit large numbers of families that would be required if tracking initial cases, and compares children with similar environments who share on average half of their genomes.

Studies have found that siblings of children with ASD face a 12-fold higher risk relative to the general population, with an ASD incidence ranging from 19% to 24%. Siblings of children with ASD are also at higher risk for language delay, attention deficit, intellectual disability, and other autistic features.

The prospective cohort study analyzed data from 241 children who have a sibling diagnosed with ASD. Of the children, 140 (58.1%) were male, with a mean age of 36.5 months.

The younger siblings were born between 2006 and 2015 and were assessed within 6 months of their third birthdays. Mothers reported their prenatal vitamin use by phone during the first and second halves of the pregnancy and after the birth.

Most of the mothers (231; 95.9%) reported taking prenatal vitamins during pregnancy, but only 87 (36.1%) took them during the 6 months before conception, and 128 (53.1%) took prenatal vitamins in the first month of pregnancy.

Overall, 55 children (22.8%) met criteria for ASD, 60 (24.9%) had non-typical development, and 126 (52.3%) had typical development.

Children in the ASD group were more likely to be male than were children in the typical development group (38/55 [69.1%] vs 65/126 [51.6%]; $P = .03$).

Among children whose mothers took prenatal vitamins in the first month of pregnancy, the prevalence of ASD was 14.1% (18/128), compared with 32.7% (37/113) in the children of women who did not. Children whose mothers took vitamins during the first month were less likely to receive an ASD diagnosis (adjusted relative risk [RR], 0.50; 95% confidence interval [CI], 0.30 - 0.81) but the risk of other non-typical development was no different between the two groups at 36 months (adjusted RR, 1.14; 95% CI, 0.75 - 1.75).

Children whose mothers took vitamins in early pregnancy also had statistically significantly lower autism symptom severity (adjusted estimated difference, –0.60; 95% CI, –0.97 to –0.23) and higher cognitive scores (adjusted estimated difference, 7.1; 95% CI,1.2 - 13.1).

In addition, the highest tertile of total mean folic acid supplementation during the first month of pregnancy was associated with the greatest reduction in ASD risk, consistent with indications that the perinatal period is particularly important. The amount recommended for pregnancy is ≥ 600 µg; multivitamins, with less than 400 µg, are not associated with decreased ASD risk.

"Considering the potential for greater genetic susceptibility in these families, these findings, if replicated, imply that susceptibility could potentially be overcome by environmental manipulation," the researchers conclude.

They call for further investigation of folic acid dose thresholds and effects of other nutrients in the prenatal environment that might elevate risk of ASD.

Limitations of the study include the observational design and the small sample size.

The researchers have disclosed no relevant financial relationships.

JAMA Psychiatry. Published online February 27, 2019. Abstract

https://wb.md/2CbF0Av

'Meticulous' Trial Overturns an Ovarian Cancer Practice

For Decades, Lymph Nodes Removed Automatically

Nick Mulcahy

For decades, patients with advanced ovarian cancer have had regional lymph nodes removed systematically as part of standard surgical "debulking" of affected abdominal organs.

While the procedure has been controversial, multiple investigations through the years — including retrospective series, population studies, and reanalyses of prospective trials — have reported that lymphadenectomy is associated with improved survival.

Now, however, a landmark trial from Europe indicates that these lesser investigations have been mistaken: Automatically removing the pelvic and paraaortic lymph nodes does not extend life.

Investigators of the LION (lymphadenectomy in ovarian neoplasms) trial report that median overall survival was 69.2 months in the no-lymphadenectomy group (n = 323) and 65.5 months in the lymphadenectomy group (n = 324; *P* = .65).

Worse yet, the nodal surgery group had more serious postoperative complications than the no-surgery group, report the team led by Philipp Harter, MD, PhD, Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany.

"Patients with advanced ovarian cancer...did not benefit from systematic lymphadenectomy," the researchers conclude.

The full results from the LION trial were published online February 27 in *The New England Journal of Medicine*.

Preliminary results from the LION trial were presented at the 2017 annual meeting of the American Society of Clinical Oncology and reported at the time by *Medscape Medical News.*

At the meeting, Linda Duska, MD, professor of obstetrics and gynecology and the associate dean for clinical research at the University of Virginia School of Medicine in Charlottesville, agreed with the investigators that the findings demonstrate that lymphadenectomy can be safely omitted because it did not improve survival outcomes.

There was no effect on survival, even though more than half of the patients — 56% — had occult nodal disease, she said.

"This debunks the 'sanctuary' node theory, which many of us learned during our training, that it's important to remove these sanctuary nodes," Duska said.

Now, in an accompanying editorial, a pair of experts explain how medical practice got things wrong for so long and how LION's "meticulous trial design" finally got it right.

Most ovarian cancers are metastatic at diagnosis and survival depends on controlling the abdominal tumor, point out the editorialists Eric Eisenhauer MD, of Massachusetts General Hospital, Boston, and Dennis Chi, MD, of Memorial Sloan Kettering Cancer Center, New York City.

"Death from ovarian cancer most often occurs from progression of abdominal disease" — either from bowel obstruction or malnutrition, they note.

Removable of *visible* disease is the primary goal of cytoreductive surgery (and may include multiple organs with disease spread). Importantly, this type of extensive surgery is associated with improved survival in randomized trials, observe the editorialists.

However, *nonvisible* disease has worried physicians. In particular, they fear cancer that may be hidden microscopically in otherwise normal-looking abdominal-area lymph nodes.

Sure enough, roughly 50% of such nodes will have disease spread that is not obvious to the eye, according to previous studies of postsurgery pathology reports. Furthermore, the editorialists point out that the cancer will exist in many nodes despite chemotherapy.

Thus, standard cytoreductive surgery also goes after potential nonvisible disease and includes lymphadenectomy.

These facts lent credence to the "large number of investigations" that previously reported improved overall survival with lymphadenectomy, the editorialists suggest.

