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OHSU study: Tetanus shots needed every 30 years, not every 10

A revised adult vaccination schedule could save millions in health-care costs

PORTLAND, Ore. - Researchers at Oregon Health & Science University are challenging the convention that tetanus and diphtheria vaccine boosters need to be administered every 10 years. Their paper in Clinical Infectious Diseases recommends current adult vaccination schedule should be revisited.

"We have always been told to get a tetanus shot every 10 years, but actually, there is very little data to prove or disprove that timeline," says Mark K. Slifka, Ph.D., a professor at the Oregon National Primate Research Center at OHSU. "When we looked at the levels of immunity among 546 adults, we realized that antibody titers against tetanus and diphtheria lasted much longer than previously believed."

In this study, Slifka and colleagues looked at the magnitude and duration of immunity to tetanus and diphtheria to provide an evidence-based evaluation of the current adult vaccine schedule. Their analysis shows adults will remain protected against tetanus and diphtheria for at least 30 years without the need for further booster shots, after completing the standard five-dose childhood vaccination series, If a revised adult vaccination schedule were implemented, the authors believe that a simplified age-based vaccination plan could be designed to involve a single vaccination at age 30 and again at age 60.

"If you ask around, you often find that it is hard for people to remember if they had their last tetanus shot eight years ago or even 11 years ago," says Slifka. "If we were to use a simple age-based system, people would only have to remember to get their shots when they turn 30 and again when they turn 60."

The idea of changing our vaccination schedule is not as radical as it sounds, the authors note. Other countries, including the United Kingdom, recommend no adult booster shots - and the World Health Organization recommends only a single adult booster vaccination at the time of first pregnancy or during military service. In other words, if the U.S. switched from a 10-year schedule to a 30-year schedule, this approach would still be more conservative than other countries while reducing the number of potentially unnecessary vaccinations.

Modification of the adult vaccination schedule could also have a substantial impact on U.S. health care costs, the authors suggest. Based on the number of adults who get booster shots within the recommended 10-year interval, they estimate that changing to a 30-year schedule would reduce the costs of vaccination by two-thirds, a reduction of approximately $280 million per year in health care costs, and approximately $1 billion in cost savings within four years.

Vaccination against tetanus and diphtheria has resulted in a significant decline in the incidence of these two serious diseases. Deaths attributable to tetanus have declined 99 percent since the prevaccine era, and diphtheria is virtually nonexistent in the U.S.

"Over the last decade, we have seen that mainly recent immigrants or older people who did not receive at least three doses of the tetanus vaccine are the ones at highest risk for a fatal case of tetanus," said Slifka, "Even with this in mind, the odds of dying from tetanus in the U.S. are approximately 1 in 100 million." Diphtheria is even more rare, Slifka noted. "There have been only 5 cases of diphtheria reported in the U.S. in the last 15 years. Believe it or not, there are actually more cases of anthrax reported each year than diphtheria."

Together, these numbers indicate that tetanus and diphtheria vaccines are working well, but continued vigilance is still needed. "We need to make sure our kids get all of their recommended vaccinations. I can't emphasize this enough. Only by getting the complete childhood series will these children grow into adults who will maintain strong vaccine-mediated protection against these important diseases."

So when can we switch to a 30-year booster schedule? "This must be reviewed and approved by the Advisory Committee on Immunization Practices, the group responsible for determining the vaccination schedules in the U.S.," says Slifka. "However, based on our results and the vaccination schedule already recommended by other countries and the World Health Organization, it might not be long before we can say goodbye to the traditional 10-year booster program."

Contributors to this study include: Erika Hammarlund, M.S.; Archana Thomas, B.S.; Abby Rynko, Ph.D.; Elizabeth A. Poore, B.S.; Ian J. Amanna, Ph.D.; Motomi Mori, Ph.D.; and Zunqiu Chen, Ph.D.

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New treatment reduces precancerous polyps in hereditary cancer patients

Two-drug combination significantly reduces the number and size of precancerous polyps in the small intestine

SALT LAKE CITY - Inheriting a mutation in the APC gene leads to a nearly 100% lifetime risk of colorectal cancer. While colon cancer can be kept at bay by removing the large intestine, these patients also have up to a 15% risk of getting cancer in the small intestine, which is the leading cause of cancer death in this patient group. A new study published in the Journal of the American Medical Association (JAMA), has identified the first prevention treatment for these

patients, a two-drug combination that significantly reduces the number and size of precancerous polyps in the small intestine.

Jewel Samadder, MD, is the lead researcher on the study from Huntsman Cancer Institute (HCI) at the University of Utah. He says that medical and surgical management of these patients is difficult since it is hard to remove precancerous polyps in the small intestine and surgical removal of this region of the small, as well as the large intestine, means that patients have a hard time absorbing nutrients. "We have been left with very few, really no options to offer treatment."

Familial adenomatous polyposis (FAP) is an inherited disorder that occurs in 1 out of 10,000 people. It is caused by a mutation in the APC (adenomatous polyposis coli) gene that is inherited from one parent. Patients with FAP form hundreds to thousands of polyps in their large and small intestine. Many patients have their large intestine removed to prevent colon cancer, but for some patients with a large number of small intestine polyps, it is difficult to prevent cancer from occurring.

Research studies using cultured colon cancer cells and in a mouse model for FAP, suggested that blocking two different biochemical pathways at the same time may inhibit cancer growth. Specifically, in the mouse FAP model, giving a drug that blocked an inflammation pathway driven by cyclooxygenase-2 (COX-2) and a drug that blocked the epidermal growth factor receptor (EGFR), reduced the development of small intestine cancer in the animals by 87%.

Deborah Neklason, PhD, a researcher on the study, says the current clinical trial used the information obtained in basic science to test a drug combination of sulindac (inhibitor of COX-2) and erlotinib (inhibitor of EGFR). "This trial is an effort to go at two pathways that intersect and see if we could drive down the development of polyps and cancer in the small intestine," says Neklason.

Ninety-two FAP patients were identified from the Huntsman Cancer Institute Hereditary Gastrointestinal Cancer Registry, one of the largest registries in the world, and were entered into a trial where half received drug and half placebo. The trial was blinded so neither the patients nor researchers knew who was getting the drug. Both groups of patients received an endoscopy before the trial began and again after six months in order to visualize and characterize the size and number of polyps before and after treatment.

At the time of the six-month endoscopy, the drug treatment group had significantly fewer ($p<0.001$) and smaller polyps than the placebo group with an overall reduction in polyps of 71% ($p<0.001$). "This is an important example of bench to bedside science where discoveries in cell biology and preclinical mouse models have translated into a precision prevention clinical trial in a high risk patient group," says Samadder.

The most common side effects in patients receiving treatment were an acne like rash (87%) and canker sores (39.1%). Many patients had their drug dose reduced during the six months of the trial, but this did not appear to affect the reduction in polyp burden or number suggesting that lower doses of drug could be used in future trials.

Samadder says most of the side effects were tolerable, "for a drug treatment that provides precision prevention, where you identify a precise group of patients at the highest cancer risk, the medication may have a risk profile, but the risk benefit ratio changes because the patient may have a few side effects, but reducing the risk of cancer is more important."

According to Samadder, while this preliminary trial is encouraging, it is still not known if the drug combination prevents cancer altogether. The patients are being followed for the next two years, which will help determine long-term outcomes. Future multi-center trials will look at using the drugs at different dosage, as well as using erlotinib and sulinac alone or in combination.

Samadder and co-authors Deborah W. Neklason, Kenneth M. Boucher, Kathryn Byrne, Priyanka Kanth, Wade Samowitz, David Jones, Sean V. Tavtigian, Michelle W. Done, Therese Berry, Kory Jasperson, Lisa Pappas, Laurel Smith, Danielle Sample, Rian Davis, Matthew K. Topham, and Randall W. Burt are from Huntsman Cancer Institute and the University of Utah. Patrick Lynch is from the University of Texas MD Anderson Cancer Clinic, Elena Strait is from Penrose Hospital in Colorado Springs, Wendy McKinnon is from the University of Vermont Cancer Center, and Scott K. Kuwada is from the Department of Medicine at the University of Hawaii.

This work was supported by National Cancer institute (NCI) grants P01-CA073992 (RWB and SVT) and Huntsman Cancer Institute Cancer Center Support Grant (NCI P30CA042014), as well as by the Huntsman Cancer Foundation. Samadder was supported by a junior faculty career development award from the American College of Gastroenterology (ACG). Research reported in this publication was also supported by the National Institutes of Health National Center for Advancing Translational Sciences, under Award Number 1ULTR001067.

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Cricket players more successful when batting the 'wrong' way

Current T20 World Cup batsmen like Chris Gayle and David Warner use the opposite stance

Cricket batsmen who bat the 'wrong' way have a stunning advantage according to new research published in the scientific journal Sports Medicine. Batsmen who adopt a reversed stance (right-handed people who bat left-handed, and left-handers who bat right-handed) are far more likely to reach the first-class and international level, with professional batsmen being seven times more likely to adopt a reversed stance than the rest of the population. These are the results of research on professional and inexperienced cricket batsmen conducted by David

Mann at Vrije Universiteit Amsterdam in the Netherlands, in collaboration with Oliver Runswick (St Mary's University, UK) and Peter Allen (Anglia Ruskin University, UK). The results suggest that a reversed stance leads to greater success and questions the way that similar sports (e.g. golf and baseball) are taught and performed.

A reversed stance may provide technical advantages

The reason for the advantage appears to be that the reversed stance places the dominant hand at the top rather than the bottom of the bat handle. VU-scientist David Mann: "The top hand is typically responsible for controlling and guiding the path of the bat to hit the ball, so it appears to be an advantage for the dominant hand to perform this role. The results suggest that by teaching batsmen to use a conventional stance, coaches may be inadvertently teaching players to bat 'back-to-front' and could be harming their players' chances of developing expertise. By adopting the conventional stance, batsmen may have been unintentionally taught to bat 'back-to-front' and might not have maximized their potential in the game."

Why do we bat the way we do?

When playing cricket, baseball or golf, people are usually taught to adopt a 'right-handed' or 'left-handed' stance that places their dominant hand closer to the striking end of the bat. David Mann: "Surprisingly, it is not clear why this is the case, and until now it has been unknown whether doing so provides the best chance of developing skill."

Professional cricket players already use a reversed stance

The list of batsmen who have used a reversed stance over recent years at the international level is striking. In particular, some of the greatest batsmen of the modern era including Brian Lara, Clive Lloyd, David Gower, Adam Gilchrist, Alistair Cook, Michael Hussey, Kumar Sangakkara, and Matthew Hayden all bat left handed yet are actually right-hand dominant. The reversed-stance advantage also extends to people who are left-hand dominant but bat right-handed, with famous examples including Michael Clarke, Inzamam-ul-Haq, and Adam Voges. Even Sachin Tendulkar, probably the best batsmen of the modern era, batted and bowled right-handed, but is known to write with his left hand. It appears that in many cases the players adopted the reversed stance by chance. Mann: "Michael Hussey, one of Australia's finest cricketers, is right-hand dominant but learned to bat left handed to emulate his childhood idol, Allan Border."

The effect is present in the ICC T20 World Cup currently being played in India

The number of reversed-stance batsmen competing in the ICC T20 World Cup presently taking place in India is compelling, with the list including David Warner and Usman Khawaja (Australia); Chris Gayle (West Indies); Suresh Raina and Shikhar Dhawan (India); JP Duminy (South Africa); Thisara Perera (Sri Lanka); Eoin Morgan and Ben Stokes (England); Colin Munro (New Zealand), and Tamim Iqbal (Bangladesh). Surprisingly, half of the Australian batsmen/all-rounders bat using a reversed stance, as do 40% of the English and 33% of the South African, Sri Lankan, and Bangladesh batsmen/all-rounders.

The research "Hand and Eye Dominance in Sport: Are Cricket Batters Taught to Bat Back to Front?" Is published in Sports Medicine.

http://www.eurekalert.org/pub_releases/2016-03/b-atj031816.php

Adherence to Japanese diet guidelines linked to longer life

Adherence to Japanese dietary guidelines is associated with a lower risk of death from all causes and death from cardiovascular disease

Closer adherence to Japanese dietary guidelines is associated with a lower risk of death from all causes and death from cardiovascular disease, particularly stroke, finds a study published by The BMJ today.

The findings suggest that balanced consumption of grains, vegetables, fruits and adequate intake of fish and meat, can contribute to longevity in the Japanese population.