But there have also been criticisms of "the many previous studies," say the editorialists.

And, notably, the "novel trial design" of LION addresses these criticisms.

For example, treatment (lymphadenectomy or no lymphadenectomy) was assigned only after complete visible cytoreduction.

"This was essential," write the editorialists, "because it has been difficult in other studies to distinguish whether lymphadenectomy had an independent effect on survival or was a surrogate for a more complete cytoreduction" (ie, more comprehensive cytoreductive procedures tended to include a lymphadenectomy).

Approached for comment, Jason Wright, MD, chief the of the gynecologic oncology division at New York-Presbyterian/Columbia University Medical Center echoed the editorialists in his assessment of the new study.

"This is definitely an important study," said Wright, who was not involved in the research.

Cytoreduction or debulking surgery is the standard of care for advanced stage ovarian cancer but is associated with a significant rate of complications, he told *Medscape Medical News* in an email.

The study suggests that lymphadenectomy, which is part of that surgery, is not beneficial, may be harmful, and should be avoided if the lymph nodes are not enlarged, said Wright.

"This will help guide surgical management of women with ovarian cancer and hopefully reduce complication rates," he said.

Study Details

Patients in the LION study were enrolled at multiple centers in several countries, including Germany, Italy, Czech Republic, Belgium, Austria, and South Korea.

Eligible patients had a primary diagnosis of advanced epithelial ovarian cancer of stage IIB through IV (per the International Federation of Gynecology and Obstetrics staging system of gynecologic cancer).

The authors point out that in stage IIB through III of the disease, the cancer has not spread outside the peritoneal cavity. Patients with metastases outside the peritoneal cavity (stage IV) were included if resectable metastases were present in the pleura, liver, spleen, or abdominal wall. In short, stage IV patients were included if macroscopically complete resection seemed feasible and they had a good Eastern Cooperative Oncology Group performance status score.

The authors report that, like overall survival, median progression-free survival was not significantly different between the study groups; it was 25.5 months in both groups ($P = .2$).

Serious postoperative complications occurred more frequently in the lymphadenectomy group than in the no-lymphadenectomy group. For example, the incidence of repeat laparotomy was 12.4% vs 6.5% ($P = .01$); this refers to surgery performed on the abdomen using the traditional full-size incision.

The most common reason for repeat laparotomy was bowel leak or fistula. The study authors suggest that lymphadenectomy may have increased this risk by extending an already long, complex surgical procedure.

Also, mortality within 60 days after surgery was 3.1% vs 0.9% ($P = .049$) for the two groups, respectively.

The results of the international, multicenter LION, say the investigators, "add level 1 evidence to the long-standing discussion

about the role of lymphadenectomy in advanced ovarian cancer and once more underline the importance of the use of proper research methods in generating clinical evidence."

The study was supported by the Deutsche Forschungsgemeinschaft and the Austrian Science Fund. Multiple authors have reported relevant financial relationships; see the study for a full list.

N Engl J Med. 2019; 380:822-832, 871-873. Abstract, Editorial

https://go.nature.com/2NCYqT8

Night-vision 'super-mice' created using light-converting nanoparticles

The particles bind to photoreceptors in the eyes and convert infrared wavelengths to visible light.

Matthew Warren

Cue the super-mouse. Scientists have engineered mice that can see infrared light normally invisible to mammals — including humans. To do so, they injected into the rodents' eyes nanoparticles that convert infrared light into visible wavelengths[1].

Humans and mice, like other mammals, cannot see infrared light, which has wavelengths slightly longer than red light — between 700 nanometres and 1 millimetre.

But Tian Xue, a neuroscientist at the University of Science and Technology of China in Hefei, and his colleagues developed nanoparticles that convert infrared wavelengths into visible light. The nanoparticles absorb photons at wavelengths of around 980 nanometres and emit them at shorter wavelengths, around 535 nanometres, corresponding to green light.

This mouse has been given a 'super-power' of infrared vision. **Tian Xue, University of Science and Technology of China**

Xue's team attached the nanoparticles to proteins that bind to photoreceptors — the cells in the eye that convert light into electrical impulses — and then injected them into mice.

The researchers showed that the nanoparticles successfully attached to the photoreceptors, which in turn responded to infrared light by producing electrical signals and activating the visual-processing areas of the brain.

Night-vision games

The team conducted experiments to show that the mice did actually detect and respond to infrared light.

In one test, they gave mice the choice between a dark box and a box 'illuminated' with infrared light. Normally, mice — which are nocturnal — will seek out the safety of a darker box. The ordinary mice showed no preference between the two boxes because they couldn't see the infrared light. But the modified mice favoured the dark box.

In another experiment, the team taught both types of mouse to associate green light with an electric shock, but the modified mice also froze in fear when an infrared light was turned on.

Finally, the researchers placed the rodents in a water maze that had two arms illuminated by different light patterns, only one of which led to a hidden, dry refuge. The modified mice chose the correct arm of the maze according to the light pattern, regardless of whether the patterns were displayed in visible or infrared light.

"It's sometimes a little bit creepy," says Xue. "You show different patterns to the mouse which you cannot see — to you, it's just an empty screen. But the mouse can choose it correctly."

Application questions

Other groups have also sought to give rodents infrared vision. Eric Thomson, a neuroscientist at Duke University in Durham, North Carolina, developed a system that allowed rats to detect infrared light through four sensors connected directly to the brain[2]. But the small number of sensors only provided enough visual information for the rats to find the location of a light, says Thomson.

"What is really exciting here is that they actually showed that they got real image information," he says.

Xue says that his technique could have several applications, including giving people "super-vision". Seeing infrared light could help people to see at night, by detecting infrared wavelengths emitted by, or reflected off, people and objects in the environment. This could be useful for military and security operations, for example.

The team also hopes to adapt the nanoparticles to carry drugs for later release in the eye. But there are several hurdles, including safety concerns, before any use in humans can be tested.

For example, the team's nanoparticles contained heavy metals and regulators would be unlikely to approve them for use in humans, Xue says, so the team is developing organic versions.

But not everyone thinks this technique could be used to augment human vision.

The human visual system has evolved over millions of years to be sensitive to a highly specific part of the electromagnetic system, says Glen Jeffery, a visual neuroscientist at University College London, and the retina is not used to seeing infrared. It's uncertain how people would interpret the image: the environment would appear a lot brighter, for example, and the images could be overwhelming.

So although the science is technically impressive, says Jeffery, it's unclear what impact the technique will have. Given his apprehensions, he adds, "I am the last person in the world who would want to see infrared."

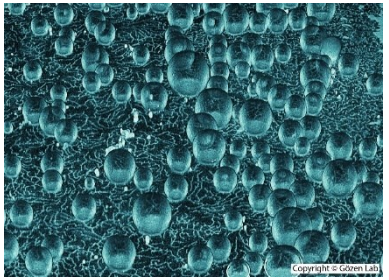
doi: 10.1038/d41586-019-00735-4 *References*

http://bit.ly/2VuYSWq

Scientists discover how surfaces may have helped early life on Earth begin

Spontaneous formation of lipid tubes and the emergence of thousands of vesicles when lipids were left on a silicon dioxide surface

BALTIMORE, MD - On early earth, a series of spontaneous events needed to happen in order for life as we know it to begin. One of those phenomena is the formation of compartments enclosed by lipid membranes. New research by Irep Gözen, Elif Koksal, and colleagues at the University of Oslo reveals, for the first time, how these vesicles can self-assemble on surfaces without external input.



Spontaneously formed protocells, which resemble balloons anchored to a surface by a network of ropes, are visualized by 3D confocal microscopy.
Irep Gözen

The team discovered the most straight-forward and plausible explanation so far with the simplest assumptions. They will present their research at the 63rd Biophysical Society Annual Meeting, to be held March 2 - 6, 2019 in Baltimore, Maryland.

Gözen's lab was originally focused on biomaterials, not origins of life research.

"We were actually trying to do another experiment and this came as a discovery," said Gözen. "The formation of lipid tubes and the emergence of thousands of vesicles was happening spontaneously when we left lipids on a silicon dioxide surface."

The lipids in their experiment were similar to those in bacteria membranes and have water-loving heads and water-avoiding tails. Because of these water-preferring properties, they spontaneously organize with their tails facing inward and their heads facing out. On the silicon dioxide surface, the lipids became sheets, with layers of these organized lipids.

Due to the stickiness of the surface, at some points the two layers separate, and the top layer bulges out, creating tubes and then round balls as they gain more lipids.

The entire process is fully autonomous. A gentle flow from the movement of liquid can then cause these vesicles to detach from the surface creating protocells, like those believed to be a stepping-stone to the origin of life.

"This is a new and novel means of compartmentalization," Gözen said.

It is conceivable that something similar happened on early earth. Silicone dioxide, or silica, is one of the most abundant minerals on the earth's surface. Fatty molecules could have easily existed in the previological era, as confirmed by the results of their successful synthesis performed in possible primitive Earth conditions, together with their traces found in fossils and meteorites.

Intriguingly, silicon dioxide was recently detected on Mars by the Curiosity Rover.

Another puzzle in life's beginnings is how genetic material got inside of protocells. It is not known whether the compartments formed around the already-existing lengthy genetic chains such as RNA, or if the small building blocks somehow found their way inside these tiny bubbles and made the chains inside.

Gözen and colleagues added a light-emitting organic molecule similar in size to nucleotides, the genetic building blocks, to the surrounding of the bubbles. Such molecules which were too big to diffuse through the wall of the bubble, could get inside without compromising the protocells.

They speculate it gets through transient defects or pores in the protocell wall.

"Our research may explain, for the first time, the details of self-directed transition from weakly organized lipids on solid surfaces to protocells with secluded internal contents," Gözen said.

https://wb.md/2GWa9f6

A 'Cure' for Peanut Allergy?

Peanut allergy is a common and potentially life-threatening condition. To date, the primary means of preventing serious events has been peanut avoidance.

William T. Basco, Jr., MD, MS

Attempting Oral Desensitization to Peanuts

The PALISADE,[1] a recent, large, double-blind, placebo-controlled, randomized trial, sought to determine whether a test agent containing 300 mg of peanut protein could produce desensitization in patients who were allergic to peanuts. The study was conducted at 66 international sites. The participants, aged 4 to 55 years, had peanut-specific immunoglobulin E levels above a predetermined threshold or a significant reaction on skin prick testing. Of interest, the final report focuses on the younger subjects (aged 4-17 years) because little efficacy was found among adults (aged ≤18 years) with peanut allergy.

During the baseline challenge, the subjects were given up to 100 mg of peanut protein (equal to one third of a peanut), and all had some degree of an allergic reaction. The randomization was 3:1, treatment:placebo. Both groups of subjects were given similar oral powders meant to be taken daily. Patients began on low doses, 0.5 mg/day, and escalated up to the amount they could tolerate, with a goal of 300 mg/day. Patients who were unable to reach the maintenance dose by week 40 were considered noncompleters. Those who reached the maintenance dose of 300 mg/day were expected to do so for at least 24 weeks. The primary endpoint was the ability to tolerate a single dose of at least 600 mg peanut protein, equal to approximately two peanuts.

PALISADE Study Findings

There were 496 participants, aged from 4 to 17 years, with a slight male majority of 57%. Most (72%) of the participants had

experienced at least one previous anaphylaxis episode after peanut ingestion, and 53% had a history of asthma. This was a largely atopic group, with 66% having multiple food allergies.

There was a notable difference in the proportion of patients who could tolerate the final peanut protein challenge. In the treatment group, 67.2% were able to ingest the test dose of 600 mg peanut protein with no more than mild symptoms, but only 4% of the placebo group were able to do so.