In 2005, the Japanese government developed the spinning top - a Japanese food guide - to illustrate the balance and quantity of food in the daily Japanese diet.

A team of researchers, led by Kayo Kurotani at the National Centre for Global Health and Medicine in Tokyo, set out to examine the association between adherence to the food guide and total and cause specific mortality.

They used data from detailed food and lifestyle questionnaires completed by 36,624 men and 42,920 women aged 45-75. Participants had no history of cancer, stroke, heart disease, or chronic liver disease and were followed-up for 15 years.

They found that both men and women with higher scores on the food guide (better adherence) had a 15% lower total mortality rate over 15 years. This protective association was mainly attributable to a reduction in mortality from cerebrovascular disease.

The researchers conclude: "Our findings suggest that balanced consumption of energy, grains, vegetables, fruits, meat, fish, eggs, soy products, dairy products, confectionaries, and alcoholic beverages can contribute to longevity by decreasing the risk of death, predominantly from cardiovascular disease, in the Japanese population."

http://www.eurekalert.org/pub_releases/2016-03/uomh-mav032216.php

More ancient viruses lurk in our DNA than we thought

One whole endogenous retrovirus genome -- and bits of 17 others -- were spotted in a study of 2,500 human genomes

BOSTON and ANN ARBOR, Mich. -- Think your DNA is all human? Think again. And a new discovery suggests it's even less human than scientists previously thought.

Nineteen new pieces of non-human DNA -- left by viruses that first infected our ancestors hundreds of thousands of years ago -- have just been found, lurking between our own genes.

And one stretch of newfound DNA, found in about 50 of the 2,500 people studied, contains an intact, full genetic recipe for an entire virus, say the scientists who published their findings in the *Proceedings of the National Academy of Sciences*.

Whether or not it can replicate, or reproduce, it isn't yet known. But other studies of ancient virus DNA have shown it can affect the humans who carry it.

In addition to finding these new stretches, the scientists also confirmed 17 other pieces of virus DNA found in human genomes by other scientists in recent years.

The study looked at the entire span of DNA, or genome, from people from around the world, including a large number from Africa -- where the ancestors of modern humans originated before migrating around the world. The team used sophisticated techniques to compare key areas of each person's genome to the "reference" human genome.

Working at Tufts University and the University of Michigan Medical School, the researchers made the findings with funding from the National Institutes of Health.

HERV-enly find

The findings add to what science already knows about human endogenous retroviruses, or HERVs. That's the name for the ancient infectious viruses that inserted a DNA-based copy of their own RNA genetic material into our ancestors' genomes. They're part of the same type of virus that includes the modern human immunodeficiency virus, which causes AIDS.

Over generations, the virus-generated DNA kept getting copied and handed down when humans reproduced. That's how it ended up in our DNA today. In fact, about 8 percent of what we think of as our "human" DNA actually came from viruses. In some cases, HERV sequences have been adopted by the human body to serve a useful purpose, such as one that helps pregnant women's bodies build a cell layer around a developing fetus to protect it from toxins in the mother's blood.

The new HERVs are part of the family called HERV-K. The intact whole viral genome, or provirus, just found was on the X chromosome; it's been dubbed Xq21. It's only the second intact provirus found to be hiding in human DNA.

In the researchers' own words:

"This one looks like it is capable of making infectious virus, which would be very exciting if true, as it would allow us to study a viral epidemic that took place long ago," says senior author and virologist John Coffin, Ph.D. of the Tufts University School of Medicine. "This research provides important information necessary for understanding how retroviruses and humans have evolved together in relatively recent times."

"Many studies have tried to link these endogenous viral elements to cancer and other diseases, but a major difficulty has been that we haven't actually found all of them yet," says co-first author Zachary H. Williams, a Ph.D. student at the Sackler School of Graduate Biomedical Sciences at Tufts University in Boston. "A lot of the most interesting elements are only found in a small percentage of people, which means you have to screen a large number of people to find them."

"This is a thrilling discovery," says co-first author Julia Wildschutte, Ph.D., who began the work as a Ph.D. student in Coffin's lab at Tufts. "It will open up many doors to research. What's more, we have confirmed in this paper that we can use genomic data from multiple individuals compared to the reference human genome to detect new HERVs. But this has also shown us that some people carry insertions that we can't map back to the reference."

U-M genetics researcher Jeffrey Kidd, Ph.D., worked with Wildschutte when she was a member of his laboratory team. "These are remnants of ancient events that have not been fixed in the population as a whole, but rather happened in the ancestors of some people alive today," Kidd says. "There have been a number of examples of other HERVs that insert themselves next to human genes or near them, and have impact on their expression. We're interested in applying these methods to find other types of viral or mobile element insertions."

Genetic teamwork

The Michigan team used methods for characterizing repetitive DNA sequences that Kidd and his team had developed, while Coffin and Williams used complementary techniques. Wildschutte is now at Bowling Green State University.

Many of the genomes they examined were from the 1000 Genomes Project, an international collaboration. Another set of genomes came from work Kidd and colleagues at Stanford University had done as part of the Human Genome Diversity Project, with a focus on DNA samples from African volunteers.

These latter samples showed more signs of HERVs, in line with the high level of genetic diversity in African populations. That diversity stems from the longtime stability and intermixing of the continent's population - as opposed to other populations in Europe, Asia and the Americas that stem from specific out-migrations in ancient times. Cataloging all the HERV insertions in humans will require even more scanning of whole human genomes, which are becoming easier to come by as technology improves and becomes less expensive. And although intact proviruses lurking in our DNA may be rare, the impact of other HERV sequences on our health or disease is probably not.

The research was funded by the National Institutes of Health (OD009154, CA089441, GM112339) as well as the American Cancer Society and the F.M. Kirby Foundation.

Reference: PNAS, early online publication,
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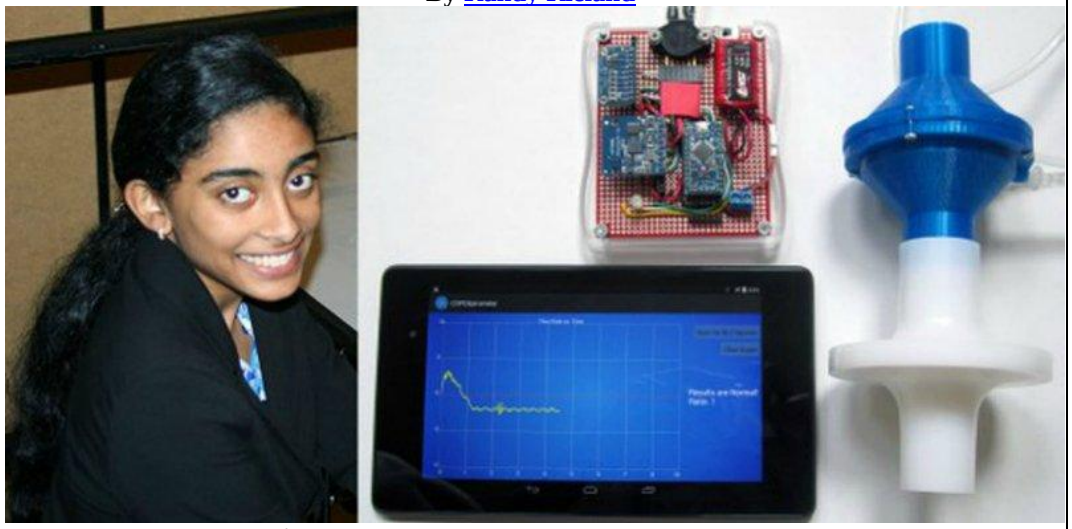
http://bit.ly/1Pv7Nfl

How a High School Senior Won $150,000 By Inventing a $35 Medical Device

When Maya Varma learned an expensive diagnostic tool is rare in the developing world, she decided to build her own

By Randy Rieland



Maya Varma won $150,000 as one of the first place winners in the prestigious Intel Science Talent Search competition. **(Maya Varma)**

A few years ago, while at summer camp, Maya Varma witnessed a close friend having a severe asthma attack. She was taken to a hospital and recovered.

For most teenagers, that would be that. But Varma isn't like most teenagers.

She started asking questions and discovered that a device called a spirometer was used to treat her friend. Varma had no idea what a spirometer was, but she inquired more. She learned that spirometers typically cost hundreds of dollars, sometimes even more, and, as result, they can be pretty rare in developing countries.

And so, she decided to design her own model, one that was just as effective in analyzing lung conditions, but considerably cheaper.

The result, a device that cost her only $35 to build and can diagnose five different lung ailments, is already paying dividends. Last week, Varma, now a high school senior, won $150,000 as one of the first place winners in the prestigious Intel Science Talent Search competition.

A born inventor

"I just felt there was something I could do about this," Varma says matter-of-factly.

And why not. The daughter of two Silicon Valley engineers, she has been inventing things for a while now. In the sixth grade, after she became aware of the dangers of distracted driving, she devised a signaling system that would let drivers know when a stoplight was about to turn red. Last year, she was awarded a patent for that one. Then, in the eighth grade, she developed a cost-effective way to detect foot neuropathy in patients with diabetes. That won the grand prize in the California State Science Fair. It also sparked her interest in biomedical research, specifically designing technological solutions to health issues. That's where she felt she could really make a difference.

Through her research on spirometers, Varma learned that their high cost is a big barrier to the treatment of chronic obstructive pulmonary disease (COPD), the fourth leading cause of death around the world and a condition for which early detection is critical.

After she was awarded a $600 research grant from Johns Hopkins University in 2014, Varma got to work building a cheap spirometer prototype. Muhammad Ali Yousuf, a biomedical engineer at Johns Hopkins, provided mentoring advice on medical matters by email. But Varma actually built her device at home.

How it works

Varma's spirometer has three main components. First, there's the shell, made on a 3D printer. When a person breathes into the shell, the rate of the air flow is measured by a pressure sensor as his or her breath passes through a fine, stainless steel mesh. The sensor converts the pressure change to digital data, which is monitored by a microcontroller and transmitted through a Bluetooth connection to a mobile app that Varma created.

The app computes lung performance and illustrates it on the person's smartphone, taking into account age, gender, weight and other factors. It's able to diagnose five different respiratory illnesses—COPD, asthma, emphysema, chronic bronchitis and restrictive lung disease—and also has a disease management tool that allows patients to record their symptoms and test results, and track the severity of their illness.

Varma has applied for a patent for her spirometer. Her next step is to build more so she can send them to universities and medical schools for testing. It's no small undertaking. She figures she needs 100 spirometers. So far, she's built 10.

"There are still a lot of challenges," she concedes. "But it's so rewarding when you're able to do something that can make a difference in people's lives."

She also has some pretty simple advice for others with an innovative idea. "It can get discouraging, but you can learn a lot from your failures. Always persevere," she says. Next fall, Varma will start her college career. She hasn't decided yet where she'll go, but her choices include MIT, Harvard and Stanford.

http://bit.ly/1Pv7Nfl

What Really Causes Alzheimer's? New Idea Points to Germs

Scientists argue that the complex disease may have a surprisingly simple trigger

by Melinda Wenner Moyer

Scientists have long puzzled over the root causes of Alzheimer's disease, a devastating and typically fatal condition that currently denies more than five million Americans their cognition and memory. But in a provocative editorial soon to be published in the Journal of Alzheimer's Disease, a cadre of scientists argue that the complex disease may have a surprisingly simple trigger: tiny brain-infecting microbes. This controversial view, which is not new, has long been dismissed as outlandish, but a growing body of work suggests it may be worth considering and further studying. If researchers can prove the theory and iron out the many argued-over details — both formidable tasks, as brain infections are difficult to study — Alzheimer's could become a preventable illness.

The editorial, signed by 31 scientists around the world, argues that in certain vulnerable individuals — such as those with the APOE ε4 gene variant, a known Alzheimer's risk factor — common microbial infections can infect the aging brain and cause debilitating damage. These microbes may include herpes simplex virus 1 (HSV-1), the ubiquitous virus that causes cold sores as well as Chlamydophila pneumoniae and Borrelia burgdorferi, the bacteria that cause pneumonia and Lyme disease, respectively.

The controversial idea butts heads with the long-standing theory that amyloid-beta proteins and tau tangles, both of which build up inside the brains of those with Alzheimer's, are the main drivers of disease-induced cell death. Instead, supporters of the pathogen hypothesis, as it is called, posit that either pathogens induce brain cells to produce the amyloid proteins and tau tangles or that nerve cells that have been damaged by infection produce them as part of an immune response. "We think the amyloid story does come into play, but it's secondary to the initial inflammation," says editorial co-author Brian Balin, who directs the Center for Chronic Disorders of Aging at the Philadelphia College of Osteopathic Medicine.