Similarly, notable differences were found in the proportion of patients who were able to tolerate 300 mg (76.6% vs 8.1%) and the proportion who were able to tolerate 1000 mg (50.3% vs 2.4%) peanut powder at the end of the trial. Only 5% of the intervention group compared with 11% of the placebo group experienced a severe reaction during the exit food challenge. Rescue epinephrine during the final food challenge was required by 10% of the intervention group compared with 53% of the placebo group. There was a differential in withdrawal from the trial, however, with 11.6% of the active treatment group compared with 2.4% of placebo group discontinuing the trial because of adverse events. In addition, 14% of the intervention group and 6.5% of the placebo group required rescue epinephrine during the year-long treatment phase. The authors concluded that the study preparation induced desensitization among the children who completed the trial.

Viewpoint

I have said it before, but it is worth repeating: Much, although certainly not all, of what we thought we knew for the past 20 years about how to prevent food allergies, particularly nut allergies, is exactly wrong. And this stands out as an example of when the prevailing wisdom has reversed completely.

In an accompanying editorial, Perkin[2] succinctly identifies several take-home points. First, the notable percentage of subjects who required rescue epinephrine doses in both groups, but especially the treatment group, demonstrates that this process should be carefully monitored. For now, that means that this is not the purview of primary care physicians. Second, daily dosing for 12 months is difficult to maintain, and the study does not establish how long protection might last should a patient discontinue therapy. Third, long-term ingestion with even low-doses of a substance by someone who is sensitive to it could induce other allergic disease, including mucosal eosinophilia, down the line.

Regardless, for patients who fear eating outside of the home, where they have less control over avoidance of an allergen, this therapy could certainly be life-saving. And I suspect there is no shortage of patients willing to participate in such trials for the prospect of gaining protection from inadvertent peanut exposure.

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https://wb.md/2GVFm1V

'Hero' Doctor Shot While Stopping Gunman at Florida Hospital

Physician working in the emergency department, is being called a hero after jumping in front of an armed gunman who opened fire

Megan Brooks

A physician working in the emergency department (ED) at the West Palm Beach Veterans Affairs (VA) Medical Center in Riviera Beach, Florida, is being called a hero, after jumping in front of an armed gunman who opened fire in the ED on the evening of February 27.

"One injured employee (a physician) has been released from the hospital and is doing well," the VA said in a statement sent to *Medscape Medical News*. "We thank him for his efforts to subdue

the suspect. Another employee (non-clinical) was slightly grazed by a ricocheted bullet fragment and is also doing well."

The FBI identified the suspect as Larry Bon, age 59, a homeless veteran and double-amputee. Bon was taken into custody at the scene.

According to multiple media reports, the injured doctor is Bruce Goldfeder, MD.

According to the reports, Bon came to the hospital for treatment but became combative with staff and was taken to the ED, where he pulled a small gun from his wheelchair and started firing as he was about to undergo a mental health evaluation.

"I Ran Towards Him"

ED staff heard about three shots before they were confronted by Bon, who was screaming about cigarettes. In an attempt to distract Bon, Goldfeder told him that there were cigarettes behind him before rushing to Bon to try to disarm him.

During the struggle, Bon fired about three more shots, one of which grazed Goldfeder's left ear before entering his neck and exiting near the base of his skull. Goldfeder gained control of the gun and with the help of others in the ED pinned Bon against a wall with a chair as they waited for police to arrive.

Justin Fleck, assistant special agent in charge at the FBI's Miami field office, said the wounded doctor was "very brave," adding, "he did a heroic thing today. Probably saved a lot of lives," according to *ABC News* .

"I saw the gun, and you know, I saw that it was being pointed and waved in different directions and I heard gunshots, so you know I ran towards him," Goldfeder said after the shooting, according to the *South Florida Sun Sentinel*. "He was waving the gun, and so I kind of did like a football tackle. I tackled him and the gun at the same time and restrained the gun, and then I got shot when it hit the floor."

But Goldfeder doesn't want the "hero" label.

"I think the heroes are the veterans and I think we need to allocate more for their well-being," he said, according to the *Sentinel*. Goldfeder also said that there is a critical shortage of psychiatrists at the West Palm Beach VA Medical Center to treat veterans.

As for his injuries, he said he'll be fine. "I'm lucky, I'm blessed. It's a good day for me. I'm fine. If it were another inch lower maybe...it'd be a different day," Goldfeder said.

"The West Palm Beach VA medical center continuously conducts safety training and exercises to help ensure appropriate responses to active threat situations, and that training was put to great use yesterday. Security measures at the West Palm Beach VAMC are consistent with health care industry standards," the VA said in the statement.

http://bit.ly/2UiEkjB

Doctors plan to test a gene therapy that could prevent Alzheimer's disease

A novel dementia treatment will flood people's brains with a low-risk version of a key gene.

by Antonio Regalado

No one knows for certain what causes Alzheimer's disease. But one fact about the condition has gained nearly irrefutable status. Depending on what versions of a gene called *APOE* you inherit, your risk of the brain disorder can be half the average—or more than 12 times as high.

Sometimes called "the forgetting gene," *APOE* comes in three common versions, called 2, 3, and 4. Type 2 lowers a person's risk, 3 is average, and 4 increases the chance dramatically. The risk is so great that doctors avoid testing people for *APOE* because a bad result can be upsetting, and there's nothing to do about it. There's no cure, and you can't change your genes, either.

Well, today you can't. But doctors in New York City say that beginning in May, they will start testing a novel gene therapy in which people with the unluckiest *APOE* genes will be given a huge dose to their brain of the low-risk version.

If that slows the brain-wasting illness in people who already have Alzheimer's, it could eventually lead to a way to prevent the disease.

The clinical trial, led by Ronald Crystal at Weill Cornell Medicine in Manhattan, is a novel tactic against dementia as well as a new twist for gene therapy. Most gene replacement efforts, which rely on viruses to carry DNA instructions into a person's cells, aim to fix rare diseases such as hemophilia by replacing a single malfunctioning gene.

But common diseases don't have singular causes, so gene therapy has never seemed as promising. The Alliance for Regenerative Medicine, a trade group, says it knows of no gene therapies currently being tried on patients with Alzheimer's disease.

"It seems like a long shot to go into human clinical trials, but there's a desperate need for any treatment," says Kiran Musunuru, a professor at the University of Pennsylvania's medical school. Musunuru, who studies genetic treatments for heart disease, says the experiment planned in New York represents a new category of gene therapy in which the aim isn't to cure, but to "reduce the risk of future disease in healthy people."

Crystal says his plan also sidesteps the debate over the true cause of Alzheimer's disease, which has become a multibillion-dollar roulette wheel where drug companies, and patients, keep losing. In January, Roche called off two big studies of an antibody meant to clear up characteristic plaques of a protein called beta-amyloid, the latest blow to the theory that these plaques around neurons are the fundamental cause of Alzheimer's.

"There are those in the field that believe strongly that amyloid does it," says Crystal, while others think it's another protein called tau, tangles of which are found in dying neurons. "Probably the answer is that it's very complex," he says. "The approach we took is to ignore all that and think about it from a genetic point of view."

In doing so, Crystal's team is relying on a 25-year-old discovery. In the 1990s, researchers at Duke University went fishing for any proteins they could find attached to amyloid plaques. They identified apolipoprotein-e, the protein encoded by the *APOE* gene. By sequencing the gene in 121 patients, they determined that one version, *APOE4*, was inexplicably common in those suffering from the disease.

The gene's function still isn't fully understood (it has a role in transporting cholesterol and fats) but its status as a risk factor remains fearsome. According to the Alzheimer's Association, about 65% of people with Alzheimer's have at least one copy of the risky gene. For people born with two high-risk copies, one from each parent, dementia becomes close to a sure thing if they live long enough.

However, some people inherit one 4 and one 2, the lowest-risk version of the gene. Those individuals have closer to the average risk, suggesting that the protective version of the gene is offsetting the risky one.

This is the effect the Weill Cornell doctors will try to copy. The center is now looking for people with two copies of the high-risk gene who already have memory loss, or even a diagnosis of Alzheimer's. Starting in about a month, Crystal says, the first volunteers will receive an infusion into their spinal cords of billion of viruses carrying the 2 gene.

On the basis of tests in monkeys, Crystal expects the viruses to spread the lucky gene to cells throughout the patients' brains. Mice treated in the same way, his center found, accumulated less amyloid in their brains.

The strategy, Crystal says, doesn't depend on knowing everything about what really causes the illness. "What attracts us to Alzheimer's is that the genetic epidemiology is so obvious," he says. "So the strategy is, can we bathe the brain in E2? We have the infrastructure to do it, so we thought, why not? It gets around the problem of the mechanism of the disease."

"The concept is rational," Crystal adds. "Whether it works in a human is another thing."

The New York study is preliminary. Crystal says his team needs to determine if the added gene is even functioning at a detectable level. Doctors will draw spinal fluid from the patients and see if it contains the expected mix of proteins—the expected type 4, but now with an equal or greater amount of 2 mixed in.

By the time people start forgetting names and where the car keys are, it's a result of brain changes that began taking place a decade before. That means the patients who join the trial can't expect much. It's probably too late for them.

Even so, the Alzheimer's Drug Discovery Foundation is giving Crystal $3 million to pay for the study, its largest grant to date. "We don't know yet what will happen," says Nick McKeehan, an assistant director at the foundation. "But it's a stepping stone. Maybe we will need to treat people earlier. It's opening the door for this type of therapy."

Eventually, the hope is, middle-aged people with risky genes might undergo one-time genetic tune-ups. Even a small reduction in the pace at which brain changes occur could make a difference over time.

"Alzheimer's is the most feared disease in the world, because losing your mind is horrifying. People would rather have cancer or a heart attack," says Susan Hahn, a genetic counselor who doesn't think people should get their *APOE* gene tested without good reasons. "You have to be prepared for what you are going to hear, because it's permanent. You can't change your genes—although maybe with this study you can."

http://bit.ly/2H3cDsj

Women call ambulance for husbands with heart attacks but not for themselves

International Women's Day is on March 8

Malaga, Spain - Women call an ambulance for husbands, fathers and brothers with heart attack symptoms but not for themselves. "It's time for women take care of themselves too" is the main message of two studies from the Polish Registry of Acute Coronary Syndromes (PL-ACS) presented today at Acute Cardiovascular Care 20191,2 a European Society of Cardiology (ESC) congress.

The findings come ahead of International Women's Day on 8 March. This year's campaign theme - #BalanceforBetter - is a call-to-action for driving gender balance across the world. Ischaemic heart disease is the leading cause of death in women and men3 yet today's research shows disparities in management.

Professor Mariusz Gąsior, principal investigator of the registry, said: "Very often women run the house, send children to school, and prepare for family celebrations. We hear over and over again that these responsibilities delay women from calling an ambulance if they experience symptoms of a heart attack."

Dr Marek Gierlotka, registry coordinator, added: "In addition to running the household, women make sure that male relatives receive urgent medical help when needed. It is time for women to take care of themselves too."

A total of 7,582 patients with ST-elevation myocardial infarction (STEMI) were included in the analyses. STEMI is a serious type of heart attack where a major artery supplying blood to the heart is blocked. Faster restoration of blood flow translates into more salvaged heart muscle and less dead tissue, less subsequent heart failure, and a lower risk of death. Guidelines4 therefore recommend

opening the artery with a stent within 90 minutes of diagnosis in the ambulance by electrocardiogram (ECG).

Overall, 45% of patients were treated within the recommended timeframe - these patients were less often women. After adjusting for factors that could influence the relationship, male sex remained an independent predictor of treatment within the recommended timeframe.