Critics of the pathogen theory point out that much of the supportive human research does not establish cause and effect. In a study published in The Lancet in 1997, a team led by Ruth Itzhaki, one of the editorial's co-authors and a molecular neurobiologist at the University of Manchester in England, reported that people whose brains were infected with HSV-1 and who also had the APOE ε4 gene variant were 12 times more likely to develop Alzheimer's than those with either the gene variant or the infection alone. One hypothesis is that the APOE ε4 variant makes it easier for HSV-1 to infect brain cells — but, critics say, it could also be that the gene variant and the infection are associated with Alzheimer's in ways that are not causal.

Scientists have tried to nail down the mechanics of the relationship using animals. Researchers in Spain have found, for instance, that mice whose brains have been infected with HSV-1 produce nearly 14 times as much viral DNA when they have the APOE ε4 variant compared with when they do not. And after infecting the brains of mice with HSV-1, Itzhaki's group showed that their brains accumulated amyloid plaques. But these studies are criticized, too — after all, what happens in a mouse's brain may not happen in a human's.

The burden of proof is formidable for this theory, in part because it is impossible to detect infections like HSV-1 in the brains of living people — they can only be seen postmortem. '"Proof of causation is a major, critical and very complex issue," says David Relman, an infectious disease specialist at Stanford University. Itzhaki agrees, noting that one cannot just inject people with the virus and wait to see if they develop Alzheimer's. (That said, Australian microbiologist Barry Marshall finally convinced skeptics that Heliobactor pylori bacteria cause gastric ulcers by infecting himself.) Itzhaki says that one potential solution would be to conduct a pilot clinical trial that evaluates whether HSV-1-infected individuals with mild Alzheimer's and the APOE ε4 variant improve if they are treated with antiviral drugs. They have already shown in the lab that these drugs inhibit amyloid plaque production in HSV-1 infected cells. But she has applied for funding for a human study multiple times and has so far has been unsuccessful.

Rudolph Tanzi, a neurologist at Harvard University who directs the Genetics and Aging Research Unit at Massachusetts General Hospital, agrees that microbes likely play a role in Alzheimer's — but his work suggests that the brain's response to the infection is more dangerous than the infection itself. "We do need to take the role of microbes in the brain seriously, but it's going to be a lot more involved than simply saying 'infection causes Alzheimer's disease,'" he notes. (He was not involved in the editorial.) In a 2010 study Tanzi and his colleagues reported that the amyloid protein strongly inhibits microbial growth in the brain, which suggests that it accumulates as a protective response to infection. "Over the last five years, following up from that 2010 paper, we've showed that in every Alzheimer's model tested — from cells to flies to dirt worms to mice — beta amyloid potently protects from infection," he explains. The presence of even just a few microbes in the brain, he says, triggers its accumulation.

Infections induce potent immune responses, too, and they likely worsen the problem. Normally, brain immune cells called microglia clear amyloid proteins from the brain. But when these cells get fired up in response to infection, they stop, causing the proteins to build up even faster. As Tanzi's team showed in a

2014 Nature paper, the amyloid proteins that fill up the brain then spark the creation of tau tangles, which cause more brain cell death. "And now, you have the full-blown disease," he says. (Scientific American is part of Springer Nature.)

As for which pathogens might be triggers, HSV-1 is a contender, Tanzi says, but it is too soon to know for sure. "I think we have to take a couple of steps back and say, 'What types of bacteria, viruses and fungus accumulate in the brain as we age?' and study this systematically in an unbiased, agnostic way," he says. He is leading a consortium funded by the nonprofit Cure Alzheimer's Fund to map the microbiome of the human brain; once potentially important microbes are identified, it might be possible to develop neuroimaging techniques to track them in the brains of living individuals, he says.

Other Alzheimer's scientists still are not convinced, however. David Holtzman, chair of the department of neurology at Washington University School of Medicine in St. Louis and associate director of its Knight Alzheimer's Disease Research Center, told Scientific American that although more research on the idea is warranted, "there is not clear or conclusive evidence of whether or how different infections influence risk for Alzheimer's disease." Tanzi says that when he presents his findings and ideas at scientific meetings, reactions are indeed mixed. One comment Itzhaki often hears is that HSV-1 cannot cause Alzheimer's if it is also found, as it is, in the brains of elderly healthy people. But she points out that other pathogens, including tuberculosis, only cause symptoms in subset of vulnerable individuals, too.

If microbes do turn out to be a potential trigger for Alzheimer's — and to most in the field, this is still a big "if" — the implications would be huge: It might be possible to vaccinate against the debilitating disease simply by inoculating against offending infections. At the very least, doctors might be able to treat infections with antimicrobial drugs before they harm the brain. But building enough evidence to prove the theory could take decades. Among other challenges, researchers working in the area complain of funding woes. "Over the 50-plus years that I've been doing the work, our group has had extreme difficulties nearly all the time — we've been working on a shoestring," Itzhaki says.

But given that hundreds of clinical trials for Alzheimer's drugs have failed based on the prevailing dogma, those working on the various versions of the pathogen theory believe it is worth pushing forward. More than anything, they hope their editorial will encourage skeptics to at least consider the possibility that microbes could play a role in Alzheimer's disease and support their desire to study it more. "We're saying 'wait a minute, folks — we have a body of evidence here from decades of work that we have to stop ignoring,'" Balin says.

http://bit.ly/1Pv7Nfl

Ghostly galaxies are light on stars but heavy on dark matter

There's more than meets the eye. Astronomers have weighed a so-called ultra-diffuse galaxy for the first time, and found that it is over 99.96 per cent dark matter.

An ultra-diffuse galaxy can be as large as the Milky Way but as dim as a dwarf. The galaxy's few stars are spread out, so it looks ghostly, making it hard to study.

Although observers spotted the first few examples three decades ago, they didn't have a name until 2014, when a team led by Pieter van Dokkum at Yale University discovered 47 of them in the Coma galaxy cluster. Other astronomers studied this cluster with the giant Subaru Telescope in Hawaii and found hundreds more.

Van Dokkum's team argued that the galaxies had to consist of at least 98 per cent dark matter for gravity to hold them together. Otherwise, the many other galaxies in the Coma cluster would tear them apart.

Dark matter is thought to make up about 80 per cent of the mass in the universe overall, so that would be an impressively dense concentration of the stuff in a small space. But until now no one had directly measured an ultra-diffuse galaxy's mass.

Now Michael Beasley at the Institute of Astrophysics of the Canary Islands, Spain, and his colleagues have weighed an ultra-diffuse galaxy in the Virgo cluster named VCC 1287. The galaxy's main body is too dim to study easily, so instead they observed seven of its globular clusters – bright, tight-packed gatherings of stars that move around the galaxy.

Dim but heavy

Using the 10.4-metre Great Canary Telescope in La Palma, Beasley's team measured the clusters' speeds. They found that the clusters orbit the galaxy so fast that it must have about 80 billion times more mass than the sun. That's only 8 per cent of the Milky Way's total mass, but an impressive figure for a galaxy that has so few stars that it emits less than a thousandth as much light.

It also means the galaxy has 3000 times more dark matter than stellar mass. The Milky Way's ratio is just 15 to 1 .

"It's a very clever method," says van Dokkum. "It's a great achievement."

Beasley speculates that the galaxy he studied was born with both dark matter and gas but lost the latter as the galaxy fell into the Virgo cluster. Without gas, the galaxy couldn't create new stars, so it ended up with lots of dark matter but little light.

Journal reference: The Astrophysical Journal Letters, DOI: 10.3847/2041-8205/819/2/L20

http://www.eurekalert.org/pub_releases/2016-03/acoc-mot032116.php

Missed opportunities to avoid painful shocks at the end of life

Many patients unaware of benefits of deactivating implantable cardioverter defibrillator

Many patients who have a common medical device known as an implantable cardioverter defibrillator (ICD) are unaware that the device can be deactivated to prevent painful shocks in their final days of life, according to two studies scheduled for presentation at the American College of Cardiology's 65th Annual Scientific Session.

The Heart Rhythm Society and the European Society of Cardiology have issued recommendations encouraging physicians to inform patients about the benefits of deactivating an ICD when death is near, yet recent studies show that up to 31 percent of people with an ICD receive shocks in their last day of life. Two new studies add further evidence that doctors are not consistently implementing these recommendations, which the authors said may reflect a reticence to engage in difficult discussions about end-of-life decisions.

"When you reach the stage of palliative care, sometimes the ICD doesn't have a role in caregiving anymore," said Dilek Yilmaz, M.D., a Ph.D. fellow in cardiology at the Heart and Lung Center of Leiden University Medical Center in the Netherlands and lead author of one of the studies. "If a person is dying of a terminal cancer, for example, the ICD is not going to prolong their life, but it is fairly likely to cause pain in their last hours and prevent them from having a peaceful death."

ICDs are battery-powered, surgically implanted devices used to prevent sudden death in people with certain conditions, such as sustained ventricular tachycardia or fibrillation, that put them at risk for life-threatening heart rhythms. If the device detects a dangerous heart rhythm, it issues a shock to restore a normal heartbeat. ICDs are extremely common, with 10,000 implanted each month in the United States alone, according to the American Heart Association.

The device can be deactivated using a computer in any cardiologist's office, with no need for additional surgical intervention. Because ICDs do not maintain the heart rhythm on an ongoing basis like a pacemaker does, deactivating the device does not actively hasten death. However, if a patient experiences a dangerous heart rhythm--a common occurrence during the natural course of death from any cause--a deactivated ICD will not intervene to rescue the patient.

"These shocks are often much more frequent on the patient's last day than any other day of their life," said Silvia del Castillo, M.D., a cardiologist at Hospital Universitario de Fuenlabrada in Madrid and lead author of the second study. "I think it's cruel in many cases to leave the ICD on until the very end, and when doctors don't provide enough information about deactivation or delay that conversation until the final hours, it undercuts the patient's right to make their own decisions."

The two studies, conducted independently in the Netherlands and in Spain, revealed similar patterns. Study authors said the situation in the United States is likely to be similar, as well.

For the study conducted in Spain, del Castillo and her colleagues surveyed 243 patients with ICDs during clinic visits at three Spanish hospitals. While most respondents showed a high level of understanding about what an ICD is and what it does, far fewer demonstrated a clear understanding of the option to deactivate the ICD or what would happen if it were to be deactivated. Sixty-eight percent assumed shocks were inevitable in the presence of an abnormal heart rhythm, and 21 percent incorrectly believed that deactivation would lead to immediate cardiac arrest. Just 38 percent were aware that they could decide to deactivate their ICD after consulting with their doctor, and only 37 percent knew that ICD deactivation is ethically appropriate and recommended by major scientific societies.

In the study conducted in the Netherlands, Yilmaz and her colleagues surveyed 328 patients with ICDs during a patient educational symposium. Although 73 percent were aware that their ICD could be deactivated, just 12 percent had consulted with their doctors about the matter. Neither of the studies revealed trends in terms of factors such as gender or level of education playing a role.

Both study authors attribute the findings to communication gaps and cultural challenges around end-of-life planning.

"As doctors, we are focused on healing the patient and saving lives," del Castillo said. "It's hard to talk about death and to explain that this therapy that can save their life now could be harmful to them later. Because we have a hard time talking to patients about this, in the end doctors often make the decision about ICD deactivation alone or with the family, instead of with the person who should be the real decision-maker, the patient."

The best time to begin the conversation about ICD deactivation, according to the studies' authors, is around the time when the ICD is being implanted, which is often many years before a patient's death. Then it can be mentioned again during follow-up visits or when someone receives a terminal diagnosis.

"These shocks are painful for the patient and also painful for their family to witness," Yilmaz said. "As a doctor, if you don't even discuss it with your patient, you could be denying them the opportunity for a peaceful death."

Because many people spend their final days in hospice or under the care of a medical team that does not include their cardiologist, there is often no opportunity to deactivate an ICD before death unless the patient or the patient's family has

previously been made aware of that option and decides to actively pursue it. This context underscores the need for cardiologists to inform patients of the option of deactivation and its benefits early on, the researchers said.

del Castillo's study was funded by the Víctor Grifols i Lucas Foundation. The Leiden University Medical Center Department of Cardiology receives unrestricted research and fellowship grants from Medtronic, Biotronik and Boston Scientific.

The studies, "Patient Awareness of Implantable Cardioverter Defibrillator-therapy Deactivation When the End is Near," and "Implantable Defibrillator Management Near the End of Life: Do Patients Know Enough to Decide?" will be presented on April 2, 2016, at 10 a.m. CT/11 a.m. ET/4 p.m. UTC and 9:45 a.m. CT/10:45 a.m. ET/3:45 p.m. UTC, respectively, at the American College of Cardiology's 65th Annual Scientific Session in Chicago. The meeting runs April 2-4.

http://www.eurekalert.org/pub_releases/2016-03/nioa-btc032216.php

Blood test can predict risk of developing tuberculosis

NIH-funded study is landmark in TB research

WHAT: One-third of the world's population is thought to be infected with Mycobacterium tuberculosis (Mtb), the bacterium that causes tuberculosis (TB), but just a small fraction ever develops symptomatic illness. Now, an international team of researchers has identified biological markers in the blood of latently infected people that may give doctors a tool they have long sought: a way to predict who is at high risk of developing active TB. If validated through additional clinical trials, a test based on these blood biomarkers would allow doctors to target therapies to at-risk people, thus preventing them from getting sick.

The decade-long research effort was led by investigators from the South African Tuberculosis Vaccine Initiative at the University of Cape Town, and the Center for Infectious Disease Research, Seattle. It was funded in part by the National Institutes of Health.

The biomarkers were identified in two stages. First, researchers collected blood samples for two years from more than 6,000 Mtb-infected but otherwise healthy adolescent volunteers in South Africa. Analysis of the samples revealed patterns of gene expression that differed between volunteers who eventually developed TB and those who remained healthy. This risk "signature," confined to a set of 16 genes, could be detected in a blood sample as early as 18 months before the infected person developed active TB.

Next, the team confirmed the genetic risk signature's predictive ability in a study of more than 4,500 volunteers in South Africa and The Gambia. Volunteers in this study were healthy but lived with people who had recently been diagnosed with active TB. The second study group was more varied in age, health status, ethnicity and exposure to locally common strains of Mtb than volunteers in the first study. Despite the differences, the same risk signature found in the first study was detected in the people who eventually developed active TB during the second trial.

ARTICLE: *DE Zak et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study.The Lancet DOI: 10.1016/S0140-6736(15)01316-1 (2016).*

WHO: *Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases (NIAID), is available to comment. Christine Sizemore, Ph.D., Chief, Tuberculosis, Leprosy and Other Mycobacterial Diseases, Division of Microbiology and Infectious Diseases, NIAID, is also available.*

Support for this research included a grant from NIAID (R01-AI087915) and from the Fogarty International Center (5D43 TW000231), both components of the National Institutes of Health.

http://www.eurekalert.org/pub_releases/2016-03/aaon-ems031816.php

Exercise may slow brain aging by 10 years for older people

Exercise in older people is associated with a slower rate of decline in thinking skills that occurs with aging.

MINNEAPOLIS - People who reported light to no exercise experienced a decline equal to 10 more years of aging as compared to people who reported moderate to intense exercise, according to a population-based observational study published in the March 23, 2016, online issue of Neurology®, the medical journal of the American Academy of Neurology.

"The number of people over the age of 65 in the United States is on the rise, meaning the public health burden of thinking and memory problems will likely grow," said study author Clinton B. Wright, MD, MS, of the University of Miami in Miami, Fla., and member of the American Academy of Neurology. "Our study showed that for older people, getting regular exercise may be protective, helping them keep their cognitive abilities longer."

For the study, researchers looked at data on 876 people enrolled in the Northern Manhattan Study who were asked how long and how often they exercised during the two weeks prior to that date. An average of seven years later, each person was given tests of memory and thinking skills and a brain MRI, and five years after that they took the memory and thinking tests again.

Of the group, 90 percent reported light exercise or no exercise. Light exercise could include activities such as walking and yoga. They were placed in the low activity group. The remaining 10 percent reported moderate to high intensity exercise, which could include activities such as running, aerobics, or calisthenics. They were placed in the high activity group.

When looking at people who had no signs of memory and thinking problems at the start of the study, researchers found that those reporting low activity levels showed a greater decline over five years compared to those with high activity levels on tests of how fast they could perform simple tasks and how many words they could remember from a list. The difference was equal to that of 10 years of

aging. The difference also remained after researchers adjusted for other factors that could affect brain health, such as smoking, alcohol use, high blood pressure and body mass index.

"Physical activity is an attractive option to reduce the burden of cognitive impairment in public health because it is low cost and doesn't interfere with medications," said Wright. "Our results suggest that moderate to intense exercise may help older people delay aging of the brain, but more research from randomized clinical trials comparing exercise programs to more sedentary activity is needed to confirm these results."

The study was a collaboration between the University of Miami and Columbia University and was supported by the National Institutes of Health and National Institute of Neurological Disorders and Stroke.

http://www.eurekalert.org/pub_releases/2016-03/acoc-wmw032116.php

Women, men with suspected heart disease have similar symptoms

Large study finds chest pain, shortness of breath are most common signs in both sexes

Chest pain and shortness of breath are the most common symptoms reported by both women and men with suspected heart disease, a finding that is in contrast to prior data, according to a study scheduled for presentation at the American College of Cardiology's 65th Annual Scientific Session.

The study, which includes one of the largest cohorts of women ever enrolled in a heart disease study, also found that women had a greater number of risk factors for heart disease than men, yet these women were more likely to be characterized as lower risk not only by their health care providers, but also by scores that objectively measure and predict heart disease risk.

"The most important take-home message for women from this study is that their risk factors for heart disease are different from men's, but in most cases symptoms of possible blockages in the heart's arteries are the same as those seen in men," said Kshipra Hemal of the Duke Clinical Research Institute in Durham, North Carolina, and lead author of the study.

The finding that women have more risk factors for heart disease than men means measures to reduce risk need to be a priority for women, as well as men, Hemal said.

Some previous studies have suggested that women having a heart attack are less likely to have classic symptoms such as chest pain and more likely to have atypical symptoms such as back pain, abdominal pain and fatigue that may be less readily recognized as heart attack symptoms. Hemal and her colleagues sought to shed light on a different group of patients--those without a prior heart disease diagnosis who were being evaluated for symptoms suggestive of heart disease. Few studies, mostly several decades old, have examined sex differences in this group of patients.

The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE), a randomized trial conducted at 193 centers in the United States and Canada, enrolled 10,003 patients, of whom more than 5,200 were women. Half of the patients were randomly selected to receive a heart CT scan, which generates 3-D images of the heart's arteries that doctors can use to noninvasively assess the degree of narrowing. The rest received a functional or stress test--an exercise electrocardiogram, stress echocardiography or nuclear stress test--used to track the heart's response to stress. Hemal and her colleagues examined patient data to assess differences between women and men in age, race or ethnicity, risk factors, symptoms, evaluation and test results.

The study found that, compared with men, women were older (average age 62 vs. 59 for men), more often non-white, less likely to smoke or be overweight, and more likely to have high blood pressure, high cholesterol, a history of stroke, a sedentary lifestyle, a family history of early-onset heart disease and a history of depression. Chest pain was the primary symptom for 73.2 percent of women and 72.3 percent of men. The two sexes, however, described this pain differently--women were more likely to describe it as "crushing," "pressure," "squeezing" or "tightness, " whereas men were more likely to describe it as "aching," "dull," "burning" or "pins and needles." Equal proportions of women and men (15 percent) reported shortness of breath as a symptom.

Although women were more likely than men to have back pain, neck or jaw pain, or palpitations as their primary symptom, the percentage of patients of both sexes reporting these symptoms was very small (1 percent of women vs. 0.6 percent of men for back pain, 1.4 percent of women vs. 0.7 percent of men for neck or jaw pain, 2.7 percent of women vs. 2 percent of men for palpitations).

Women had lower scores than men on heart disease risk-assessment scores, suggesting a lower risk of heart disease, and before any diagnostic tests were conducted, health care providers were more likely to consider that women probably did not have heart disease. Nontraditional risk factors such as depression, sedentary lifestyle and family history of early-onset heart disease--risk factors that in this study were more commonly found in women than in men--are excluded from most risk-assessment questionnaires, however.

"For health care providers, this study shows the importance of taking into account the differences between women and men throughout the entire diagnostic process for suspected heart disease," Hemal said. "Providers also need to know that, in the vast majority of cases, women and men with suspected heart disease have the same symptoms."

Women were more likely than men to be referred for a stress echocardiography or nuclear stress test and less likely than men (9.7 percent vs. 15.1 percent) to have a positive test. Factors predicting a positive test differed for women compared with men. In women, body mass index and score on one of five risk-assessment questionnaires (the Framingham risk score) predicted a positive test, whereas in men scores on two risk-assessment questionnaires (the Framingham and modified Diamond-Forrester risk scores) predicted a positive test.

"The fact that this is one of the largest cohorts of women ever evaluated in a heart disease study lends validity to our findings," Hemal said. A limitation of the study is that it looks only at the diagnostic process and not at whether there are differences between women and men in numbers of heart attacks or in outcomes from heart attacks, she said. "The next step in this research will be to examine whether and how the differences we have identified between women and men influence outcomes," she said.

The study was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Pamela S. Douglas, M.D., led the study team.

The study, "Sex Differences in Demographics, Risk Factors and Presentation in Stable Contemporary Outpatients With Suspected Coronary Artery Disease: Insights From the PROMISE Trial," will be presented on Sunday, April 3, 2016, at 12:45 p.m. CT/1:45 p.m. ET/6:45 p.m. UTC at the American College of Cardiology's 65th Annual Scientific Session in Chicago. The meeting runs April 2-4.

http://www.eurekalert.org/pub_releases/2016-03/ncsu-mmc032316.php

Modified maggots could help human wound healing

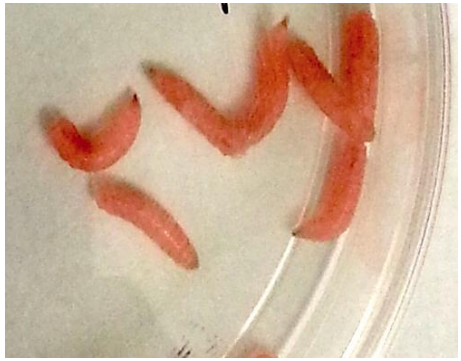
Genetically engineered green bottle fly larvae can produce and secrete a human growth factor

In a proof-of-concept study, NC State University researchers show that genetically engineered green bottle fly (*Lucilia sericata*) larvae can produce and secrete a human growth factor - a molecule that helps promote cell growth and wound healing.

Sterile, lab-raised green bottle fly larvae are used for maggot debridement therapy (MDT), in which maggots are applied to non-healing wounds, especially diabetic foot ulcers, to promote healing. Maggots clean the wound, remove dead tissue and secrete anti-microbial factors. The treatment is cost-effective and approved by the Food and Drug Administration. However, there is no evidence from randomized clinical trials that MDT shortens wound healing times.

With the goal of making a strain of maggots with enhanced wound-healing activity, NC State researchers genetically engineered maggots to produce and then secrete human platelet derived growth factor-BB (PDGF-BB), which is known to aid the healing process by stimulating cell growth and survival.

Max Scott, an NC State professor of entomology, and colleagues from NC State and Massey University in New Zealand used two different techniques to elicit PDGF-BB from green bottle fly larvae.



Genetically modified green bottle flies produce and secrete a human growth factor that helps wound healing. **Max Scott**

One technique utilized heat to trigger the production of PDGF-BB in transgenic green bottle flies. The technique worked - to a point. The human growth factor was detectable in certain structures within the larvae after the larvae were shocked with high heat - a level of 37 degrees Celsius - but PDGF-BB was not detectable in maggot excretions or secretions, making it unworthy of clinical use.

"It is helpful to know that a heat-inducible system can work for certain proteins in the green bottle fly, but the fact that maggots did not secrete the human growth factor makes this technique a non-starter for clinical applications like MDT," Scott said.

The second technique was more successful. Scott and colleagues engineered the flies such that they only made PDGF-BB if raised on a diet that lacked the antibiotic tetracycline. PDGF-BB was made at high levels in the larvae and was found in the excretions and secretions of maggots, making the technique a potential candidate for clinical use.

"A vast majority of people with diabetes live in low- or middle-income countries, with less access to expensive treatment options," Scott said. "We see this as a proof-of-principle study for the future development of engineered *L. sericata* strains that express a variety of growth factors and anti-microbial peptides with the long-term aim of developing a cost-effective means for wound treatment that could save people from amputation and other harmful effects of diabetes."