Patients within and outside the advised treatment window had similar rates of in-hospital mortality, but those treated promptly were less likely to have a left ventricle ejection fraction below 40% - meaning their heart was better able to pump blood and they had a lower chance of developing heart failure.

ECG results were transmitted from the ambulance to a heart attack centre in about 40% of patients. In women, the likelihood of ECG transfer rose with increasing age - from 34% in women aged 54 years and under to 45% in those aged 75 and above. In men, the rate of transfer was around 40% regardless of age.

Professor Gąsior said: "One of the reasons women are less likely than men to be treated within the recommended time period is because they take longer to call an ambulance when they have symptoms - this is especially true for younger women. In addition, ECG results for younger women are less often sent to the heart attack centre, which is recommended to speed up treatment."

Dr Gierlotka said: "More efforts are needed to improve the logistics of pre-hospital heart attack care in young women. Greater awareness should be promoted among medical staff and the general public that women, even young women, also have heart attacks. Women are more likely to have atypical signs and symptoms, which may contribute to a delay in calling for medical assistance."

Pain in the chest and left arm are the best known symptoms of heart attack. Women often have back, shoulder, or stomach pain. Call an ambulance if you have pain in the chest, throat, neck, back, stomach or shoulders that lasts for more than 15 minutes.

Sources of funding: The Polish Registry of Acute Coronary Syndromes (PL-ACS) is sponsored by the Polish Ministry of Health.

Disclosures: None.

References and notes

1The abstract 'Age and gender related performance of STEMI networks - how do we follow the ESC guidelines on ECG to PCI delay' will be presented during Poster Session 2: Acute Coronary Syndromes - Pathophysiology and Mechanisms, Biomarkers, Treatment, Revascularization Poster Discussant on Sunday 3 March at 09:00 to 17:30 CET in the Poster Area.

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http://bit.ly/2TqJcWB

Is DNA Left on Envelopes Fair Game for Testing?

The genealogist's dream of testing old, spit-laced artifacts is coming true—but raising questions about who controls dead people's DNA.

Sarah Zhang

pavila / shutterstock

Last fall, Gilad Japhet, the founder of a DNA-testing company, got up at an industry conference to talk about his grandmother Rosa's love letters.

Japhet's company, MyHeritage, sells cheek swabs to people interested in their family history. It now has 2.5 million people in its DNA database, making it the third largest behind 23andMe and AncestryDNA. But Japhet wasn't satisfied with only testing the living; he wanted to test the dead. Which brings us to the love letters—or really, the envelopes they came in.

The envelopes were sealed by his grandmother, and the stamps on them presumably licked by her. "Maybe our ancestors did not realize it," Japhet said, a smile growing on his face, "when they were licking those stamps and the envelope flaps, they were sealing their precious DNA for you forever." Then he made the big announcement: MyHeritage would soon begin offering DNA testing on old stamps and envelopes.

He didn't stop there. If you can test the letters of your grandmother, why not those of historical figures? Japhet is a prodigious collector of autographs, and he revealed that he possessed handwritten letters from Albert Einstein and Winston Churchill. In an intriguing if provocative PR move, he promised that "their DNA is coming to MyHeritage very, very soon."

In the past year, genealogists have been abuzz about the possibility of getting DNA out of old stamps and envelopes. In addition to MyHeritage, a British company called Living DNA began informally offering the service for $400 to $600 last year, and a small Australian start-up called Totheletter DNA, which specializes in DNA from envelopes and stamps, launched a similarly priced service in July. MyHeritage says its own service should debut later this year. (A spokesperson declined to comment on when Einstein and Churchill's DNA profiles will be uploaded to the company's site.)

Among genealogists, demand for this service has been pent up for years. "At every conference I do, every seminar I do, I always get questions about artifact DNA. I think there is enormous potential," says Blaine Bettinger, a professional genealogist. Getting the DNA of an ancestor can be tremendously helpful for finding new relatives. For example, your great-great-grandmother passes about 6.25 percent of her DNA to you. But she may have plenty of other relatives who only share DNA from the 93.75 percent that you did not inherit. One way to genetically match those relatives is to test her directly.

Ask genealogists, and you will hear a story about a grandmother's letter or a father's tissue biopsy or a great-aunt's hairbrush, full of DNA that could unlock a family mystery. While 23andMe and Ancestry require large vials of saliva for DNA analysis, which are hard to obtain without a person's cooperation, artifacts are much easier to come by. But extracting DNA from these sources opens up so many new possibilities—some unsavory, some simply uncomfortable. Should you be able to test a parent who refused to play along by digging up an old letter? Or do a secret paternity test on your child, using a cup discarded by the man suspected of having an affair with your wife? Or trace anonymous letters? Or obtain the DNA of celebrities?

In Vallejo, California, police have also sent envelopes from the Zodiac Killer for DNA extraction, in hopes of applying the same genetic genealogy tools that caught the Golden State Killer suspect. (Investigators in the Golden State Killer case had the advantage of well-preserved DNA from a rape kit, though.) Criminal-forensics labs have long analyzed DNA from objects, but they rely on a technique that looks at only 20 sites, called short tandem repeats (STR). To find their suspect in the Golden State Killer case, investigators used a technique from commercial at-home DNA tests, called genotyping, which looks at hundreds of thousands of sites in the human genome. Genotyping yields far more details than STR, revealing distant family relationships as well as genetic variants that can affect a person's health and appearance. That's a lot of information, potentially hidden in an envelope.

For these reasons, the companies offering DNA services for envelopes are drawing a line: These tests are not for living people. The only reason, after all, to resort to getting a living person's DNA from a letter is if the person is not cooperating with a cheek swab or vial of spit—in which case they probably are not consenting.

This means saying no to potential customers. Joscelyn McBain, the founder of Totheletter DNA, told me that several people have contacted her about testing anonymous poison-pen letters. She's sympathetic, but she says, "It just opens up a big can of worms." To avoid testing living people, Totheletter asks customers to explicitly state that the envelope comes from a dead relative. McBain is not against using DNA and genealogy to find violent criminals like the alleged Golden State Killer—she's actually interested in working with police in Australia—but she's uncomfortable with using it to track down just anyone.