The study was published online in the journal BMC Biotechnology.

Note to editors: An abstract of the paper follows.

"Towards next generation maggot debridement therapy: transgenic Lucilia sericata *larvae that produce and secrete a human growth factor"*

Authors: Rebecca J Linger, Esther J Belikoff, Ying Yan, Fang Li, Holly A Wantuch and Max Scott, North Carolina State University; Helen Fitzsimons, Massey University, New Zealand

Published: Online March 22, 2016, in BMC Biotechnology

DOI: 10.1186/s12896-016-0263-z

Abstract: *Diabetes and its concurrent complications impact a significant proportion of the population of the U.S. and create a large financial burden on the American health care system. FDA-approved maggot debridement therapy (MDT), the application of*

sterile laboratory-reared Lucilia sericata *(green bottle fly) larvae to wounds, is a cost effective and successful treatment for diabetic foot ulcers and other medical conditions. Human platelet derived growth factor-BB (PDGF-BB) is a secreted dimeric peptide growth factor that binds the PDGF receptor. PDGF-BB stimulates cell proliferation and survival, promotes wound healing, and has been investigated as a possible topical treatment for non-healing wounds. Genetic engineering has allowed for expression and secretion of human growth factors and other proteins in transgenic insects. Here, we present a novel concept in MDT technology that combines the established benefits of MDT with the power of genetic engineering to promote healing. The focus of this study is to create and characterize strains of transgenic* L. sericata *that express and secrete PDGF-BB at detectable levels in adult hemolymph, whole larval lysate, and maggot excretions/secretions (ES), with potential for clinical utility in wound healing.*

http://www.eurekalert.org/pub_releases/2016-03/uoct-ps032316.php

Paradigm shift: 'We need to study lumps of bacteria'

New research from the University of Copenhagen reveals that bacteria which agglutinate before entering the body are far more resistant than single-celled bacteria. This may be the cause of chronic infections.

Since the discovery of bacteria researchers have primarily studied bacteria as organisms that enter the body individually and only then accumulate or agglutinate, creating what is known as biofilm. However, a new study conducted by researchers at the Faculty of Health and Medical Sciences at the University of Copenhagen, among others, indicates that this view of bacteria needs to be revised.

"Bacteria that enter the bloodstream as biofilm are stronger than bacteria that enter the body separately. This is something we have to pay far greater attention to in trying to prevent infections, for example in connection with operations," says Professor Thomas Bjarnsholt from the Costerton Biofilm Center at the University of Copenhagen. He is the senior researcher behind the study, which is about to be published in the acclaimed online journal mBio.

Biofilm may be the cause of chronic infections. The research team behind the study has examined bacterial environments containing both biofilm and single-celled bacteria.

Here the researchers have found a significantly different type of growth than previously seen. The biofilm takes the main part of the nourishment available and thus outmatches the single-celled bacteria. This makes biofilm the most important player. According to Thomas Bjarnsholt, this is something we need to pay attention, for example when performing operations.

"We have a lot of bacteria on and in our skin which are clustered as biofilm and potentially pathogenic if they enter the skin. In this way biofilm can penetrate or be pushed into the body when the surgeon cuts a hole in the skin containing the biofilm," says Thomas Bjarnsholt.

"Antibiotics are not designed to fight biofilm," says Postdoc Kasper Kragh, who is the main author of the research article. "Often antibiotics are not sufficient to fight chronic infections. This may partly be because antibiotics are to a large extent designed to fight single-celled bacteria, not biofilm."

"We have to take a few steps backwards and, with an open mind, examine how bacteria cause infections and how we can fight them," he adds.

"Hopefully by learning how and when bacteria form biofilm we will be able to find a better way to prevent and treat chronic bacterial infections," concludes Kragh.

http://www.eurekalert.org/pub_releases/2016-03/htcs-bss032316.php

Botswana study shows 96 percent rate of viral suppression for patients on HIV drugs

Ahead of many Western nations, African country close to meeting new UNAIDS testing and treatment targets

Boston, MA - Botswana appears to have achieved very high rates of HIV diagnosis, treatment, and viral suppression--much better than most Western nations, including the United States--according to a new study from Harvard T.H. Chan School of Public Health and colleagues in Botswana. The findings suggest that even in countries with limited resources where a large percentage of the population is infected with HIV, strong treatment programs can help make significant headway against the HIV/AIDS epidemic.

The study will be published online March 23, 2016 in The Lancet HIV.

"By now, we hoped to have an HIV vaccine. That hasn't happened. Ironically, treatment of HIV-infected persons may be our most effective, efficient way to prevent new infections. These results show that Botswana has made great progress in reducing the number of people who are infectious to others," said Max Essex, Mary Woodard Lasker Professor of Health Sciences, chair of the Harvard T.H. Chan School of Public Health AIDS Initiative, and chair of the Botswana Harvard AIDS Institute Partnership.

Global HIV programs have continued to face challenges in achieving the high rates of testing and treatment needed to optimize health and reduce new infections. Mounting evidence suggests that providing antiretroviral treatment (ART) to all people living with HIV, regardless of the stage of their disease, can help. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) proposed new testing and treatment targets: that 90% of all people living with HIV know their HIV status; that 90% diagnosed with HIV be given ART; and that 90% who receive treatment have virologic suppression--very low blood levels of HIV--by the year 2020.

The researchers looked at the achievability of the UNAIDS targets in Botswana--a middle-income African nation where 25% of the population aged 15-49 is HIV positive but which also has a mature public ART program--by directly measuring HIV status, treatment, and viral suppression among 12,610 people from 30 communities across the country between October 2013 and November 2015. Study participants were drawn from a large, ongoing HIV prevention study in Botswana. The participants responded to a questionnaire, had their blood tested for HIV if their status wasn't known, and, if they were infected with HIV, their viral load was checked.

Out of the 12,610 participants, 3,596 (29%) were HIV infected and 2,995 (83.3%) of these individuals already knew their HIV status. Among those who knew their status, 2,617 (87.4%) were receiving ART. Significantly, the study authors called it "remarkable" that of the 2,609 people receiving ART who had their viral load checked, 2,517 (96.5%) had viral suppression.

Until now, there has been considerable uncertainty as to whether the ambitious targets proposed by UNAIDS can be achieved, especially in countries with limited resources where the HIV burden is highest, according to the study authors. But the new findings suggest that Botswana could meet and even exceed the targets well before 2020, especially if ART eligibility is expanded--and that other countries could do the same.

"This is significant work as it provides further evidence that the UNAIDS 90-90-90 treatment target is both realistic and achievable," said UNAIDS Executive Director Michel Sidibé, who was not involved in the study.

Lead author of the study was Tendani Gaolathe of the Botswana Harvard AIDS Institute Partnership. Other Harvard Chan School authors of the study included Kathleen Wirth, Molly Pretorius Holme, Joseph Makhema, Quanhong Lei, Vlad Novitsky, Kathleen Powis, Nealia Khan, Hermann Bussmann, Scott Dryden-Peterson, Rui Wang, Eric Tchetgen Tchetgen, Victor DeGruttola, and Shahin Lockman.

Funding came from The United States President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention under the terms of cooperative agreement U01 GH000447.

"Botswana's Progress Toward Achieving the 2020 UNAIDS 90-90-90 Antiretroviral Treatment and Virologic Suppression Goals: Results of a Population-Based Survey," Tendani Gaolathe, Kathleen E. Wirth, Molly Pretorius Holme, Joseph Makhema, Sikhulile Moyo, Unoda Chakalisa, Etienne Kadima Yankinda, Quanhong Lei, Mompati Mmalane, Vlad Novitsky, Lillian Okui, Erik van Widenfelt, Kathleen M. Powis, Nealia Khan, Kara Bennett, Hermann Bussmann, Scott Dryden-Peterson, Refeletswe Lebelonyane, Shenaaz el-Halabi, Lisa A. Mills, Tafireyi Marukutira, Rui Wang, Eric J. Tchetgen Tchetgen, Victor DeGruttola, M. Essex, Shahin Lockman, and the BCPP study team, Lancet HIV, March 23, 2016, doi: 10.1016/S2352-3018(16)00037-0.

http://www.eurekalert.org/pub_releases/2016-03/uok-rsp032416.php

Research shows potential for emergence of new Ebola virus that causes disease in humans

New research at the University of Kent has highlighted the potential for the emergence of a new form of Ebolavirus.

A team from the University's School of Biosciences examined the differences between Ebolaviruses that cause severe disease in humans and the Reston virus that does not.

The Reston virus, which is known to circulate in domestic pigs in Asia and occasionally infect humans, is currently the only member of the Ebolavirus family not to have been reported as causing life-threatening disease in humans.

Using computational analysis of the sequences of the genomes of Ebolaviruses and a computational prediction of the effects of sequence variations on virus function, the researchers, Dr Mark Wass, Senior Lecturer in Computational Biology, Professor Martin Michaelis, Professor of Molecular Medicine, and Dr Jeremy Rossman, Lecturer in Virology, and their teams, identified characteristic differences in a number of virus proteins.

The results suggested that only a few changes in one Ebolavirus protein, VP24, may be necessary to render the Reston virus into a virus that can cause human disease. There may be a risk therefore that Reston viruses acquire the few mutations necessary to cause disease in humans and to develop into a novel health threat.

The research, entitled Conserved differences in protein sequence determine the human pathogenicity of Ebolaviruses, is published in Scientific Reports. See here: http://www.nature.com/articles/srep23743.

http://nyti.ms/1VNXRFc

Researchers Find Fish That Walks the Way Land Vertebrates Do

In a cave in Thailand is a blind fish walks the way land vertebrates do

Carl Zimmer MATTER MARCH 24, 2016

It’s one of the most famous chapters in evolution, so familiar that it regularly inspires New Yorker cartoons: Some 375 million years ago, our ancestors emerged from the sea, evolving from swimming fish to vertebrates that walked on land. Scientists still puzzle over exactly how the transition from sea to land took place. For the most part, they’ve had to rely on information gleaned from fossils of some of the intermediate species.

But now a team of researchers has found a remarkable parallel to one of evolution’s signature events. In a cave in Thailand, they’ve discovered that a blind fish walks the way land vertebrates do.

The waterfall-climbing cave fish, Cryptotora thamicola, has even evolved many of the skeletal features that our ancestors did for walking, including a full-blown pelvis.

Cryptotora thamicola, a waterfall-climbing cave fish that appears to walk the way land vertebrates do, researchers say. **Danté Fenolio/Science Source**

"It's really weird," said John R. Hutchinson, a biologist at the Royal Veterinary College at the University of London who was not involved in the new study. "It's a good example of how much fish diversity there's left to be discovered."

Drop an ordinary fish on the ground, and it will flop around helplessly: Its fins are adapted for pushing against water, not fighting gravity.

The early land vertebrates, known as tetrapods, evolved adaptations that enabled them to move efficiently over solid ground. A pelvis joined their hind limbs to their spines, for example. Their vertebrae grew flanges so that they interlocked, helping the spine hold itself stiff and straight even when being pulled down by gravity.

These adaptations led tetrapods to walk in a distinctive fashion, moving their forelegs and hind legs together in a cycle. Early tetrapods probably walked much the way salamanders do today, bending their trunk from side to side as they traveled.

All tetrapods descend from a single ancestor — a single lineage of fish that managed to spread on land. Some other fishes evolved vaguely similar ways of moving around. On coral reefs, for example, frogfish can push off surfaces with their fins. They have a gait that looks something like a slow-motion walk. But they can manage this movement only underwater.

Other fish can move on land, although none of them use a tetrapod gait to do so. Some simply squirm, while others, like mudskippers, rely on their front fins as crutches. In Hawaii, the Nopili rock-climbing goby climbs up rock faces by using its mouth as a suction cup.

The waterfall-climbing cave fish is leaps ahead of them, it turns out. Pale and blind, the two-inch-long fish feeds on microbes and organic matter growing on the cave walls. It was discovered in 1985, deep inside a system of caves in northern Thailand, and has been found nowhere else. While other fish in the caves enjoy a life in quiet pools, the waterfall-climbing cave fish clambers up slick rocks as water crashes over it.

On a recent expedition to the caves, Apinun Suvarnaraksha, a biologist at Maejo University in Thailand, and Daphne Soares, of the New Jersey Institute of Technology, came across the climber and took some grainy videos of it.