To limit the possibility for abuse in this, MyHeritage does not plan to test items such as toothbrushes, dentures, and old clothing. Since envelopes are usually postmarked and have a sender's name written on them, it's easier to validate that the item is what the customer says it is and not some secretly obtained sample. MyHeritage told me it plans to update its terms and services to prohibit uploading DNA profiles of living people that have been obtained through stamps or envelopes. But DNA from dead people, including dead celebrities like Einstein and Churchill, will be allowed.

The ethics of testing a deceased person's DNA are more ambiguous, says Bettinger. Dead people usually don't have privacy rights. Dead celebrities, having been public figures, have even less of an expectation of privacy. But dead people still often have living descendants, who share some portion of their ancestors' DNA and who do have privacy rights. What if Einstein's living descendants aren't thrilled about a company uploading his DNA, just so random people online can find out if they're distantly related to a genius?

On the other hand, says Bettinger, we don't ask all our living relatives and future unborn descendants for consent when we ourselves mail in a DNA test—even though it affects them all. The alleged Golden State Killer, for example, was identified through third and fourth cousins who took DNA tests. Right now, any one individual has relatively little control over his or her own genetic privacy.

Living DNA's terms of service would allow testing envelopes for the DNA only when the target person is deceased and the customer has obtained the envelope legally. Of course, these terms of service rely on the honesty of the customer. A lab technician reviews materials to make sure they are what customers claim they are, but cost might be the most practical deterrence. Living DNA's co-founder, David Nicholson, brought up the example of paternity tests. They're available in drugstores for around a hundred dollars, while Living DNA's service costs $400 to $600. "It's a very expensive way to do that," says Nicholson.

The cost of testing envelopes for DNA is unlikely to come down soon. 23andMe, AncestryDNA, and MyHeritage are able to offer ordinary ancestry tests for less than $100 because they use standardized vials and swabs. That process is easy to automate with robots. In contrast, every envelope is different. A human hand needs to carefully cut out the envelope flap or stamp, dissolve the glue, and extract the DNA. Nicholson says different types of glue might require different extraction techniques. DNA also degrades over time, so the success rate of testing old letters hovers around 50-50.

So for now, the commercial viability of envelope DNA testing is still uncertain. "At the moment, we're doing it as a token to help people," Nicholson says. It's not really making the company any money. He's considered offering a two-tiered service, where customers pay a smaller free upfront and only pay for the full genetic analysis after it looks like it will work. McBain has been open about similar challenges for Totheletter. She's currently refunding customers whose samples are not successful. "We have to improve our results if it's something we can commercially sustain," she says. The entrance of MyHeritage, a big player in the consumer DNA industry, will be an important test case.

Genealogists are, by disposition, people who enjoy thinking about ways of the past. It is not lost on them that we have stopped writing letters and licking stamps. "There's kind of this golden period from the late 1800s to maybe the past decade or so," Bettinger says. Then he adds, "Maybe DNA testing is picking up that slack." In other words, now we have a generation of people who are voluntarily testing themselves and sharing their DNA—what more could you ask for?

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One Twin Committed the Crime — but Which One? A New DNA Test Can Finger the Culprit

A handful of criminal prosecutions have stalled because DNA tests cannot distinguish between suspects who are twins. Then scientists decided to create one.

By Carl Zimmer

One night in November 1999, a 26-year-old woman was raped in a parking lot in Grand Rapids, Mich. Police officers managed to get the perpetrator's DNA from a semen sample, but it matched no one in their databases.

Detectives found no fingerprints at the scene and located no witnesses. The woman, who had been attacked from behind, could not offer a description. It looked like the rapist would never be found.

Five years later, there was a break in the case. A man serving time for another sexual offense submitted a DNA sample with his parole application. The sample matched DNA from the rape scene.

There was just one catch: The parolee had an identical twin, and standard DNA tests can't distinguish between identical twins. Prosecutors had no additional evidence to rule out one or the other. Because they couldn't press charges against either of the men, the case remains open nearly 20 years later.

But maybe not forever.

In recent years, scientists have gained a clearer picture of the early development of the embryos of identical twins. Originating from a single fertilized egg, they later acquire unique genetic mutations. New advances in DNA sequencing are making it possible to pinpoint those mutations — and to tell identical twins apart.

This kind of test could well determine which of the brothers committed the rape. In a recently published study, researchers concluded that the technique is "a realistic option, fit for practical forensic casework."

Forensic DNA testing arose in the 1990s, years before the first human genome was sequenced. Scientists found that they needed only tiny snippets of genetic material to tell people apart.

That's because our genomes are sprinkled with segments, known as short tandem repeats (STRs), that mutate much faster than the rest of our DNA. Because of this rapid changeability, these genetic bits tend to vary distinctively from person to person.

Researchers identified 13 STRs that were very effective in matching people to DNA samples. The probability of the STRs all being identical in two unrelated people is less than 1 in a trillion.

DNA testing became a standard legal tool for identifying criminal suspects and resolving paternity disputes. But for all its power, the test could not tell identical twins apart. And that led to some Kafkaesque impasses.

In 2004, for example, Holly Marie Adams won a paternity suit in Missouri against Raymon Miller for child support. A standard DNA test indicated he was the alleged father. Mr. Miller appealed the case because Ms. Adams had also had sex with his twin brother, Richard. A DNA test on Richard also yielded a match.

"The results of blood tests performed on the two brothers demonstrated that both had a 99.999 percent probability of being the father," Judge Phillip Garrison wrote. The court was forced to rely on other evidence — the timing of the woman's pregnancy, for example — to decide that Raymon Miller was in fact the father.

Faced with such cases, forensic DNA experts tried something once thought impossible: building a test that could tell twins apart. The researchers took advantage of the fact that identical twins are not, in fact, genetically identical.