Back in New Jersey, Dr. Soares showed the videos to her colleague, Brooke E. Flammang, an expert on biomechanics. "I was completely blown away," Dr. Flammang said. Instead of flopping or crutching, the cave fish were using what looked like a full-blown tetrapod gait. "These guys seemed to be very leisurely walking up the rock face," Dr. Flammang said.

She wanted to study the fish more closely, but the species is rare and protected, and she could not bring any of them into her lab.

Dr. Suvarnaraksha did the next best thing. In a Thai museum collection, he found one of the few preserved specimens of the fish. He took it to a dental school and used a high-resolution CT scanner to make images of the fish.

After Dr. Suvarnaraksha emailed the images to Dr. Flammang, she was able to line up the images together to reconstruct the fish's three-dimensional anatomy.

In many ways, the skeleton of the fish looked like what you'd see on a walking tetrapod. "I literally thought someone was playing a trick on me," she said.

In typical fish, the pelvis is just a pair of small bones floating in the body wall. Fish use the bones only to stabilize their pelvic fins, so that they can stop themselves from rolling over.

In the waterfall-climbing cave fish, on the other hand, the pelvis is a complex of bones that is fused to the spine by elongated ribs. It's the same arrangement that tetrapods evolved, allowing them to hold themselves up with their hind legs.

Typical fish also have small vertebrae that don't overlap, allowing them to bend their bodies as they swim. But the waterfall-climbing cave fish has the same overlapping growths on their vertebrae that stiffen the spine in tetrapods.

"Functionally, it makes perfect sense, but to see it in a fish is incredibly wild," Dr. Flammang said. In Thailand, Dr. Suvarnaraksha then went back to the caves with a video camera. He scooped two of the fish into an aquarium and made videos of them walking at different angles.

When Dr. Flammang and her colleagues analyzed the images, they confirmed their initial hunch: The fish were using their tetrapod-like bodies to walk with a tetrapod-like gait. It most closely resembles that of a salamander. The researchers published their study on Thursday in the journal Scientific Reports.

Dr. Flammang said that the waterfall-climbing cave fish eventually might give scientists hints about how fish originally arrived on land. "The physics are the same," she said.

Scientists have found trackways in Poland dating back almost 400 million years that look as if they were made by a walking tetrapod. But the oldest tetrapod fossils found so far date only to 375 million years.

It's possible that a fish, rather than a primitive tetrapod, made those tracks by moving as the waterfall-climbing cave fish does today. "We see these footprints in a fish today, doing something very unfishlike," Dr. Flammang said.

http://www.eurekalert.org/pub_releases/2016-03/uoea-rml031816.php

Read my lips: New technology spells out what's said when audio fails

New lip-reading technology developed at the University of East Anglia (UEA) could help in solving crimes and provide communication assistance for people with hearing and speech impairments.

The visual speech recognition technology, created by Dr Helen L. Bear and Prof Richard Harvey of UEA's School of Computing Sciences, can be applied "any place where the audio isn't good enough to determine what people are saying," Dr Bear said.

Dr Bear, whose findings will be presented at the International Conference on Acoustics, Speech and Signal Processing (ICASSP) in Shanghai on March 25, said unique problems with determining speech arise when sound isn't available - such as on CCTV footage - or if the audio is inadequate and there aren't clues to give the context of a conversation. The sounds '/p/,' '/b/,' and '/m/' all look similar on the lips, but now the machine lip-reading classification technology can differentiate between the sounds for a more accurate translation.

Dr Bear said: "We are still learning the science of visual speech and what it is people need to know to create a fool-proof recognition model for lip-reading, but this classification system improves upon previous lip-reading methods by using a novel training method for the classifiers.

"Potentially, a robust lip-reading system could be applied in a number of situations, from criminal investigations to entertainment. Lip-reading has been used to pinpoint words footballers have shouted in heated moments on the pitch, but is likely to be of most practical use in situations where are there are high levels of noise, such as in cars or aircraft cockpits.

"Crucially, whilst there are still improvements to be made, such a system could be adapted for use for a range of purposes - for example, for people with hearing or speech impairments. Alternatively, a good lip-reading machine could be part of an audio-visual recognition system."

Prof Harvey said: "Lip-reading is one of the most challenging problems in artificial intelligence so it's great to make progress on one of the trickier aspects, which is how to train machines to recognise the appearance and shape of human lips."

The research was part of a three-year project and was supported by the Engineering and Physical Sciences Research Council (EPSRC).

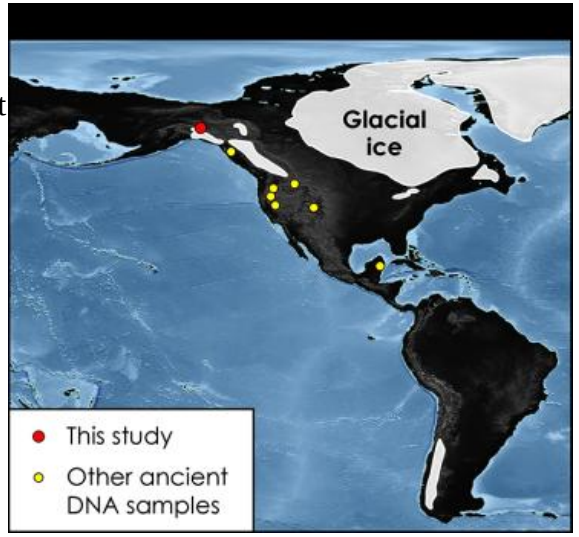
The paper, Decoding visemes: Improving machine lip-reading, will be published on March 25, 2016 in the Proceedings of the IEEE International Conference on Acoustics, Speech and Signal Processing 2016.

http://www.earthmagazine.org/article/long-layover-bering-land-bridge

A long layover on the Bering land bridge

After migrating across the Bering land bridge from Asia, first Americans spent up to 10,000 years in Beringia before moving south into the Americas

Mary Caperton Morton



About 11,500 years ago, two infants were laid to rest side by side in a shallow grave 80 kilometers southeast of what is now Fairbanks, Alaska. The area was once part of Beringia, a strip of ice-free land connected to Asia during the last ice age. Researchers found the remains in 2013, and have now sequenced the complete mitochondrial genomes of the two children. The results revealed that the infants had different mothers and that their genetic signatures are found today throughout North and South America.

The Late Pleistocene remains of two infants recovered from the Upper Sun River campsite in eastern Alaska are shedding light on the peopling of the Americas. **K. Cantner, AGI, after Tackney, et al. 2015**

Anthropologists have long suspected that the Americas were populated by nomadic people from Asia who migrated over the Bering land bridge during the last ice age, when sea levels were much lower. Glacial evidence suggests that this land bridge was open between 28,000 and 18,000 years ago. However, the oldest evidence of people in the Americas dates to about 15,000 years ago, leaving researchers to wonder what took these nomads so long to move south from Beringia after crossing the land bridge.

The newly published mitochondrial DNA sequences — the oldest sequences recovered to date this far north — lend support to an idea called the Beringian

standstill hypothesis. The hypothesis suggests that after the first Americans migrated across the Bering land bridge from Asia, they spent up to 10,000 years in Beringia before moving south into the Americas, possibly because ice blocked the route.

The DNA results are helping answer some long-standing questions about the Beringians, says Justin Tackney, an anthropologist at the University of Utah and lead author of the new study, published in Proceedings of the National Academy of Sciences. "These remains are the closest we've gotten yet to figuring out who lived in Beringia," he says. "Did they have genetic signatures that look like Asians? Or Native Americans?"

Because the remains were found far north in a cold environment, they were well preserved, enabling the team at the University of Utah's Ancient DNA Laboratory to extract and sequence the complete mitochondrial genomes of both infants. The initial findings revealed that the children — a 6- to 12-week-old baby and a preterm 30-week fetus — had different mothers, raising questions about social structures and burial practices among the Beringians. The researchers also found that the two lineages represented by the children are still present today throughout North and South America.

"These lineages aren't Asian; they're distinctly North American," Tackney says. That means that the population to which the children belonged had already been genetically isolated from Asian populations for enough time to differentiate into a unique genotype. "The most likely geographical place for this isolation to occur was in Beringia," Tackney says, as it was surrounded by ice and water on three sides.

The findings help constrain when the first North American genomes likely evolved, says Ripan Malhi, a geneticist at the University of Illinois at Urbana-Champaign who was not involved in the new study. They don't "tell us exactly where or when these mitogenomes evolved," he says, but "we can now say with certainty that these two mitochondrial genomes were present by 11,500 years ago."

The competing theory to the standstill hypothesis suggests that Native American lineages evolved only after people moved south, not while they were still in Beringia, Tackney says. But finding North American lineages in the infants only a few thousand years after the migration south began indicates those lineages were already present before the migration started.

The next step will be to sequence the nuclear genomes of the two infants, Malhi says. Sequencing nuclear DNA is more time-consuming and much more expensive than sequencing mitochondrial DNA, Malhi says, but whereas "mitochondrial DNA only tells us about the maternal line, nuclear DNA can trace all of an individual's ancestral lines, giving us a complete picture of relatedness between both ancient and living individuals." Sequencing the nuclear DNA may reveal whether the two infants shared the same father or were otherwise related, and could shed more light on their relationship to modern Native Americans, he says.

"This kind of sequencing has revolutionized our understanding of how people came to populate the Americas, but we're still very much at the very beginning stages of realizing its potential," Malhi says. "As we sequence more genomes of ancient individuals, the picture of the peopling of the Americas is going to become clearer and clearer."

http://www.eurekalert.org/pub_releases/2016-03/aaft-zai032116.php

Zika arrived in Americas during mid-2013, following upsurge in air travelers

Zika likely arrived more than a year before it was reported in Brazil

By sequencing a small number of Zika virus genomes from Brazil, researchers have estimated that the virus had a single entry into the Americas, likely more than a year before the virus was reported in Brazil. This timing, they say, correlates with major events in the Brazilian cultural calendar associated with increased numbers of travelers to the country, particularly from areas where the Zika virus (ZIKV) circulates. Though the sample size used in this study is small (just seven ZIKV sequences), the work represents an important result given how little is known about this emerging virus to date. Brazil is in the midst of an unprecedented epidemic of Zika virus, which was first detected in the country in May 2015. Here, to better understand the evolution and molecular epidemiology of Zika in Brazil, Nuno Faria and colleagues sampled several ZIKV genomes linked to the recent Brazilian outbreak -one from a blood donor, one from a fatal adult case, and one from a newborn with congenital malformations and microcephaly, a rare disorder in which a baby's head is much smaller than expected (Faria et al. note that work remains ongoing to establish whether ZIKV is a causal factor in microcephaly). Using next-generation sequencing, the researchers generated seven Brazilian ZIKV genomes, finding little genetic variability among them. Following comparative analyses between these and existing ZIKV genomes, they conclude that there was a single introduction of ZIKV into the Americas, likely somewhere between May and December 2013 - more than 12 months prior to the virus's detection in Brazil. Airline data reveal that this timing coincides not only with an increase in air passengers to Brazil from ZIKV endemic areas, but also with reported ZIKV outbreaks in the Pacific Islands. Preliminary results from this study do not yet shed light on the link to microcephaly of babies, the authors note.

http://www.eurekalert.org/pub_releases/2016-03/cp-yct031616.php

You can thank diverse yeasts for that coffee and chocolate

Yeasts associated with coffee and cacao beans have had a rather unique history

Humans have put yeast to work for thousands of years to make bread, beer, and wine. Wild strains of yeast are also found in the natural fermentations that are essential for chocolate and coffee production. But, as new genetic evidence reported in the Cell Press journal Current Biology on March 24 shows, the yeasts associated with coffee and cacao beans have had a rather unique history.

In comparison to the yeasts found in vineyards around the world, the new work shows that those associated with coffee and cacao beans show much greater diversity. The findings suggest that those differences may play an important role in the characteristics of chocolate and coffee from different parts of the world.

"Our study suggests a complex interplay between human activity and microbes involved in the production of coffee and chocolate," says Aimée Dudley of the Pacific Northwest Diabetes Research Institute in Seattle. "Humans have transported and cultivated the plants, but at least for one important species, their associated microbes have arisen from transport and mingling in events that are independent of the transport of the plants themselves."

Coffee and cacao trees originally grew in Ethiopia and the Amazon rainforest. They are now widely cultivated across the "bean belt" that surrounds the equator. After they are picked, both cacao and coffee beans are fermented for a period of days to break down the surrounding pulp. This microbe-driven process also has an important influence on the character and flavor of the beans.

Dudley and her colleagues wanted to know where the yeasts in these human-associated fermentations came from. Had coffee- or cacao-specific yeast strains been unknowingly transported along with the plants? Or, do particular regions of the world harbor novel yeast populations?

To find out, the researchers bought unroasted coffee and cacao beans grown in Central and South America, Africa, Indonesia, or the Middle East and isolated the associated yeast in their Seattle laboratory. Genetic analysis of those yeast strains revealed that yeasts from coffee and cacao beans were substantially more diverse than the wine yeasts. Interestingly, the genetic signatures of the yeast strains strongly clustered according to the geographic origin of the beans. In fact, Dudley says, this association was so strong that they were able to accurately determine the origin of the beans solely from the DNA sequences of their associated yeasts.

The findings show that the yeast strains associated with coffee and cacao have multiple, independent origins. In other words, not all coffee strains are related, nor are all cacao strains. What's more, the yeast strains associated with coffee or cacao in specific places appear to be hybrids that resulted from the mixing of strains from different parts of the world. In fact, one of those strains is closely related to the yeast used to make wine.

"The ancient and continuing global traffic in yeasts associated with wine fermentation may have set the stage for subsequent mingling and admixture events that gave rise to the yeasts that are now associated with the production of coffee and chocolate," Dudley says.

The researchers say the findings could lead to improvements in chocolate and coffee. Studies of wine production have shown that the yeasts associated with fermentation significantly influence the properties of the wine, including its flavor and aroma.

"Given that the yeast strains associated with coffee and cacao fermentations are substantially more genetically diverse than the wine strains, they could play an even larger role in the properties of coffee and cacao produced in different regions of the globe," Dudley says.

This work was funded by a strategic partnership between the University of Luxembourg and the Institute for Systems Biology and by a National Institutes of Health grant.

Current Biology, Ludlow et al.:"Independent Origins of Yeast Associated with Coffee and Cacao Fermentation" http://dx.doi.org/10.1016/j.cub.2016.02.012

http://www.eurekalert.org/pub_releases/2016-03/uoc-eds031616.php

Embryo development: Some cells are more equal than others even at four-cell stage

Cells of the two day-old embryo are already beginning to display subtle differences

Genetic 'signatures' of early-stage embryos confirm that our development begins to take shape as early as the second day after conception, when we are a mere four cells in size, according to new research led by the University of Cambridge and EMBL-EBI. Although they seem to be identical, the cells of the two day-old embryo are already beginning to display subtle differences.

Once an egg has been fertilised by a sperm, it divides several times, becoming a large free-floating ball of stem cells. At first, these stem cells are 'totipotent', the state at which a stem cell can divide and grow and produce everything--every single cell of the whole body and the placenta, to attach the embryo to the mother's womb. The stem cells then change to a 'pluripotent' state, in which their development is restricted to generating the cells of the whole body, but not the placenta. However, the point during development at which cells begin to show a preference for becoming a specific cell type is unclear.

Now, in a study published in the journal Cell, scientists at the University of Cambridge and the European Bioinformatics Institute (EMBL-EBI) suggests that as early as the four-cell embryo stage, the cells are indeed different.

The researchers used the latest sequencing technologies to model embryo development in mice, looking at the activity of individual genes at a single cell level. They showed that some genes in each of the four cells behaved differently. The activity of one gene in particular, Sox21, differed the most between cells; this gene forms part of the 'pluripotency network'. The team found when this gene's activity was reduced, the activity of a master regulator that directs cells to develop into the placenta increased.

"We know that life starts when a sperm fertilises an egg, but we're interested in when the important decisions that determine our future development occur," says Professor Magdalena Zernicka-Goetz from the Department of Physiology, Development and Neuroscience at the University of Cambridge. "We now know that even as early as the four-stage embryo - just two days after fertilisation - the embryo is being guided in a particular direction and its cells are no longer identical."

Dr John Marioni of EMBL-EBI, the Wellcome Trust Sanger Institute and the Cancer Research UK Cambridge Institute, adds: "We can make use of powerful sequencing tools to deepen our understanding of the molecular mechanisms that drive development in individual cells. Because of these high-resolution techniques, we are now able to see the genetic and epigenetic signatures that indicate the direction in which early embryonic cells will tend to travel."

The research was funded by the Wellcome Trust, the European Molecular Biology Laboratory and Cancer Research UK.

Heterogeneity in Oct4 and Sox2 Targets Biases Cell Fate in Four-Cell Mouse Embryos. Cell; 24 March 2016. DOI: 10.1016/j.cell.2016.01.047

http://www.eurekalert.org/pub_releases/2016-03/cu-mft032416.php

Malaria family tree has bird roots

A study published this week in the journal Molecular Phylogenetics and Evolution reveals a new hypothesis on the evolution of hundreds of species of malaria - including the form that is deadly to humans.

ITHACA, N.Y. - Extensive testing of malarial DNA found in birds, bats and other small mammals from five East African countries revealed that malaria has its roots in bird hosts. It then spread from birds to bats and on to other mammals.

"We can't begin to understand how malaria spread to humans until we understand its evolutionary history," said lead author Holly Lutz, a doctoral candidate in the fields of Ecology and Evolutionary Biology and Population Medicine and Diagnostic Sciences at Cornell University. "In learning about its past, we may be better able to understand the effects it has on us."

Lutz and her colleagues took blood samples from hundreds of East African birds, bats, and other small mammals and screened the blood for the parasites. When they found malaria, they took samples of the parasites' DNA and sequenced it to identify mutations in the genetic code. From there, Lutz determined how different malaria species are related based on differences in their genetic code. Having large sample sizes from many species was key.

"Trying to determine the evolutionary history of malaria from just a few specimens would be like trying to reconstruct the bird family tree when you only know about eagles and canaries," explained Lutz. "There's still more to discover, but this is the most complete analysis of its kind for malaria to date."

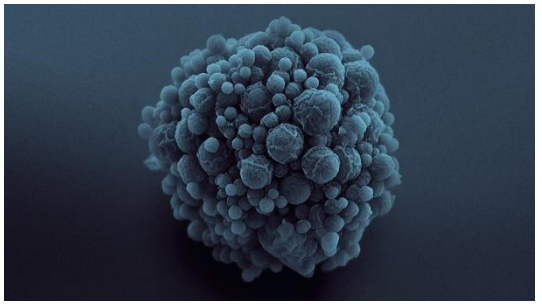
Humans cannot contract malaria directly from birds or bats. And while the study doesn't have direct implications for malaria treatment in humans, co-author and Field Museum Curator of Mammals Bruce Patterson noted, "Malaria is notoriously adaptive to treatment, and its DNA holds a host of secrets about how it's able to change and evolve. Having a better understanding of its evolutionary history could help scientists anticipate its future."

http://bit.ly/1pOXbTY

In Newly Created Life-Form, a Major Mystery

Scientists have created a synthetic organism that possesses only the genes it needs to survive. But they have no idea what roughly a third of those genes do.

By Emily Singer



Peel away the layers of a house — the plastered walls, the slate roof, the hardwood floors — and you're left with a frame, the skeletal form that makes up the core of any structure. Can we do the same with life? Can scientists pare down the layers of complexity to reveal the essence of life, the foundation on which biology is built?

The syn3.0 cells contain the minimum number of genes needed for life **Tom Deerinck and Mark Ellisman**

That's what Craig Venter and his collaborators have attempted to do in a new study published today in the journal *Science*. Venter's team painstakingly whittled down the genome of *Mycoplasma mycoides*, a bacterium that lives in cattle, to reveal a bare-bones set of genetic instructions capable of making life. The result is a tiny organism named syn3.0 that contains just 473 genes. (By comparison, *E. coli* has about 4,000 to 5,000 genes, and humans have roughly 20,000.)

Yet within those 473 genes lies a gaping hole. Scientists have little idea what roughly a third of them do. Rather than illuminating the essential components of

life, syn3.0 has revealed how much we have left to learn about the very basics of biology.

"To me, the most interesting thing is what it tells us about what we don't know," said Jack Szostak, a biochemist at Harvard University who was not involved in the study. "So many genes of unknown function seem to be essential."

"We were totally surprised and shocked," said Venter, a biologist who heads the J. Craig Venter Institute in La Jolla, Calif., and Rockville, Md., and is most famous for his role in mapping the human genome. The researchers had expected some number of unknown genes in the mix, perhaps totaling five to 10 percent of the genome. "But this is truly a stunning number," he said.

The seed for Venter's quest was planted in 1995, when his team deciphered the genome of *Mycoplasma genitalium*, a microbe that lives in the human urinary tract. When Venter's researchers started work on this new project, they chose *M. genitalium* — the second complete bacterial genome to be sequenced — expressly for its diminutive genome size.

With 517 genes and 580,000 DNA letters, it has one of the smallest known genomes in a self-replicating organism. (Some symbiotic microbes can survive with just 100-odd genes, but they rely on resources from their host to survive.)

M. genitalium's trim package of DNA raised the question: What is the smallest number of genes a cell could possess? "We wanted to know the basic gene components of life," Venter said. "It seemed like a great idea 20 years ago — we had no idea it would be a 20-year process to get here."

Minimal Design

Venter and his collaborators originally set out to design a stripped-down genome based on what scientists knew about biology. They would start with genes involved in the most critical processes of the cell, such as copying and translating DNA, and build from there.

But before they could create this streamlined version of life, the researchers had to figure out how to design and build genomes from scratch. Rather than editing DNA in a living organism, as most researchers did, they wanted to exert greater control — to plan their genome on a computer and then synthesize the DNA in test tubes.

In 2008, Venter and his collaborator Hamilton Smith created the first synthetic bacterial genome by building a modified version of *M. genitalium*'s DNA. Then in 2010 they made the first self-replicating synthetic organism, manufacturing a version of *M. mycoides*' genome and then transplanting it into a different *Mycoplasma* species. The synthetic genome took over the cell, replacing the native operating system with a human-made version.

The synthetic *M. mycoides* genome was mostly identical to the natural version, save for a few genetic watermarks — researchers added their names and a few famous quotes, including a slightly garbled version of Richard Feynman's assertion, "What I cannot create, I do not understand."

With the right tools finally in hand, the researchers designed a set of genetic blueprints for their minimal cell and then tried to build them. Yet "not one design worked," Venter said. He saw their repeated failures as a rebuke for their hubris. Does modern science have sufficient knowledge of basic biological principles to build a cell? "The answer was a resounding no," he said.

So the team took a different and more labor-intensive tack, replacing the design approach with trial and error. They disrupted *M. mycoides*' genes, determining which were essential for the bacteria to survive. They erased the extraneous genes to create syn3.0, which has a smaller genome than any independently replicating organism discovered on Earth to date.

What's left after trimming the genetic fat? The majority of the remaining genes are involved in one of three functions: producing RNA and proteins, preserving the fidelity of genetic information, or creating the cell membrane. Genes for editing DNA were largely expendable.

But it is unclear what the remaining 149 genes do. Scientists can broadly classify 70 of them based on the genes' structure, but the researchers have little idea of what precise role the genes play in the cell. The function of 79 genes is a complete mystery.

"We don't know what they provide or why they are essential for life — maybe they are doing something more subtle, something obviously not appreciated yet in biology," Venter said. "It's a very humbling set of experiments."

Venter's team is eager to figure out what the mystery genes do, but the challenge is multiplied by the fact that these genes don't resemble any other known genes. One way to investigate their function is to engineer versions of the cell in which each of these genes can be turned on and off. When they're off, "what's the first thing to get messed up?" Szostak said. "You can try to pin it to general class, like metabolism or DNA replication."

Dwindling to Zero

Venter is careful to avoid calling syn3.0 a universal minimal cell. If he had done the same set of experiments with a different microbe, he points out, he would have ended up with a different set of genes.

In fact, there's no single set of genes that all living things need in order to exist. When scientists first began searching for such a thing 20 years ago, they hoped that simply comparing the genome sequences from a bunch of different species would reveal an essential core shared by all species. But as the number of genome

sequences blossomed, that essential core disappeared. In 2010, David Ussery, a biologist at Oak Ridge National Laboratory in Tennessee, and his collaborators compared 1,000 genomes. They found that not a single gene is shared across all of life. "There are different ways to have a core set of instructions," Szostak said.

Moreover, what's essential in biology depends largely on an organism's environment. For example, imagine a microbe that lives in the presence of a toxin, such as an antibiotic. A gene that can break down the toxin would be essential for a microbe in that environment. But remove the toxin, and that gene is no longer essential.