When a fertilized egg starts dividing, there's a small chance each new cell will gain a new mutation. When the cells separate into twin embryos, one gets some of the mutant cells and the other gets the rest. Unique mutations will end up in cells throughout each twin's body.

In the mid-2000s, scientists at the University of Hanover in Germany wondered if new STRs could arise in one twin and not the other. They developed a test to examine thousands of STRs instead of just 13.

It didn't work. Their experimental test couldn't tell identical twins apart. "Our attempts with STRs were probably totally naïve," said Michael Krawczak, a geneticist who now teaches at Kiel University in Germany.

At the time, the costs of DNA sequencing were dropping drastically, raising another possibility. If a test could compare not just STRs but the entire genomes of twins, Dr. Krawczak and his colleagues wondered, could it tell them apart?

In 2012, the researchers offered some calculations suggesting that the answer was yes.

Imagine, they said, that a court heard a paternity dispute involving identical twins. Blood or saliva could be used to sequence the twins' genomes. Researchers could look for genetic mutations that only one twin — the father — shared with the child.

But the scientists' analysis also showed that such a test would have to be very precise and sensitive. Cells that will become sperm separate from other cells in an embryo early in development. Only a few mutations arise in a twin embryo before that separation.

The window for these key mutations is so narrow, in fact, that sometimes none will arise. In 20 percent of cases, the researchers concluded, twins would have no distinguishing mutations at all.

Such a test would be difficult, then — but it would also be definitive. Just a single mutation, confirmed by multiple analyses, would be enough to implicate one twin and exonerate the other.

Dr. Krawczak's thought experiment captured the imaginations of researchers at Eurofins Scientific, a laboratory testing company headquartered in Brussels. They decided to give the method a try.

They found a pair of twin brothers willing to volunteer their DNA, as well as the DNA of one twin's child and his wife. The researchers sequenced each person's whole genome and found enough mutations to tell the child's father from its uncle.

The Eurofins team published this proof of concept in 2014. Soon the news reached David Deakin, an assistant district attorney in Boston, who had been working for years on a rape case against a man named Dwayne McNair.

Mr. McNair had come under suspicion for two rapes in 2004. In 2007, police managed to get DNA from a cigarette Mr. McNair cast away, and the STRs were a match to sample from both crime scenes. But then detectives discovered that Mr. McNair had a twin brother, Dwight. Mr. Deakin got a court order for a new DNA test, hoping the McNair brothers were fraternal twins.

"No such luck," said Mr. Deakin.

Try as they might, investigators couldn't firmly determine which of the identical brothers had participated in the rapes. The case stalled until 2010, when detectives tracked down the second rapist in both crimes, Anwar Thomas.

As part of his plea deal, Mr. Thomas agreed to identify Dwayne McNair as the other rapist. He had known the McNair twins since high school and said he had no trouble telling them apart. But Mr. Deakin would have nothing to offer a jury to prove Mr. Thomas was telling the truth.

Then Mr. Deakin learned of the Eurofins test. It would be expensive — $130,000 — but Mr. Deakin became convinced it could seal the case.

"We were persuaded their science was sound," he said.

Mr. Deakin had to drop the charges against Mr. McNair to make time for the test. After three months, the Eurofins team came back with a conclusion: DNA samples from the rapes matched Dwayne McNair, not Dwight.

Based on a statistical analysis by Dr. Krawczak, Mr. Deaking told the court that it was two billion times more likely that the rapist's DNA belonged to Dwayne McNair than to his brother.

Armed with the new results, Mr. Deakin re-indicted Mr. McNair in September 2014. His lawyers filed a motion to exclude the Eurofins test from evidence. They argued that it was too new and too little studied to be reliable.

After hearing expert witnesses for both sides, Judge Linda Giles ruled that the test was based on valid scientific principles. But it had yet to be replicated by any other lab or to be laid out in sufficient detail in a peer-reviewed journal article.

"Although the court has the utmost respect for the ability of jurors to comprehend complicated scientific principles, they would not have the luxury of many days of rumination, as this gatekeeper has needed, to untie this Gordian knot," she wrote in a decision handed down in April 2017.

"So we were out of luck and back where we started," said Mr. Deakin.

The decision was not just a disappointment to Mr. Deakin. Prosecutors in Michigan had been considering using the technique to distinguish between the twins in the Grand Rapids rape case. Now they decided against it.

In Boston, the case continued, with a conventional DNA test narrowing the suspects to the twins and the testimony of Mr. Thomas specifically against Dwayne McNair.

That turned out to be enough. Mr. McNair was found guilty in January 2018 and sentenced to 16 years in prison.

Since Eurofins published the initial test in 2014, only one other court has asked the company to test twins — in a civil paternity case in Germany, according to Burkhard Rolf, director of DNA forensic services at Eurofins.

Dr. Rolf, Dr. Krawczak and their colleagues decided to write up a mathematically detailed account of their methods. The journal PLOS Genetics accepted the paper, but then required them to remove details about the McNair rape case and the German paternity case before publishing it.

Chris Becker, the prosecuting attorney of Kent County, Mich., said that the publication of the paper is a step in the right direction — but not enough for him to make arrests in the Grand Rapids rape case.

Steven A. McCarroll, a geneticist at Harvard Medical School who was not involved in the research, said that the one way to make people more confident in the new method would be to demonstrate its accuracy on a large number of twins.

“It would be really nice to know that we could do this kind of analysis over and over and over again and never get it wrong,” he said.

Mr. Deakin, the Boston prosecutor, was optimistic that such research could lead to its adoption by the courts. “If five or six labs did it, and four or five them reproduced the results and there were no negative results, I think you could you could get it in pretty easily almost anywhere,” he said.

Dr. Krawczak and his colleagues estimate roughly 1 percent of crime cases and paternity disputes may involve identical twins.

“It’s not something that’s going to happen every day in every laboratory,” said Dr. Krawczak. “But once people become aware of this, there may be a lot of cold cases that come back to life.”