Venter's minimal cell is a product not just of its environment, but of the entirety of the history of life on Earth. Sometime in biology's 4-billion-year record, cells much simpler than this one must have existed. "We didn't go from nothing to a cell with 400 genes," Szostak said. He and others are trying to make more basic life-forms that are representative of these earlier stages of evolution.

Some scientists say that this type of bottom-up approach is necessary in order to truly understand life's essence. "If we are ever to understand even the simplest living organism, we have to be able to design and synthesize one from scratch," said Anthony Forster, a biologist at Uppsala University in Sweden. "We are still far from this goal."

Synthetic Biology

Venter envisions syn3.0 as a cellular chassis that scientists can build on. Researchers can embellish the genome to create new organisms, which could help them to better understand stages of evolution lost to time.

"In theory, we should be able to add genes back to [syn3.0] to recapitulate key parts of evolution," Venter said. For example, they might try to create more advanced bacteria, or even to convert the basic chassis into different biological classes altogether.

"We could reduce billions of years of evolution to maybe years or months or weeks," he said.

Venter and his collaborators also plan to use the cells for industrial purposes, designing cells that can produce pharmaceuticals or other chemicals. "We have one cell in production to make omega-3s more efficiently than it can be isolated from fish," Venter said.

One of the challenges in synthetic biology — the quest to engineer cells for specific purposes — has been that living organisms behave unpredictably. Theoretically, a minimal cell would provide an engineering advantage because it has fewer unpredictable components. It's not yet clear whether this will prove true. Most efforts in synthetic biology employ existing microbes, such as E. coli, *and scientists may not yet see a good reason to switch.*

http://www.eurekalert.org/pub_releases/2016-03/usmc-crl032516.php

CRI researchers link absence of protein to liver tissue regeneration

Inactivating a single protein-coding gene promotes tissue regeneration in mammals.

DALLAS - Scientists at the Children's Medical Center Research Institute at UT Southwestern (CRI) report that inactivating a certain protein-coding gene promotes liver tissue regeneration in mammals.

"This research gives us ideas about new ways to treat liver damage or chronic liver disease," said senior author Dr. Hao Zhu, an Assistant Professor at CRI with joint appointments in Internal Medicine and Pediatrics at UT Southwestern Medical Center. The study was published this week in the journal Cell Stem Cell.

Tails in lizards and arms in starfish show an astounding ability to regrow, but mammals have partially lost the capacity to extensively regenerate body parts, Dr. Zhu said. The liver is unique among human solid organs in its robust regenerative capability. A healthy liver can regenerate up to 70 percent of its tissue after injury, he explained.

However, when the liver has been repeatedly damaged - by chemical toxins or chronic disease - it loses its ability to regenerate. Following repeated injuries, cirrhosis or scar tissue forms, greatly increasing the risk of cancer, said Dr. Zhu, who also treats liver cancer patients at Parkland Memorial Hospital. The Zhu laboratory studies both regeneration, when cells proliferate to repair an organ, and cancer, when cells proliferate out of control.

The National Cancer Institute (NCI) reports that liver cancer deaths increased at the highest rate of all common cancers from 2003-2012. In addition to cirrhosis, risk factors for liver cancer include infections caused by the hepatitis C virus (HCV), liver damage from alcohol or other toxins, chronic liver disease, and certain rare genetic disorders.

Dr. Zhu began his investigation by studying a mouse that lacked Arid1a, the mouse version of a gene associated with some human cancers.

"In humans, the gene ARID1A is mutated in several cancers, including liver cancer, pancreatic cancer, breast cancer, endometrial cancer, lung cancer, the list goes on," Dr. Zhu said. "It is not mutated in every type of cancer, but in a significant number. Those mutations are found in 10 to 20 percent of all cancers, and the mutations render the gene inactive."

Based on this association, the researchers hypothesized that mice lacking Arid1a would develop liver damage and, eventually, liver cancer. They were surprised

when the opposite proved to be the case - no liver damage occurred. In fact, livers of the mice regenerated faster and appeared to function better, he added.

"The livers were resistant to tissue damage and healed better, which are two good things - like playing offense and defense at the same time," he said. "These results opened up a whole new avenue of investigation for us, and through that investigation we found a new function for this gene."

On observation, livers in the mice without the gene appeared healthier. Blood tests confirmed improved liver function. When researchers deleted the gene in mice with various liver injuries, they found that the livers replaced tissue mass quicker and showed reduced fibrosis in response to chemical injury. Also, other tissues such as wounded skin healed faster in Arid1a-deficient mice.

No drugs are currently available to mimic a lack of this protein, although the researchers are using a grant from the Cancer Prevention and Research Institute of Texas (CPRIT) to search for one.

"We want to identify small molecules that mimic the effect of these genetic findings. The ideal drug would be one that helps the liver heal while inhibiting the development of cancer. That would be the perfect drug for my patients," said Dr. Zhu, a CPRIT Scholar in Cancer Research.

Dr. Zhu said loss of the gene and the protein it expresses may accelerate regeneration by reorganizing how genes are packaged in the genome so that the cells can more easily switch back and forth toward a more regenerative state, sort of like a toggle switch.

"Somehow, loss of this gene seems to make it easier for the cell to go back and forth," he said. "This study opens up new areas to investigate how to rejuvenate tissues without necessarily increasing cancer risk, although many more tests will have to be done to determine how the risk of all types of liver cancers are altered."

Co-authors included lead author Dr. Xuxu Sun and Dr. Xin Liu, postdoctoral researchers at CRI; Dr. Jen-Chieh Chuang, Assistant Instructor at CRI; Mahsa Sorouri, research assistant at CRI; Lin Li, senior research scientist at CRI; Dr. Jian Xu, Assistant Professor at CRI and Pediatrics at UTSW; graduate students Cemre Celen, Shuyuan Zhang, and Yi-Chun Kuo; Liem Nguyen, a Howard Hughes Medical Institute International Student Research fellow; Dr. Sam Wang, Assistant Professor of Surgery at UTSW; Dr. Ibrahim Nassour, surgical resident at UTSW; Thomas Maples, medical student at UTSW; Mohammed Kanchwala, a computational biologist in UTSW's Eugene McDermott Center for Human Growth and Development, and Dr. Chao Xing, Associate Professor in the McDermott Center and of Clinical Sciences.

Other contributors were from First Affiliated Hospital of Sun Yat-Sen University, UT Southwestern's sister institution in Guangzhou, China; the University of California, San Diego; Icahn School of Medicine at Mount Sinai; and the University of Michigan.

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http://bit.ly/1Tb22tR

Now There's Proof: Doctors Who Get Company Cash Tend to Prescribe More Brand-Name Medications

The more money doctors receive from drug and medical device companies, the more brand-name drugs they tend to prescribe, a new analysis shows. Even a meal can make a difference.

Charles Ornstein & Ryann Grochowski Jones

Doctors have long disputed that the payments they receive from pharmaceutical companies have any relationship to how they prescribe drugs.

There's been little evidence to settle the matter—until now.

A ProPublica analysis has found for the first time that doctors who receive payments from the medical industry do indeed tend to prescribe drugs differently than their colleagues who don't. And the more money they receive, on average, the more brand-name medications they prescribe.

We matched records on payments from pharmaceutical and medical device makers in 2014 with corresponding data on doctors' medication choices in Medicare's prescription drug program.

Doctors who got money from drug and device makers—even just a meal—prescribed a higher percentage of brand-name drugs overall than doctors who didn't, our analysis showed. Indeed, doctors who received industry payments were two to three times as likely to prescribe brand-name drugs at exceptionally high rates as others in their specialty.

Doctors who received more than $5,000 from companies in 2014 typically had the highest brand-name prescribing percentages. Among internists who received no payments, for example, the average brand-name prescribing rate was about 20 percent, compared to about 30 percent for those who received more than $5,000.

ProPublica's analysis doesn't prove industry payments sway doctors to prescribe particular drugs, or even a particular company's drugs. Rather, it shows that payments are associated with an approach to prescribing that, writ large, benefits drug companies' bottom line.

"It again confirms the prevailing wisdom ... that there is a relationship between payments and brand-name prescribing," said Dr. Aaron Kesselheim, an associate professor of medicine at Harvard University Medical School who provided guidance on early versions of ProPublica's analysis. "This feeds into the ongoing conversation about the propriety of these sorts of relationships. Hopefully we're

getting past the point where people will say, 'Oh, there's no evidence that these relationships change physicians' prescribing practices.'"

Numerous studies show that generics, which must meet rigid Food and Drug Administration standards, work as well as name brands for most patients. Brand-name drugs typically cost more than generics and are more heavily advertised. Although some medications do not have exact generic versions, there usually is a similar one in the same category. In addition, when it comes to patient satisfaction, there isn't much difference between brands and generics, according to data collected by the website Iodine, which is building a repository of user reviews on drugs.

There's wide variation from state to state when it comes to the proportion of prescribers who take industry money, our analysis found. The rate in Nevada, Alabama, Kentucky, and South Carolina was twice as high as in Vermont, Minnesota, Wisconsin, and Maine.

But, overall, payments are widespread. Nationwide, nearly nine in 10 cardiologists who wrote at least 1,000 prescriptions for Medicare patients received payments from a drug or device company in 2014, while seven in 10 internists and family practitioners did.

Dr. Walid Gellad, an associate professor of medicine at the University of Pittsburgh and co-director of its Center for Pharmaceutical Policy and Prescribing, who also reviewed our analysis, said the pervasiveness of payments is noteworthy. "You can debate if these payments are good or bad, or neither, but what isn't debatable is that they permeate the profession."

The results make sense, said Dr. Richard Baron, president and chief executive of the American Board of Internal Medicine. Doctors nowadays almost have to go out of their way to avoid taking payments from companies, according to Baron. And those who do probably have greater skepticism about the value of brand-name medications. Conversely, doctors have to work to cultivate deep ties with companies—those worth more than $5,000 a year—and such doctors probably have a greater receptiveness to brand-name drugs, he said.

"You have the people who are going out of their way to avoid this and you've got people who are, I'll say, pretty committed and engaged to creating relationships with pharma," Baron said. "If you are out there advocating for something, you are more likely to believe in it yourself and not to disbelieve it."

Physicians consider many factors when choosing which medications to prescribe. Some treat patients for whom few generics are available. A case in point is doctors who care for patients with HIV/AIDS. Others specialize in patients with complicated conditions who have tried generic drugs without success.

Holly Campbell, a spokeswoman for the Pharmaceutical Research and Manufacturers of America, the industry trade group, said in a statement that many factors affect doctors' prescribing decisions. A 2011 survey commissioned by the industry found that more than nine in 10 physicians felt that a "great deal of their prescribing was influenced by their clinical knowledge and experience," Campbell said in a written statement.

"Working together, biopharmaceutical companies and physicians can improve patient care, make better use of today's medicines and foster the development of tomorrow's cures," she wrote. "Physicians provide real-world insights and valuable feedback and advice to inform companies about their medicines to improve patient care."

Several doctors who received large payments from industry and had above-average prescribing rates of brand-name drugs said they are acting in patients' best interest.

"I do prefer certain drugs over the others based on the quality of the medication and also the benefits that the patients are going to get," said Dr. Amer Syed of Jersey City, New Jersey, who received more than $66,800 from companies in 2014 and whose brand-name prescribing rate was more than twice the mean of his peers in internal medicine. "My whole vision of practice is to keep the patients out of the hospital."

Dr. Felix Tarm, of Wichita, Kansas, likewise prescribed more than twice the rate of brand-name drugs than internal medicine doctors nationally. Tarm, who is in his 70s, said he's on the verge of retiring and doesn't draw a salary from his medical practice, instead subsidizing it with the money he receives from drug companies. He said he doesn't own a pharmacy, a laboratory, or an X-ray machine, all ways in which other doctors increase their incomes.

"I generally prescribe on the basis of what I think is the best drug," said Tarm, who received $11,700 in payments in 2014. "If the doctor is susceptible to being bought out by a pharmaceutical company, he can just as easily be bought out by other factors."

A third doctor, psychiatrist Alexander Pinkusovich of Brooklyn, also prescribed a much higher proportion of brand-name drugs than his peers in 2014 while receiving more than $53,400 from drug companies. He threatened to call the district attorney if a reporter called again. "Why are you doing a fishing expedition?" he asked. "You know that I didn't do anything illegal, so good luck."

ProPublica has been tracking drug company payments to doctors since 2010 through a project known as Dollars for Docs. Our first look-up tool included only seven companies, most of which were required to report their payments publicly as a condition of legal settlements. The tool now covers every drug and device

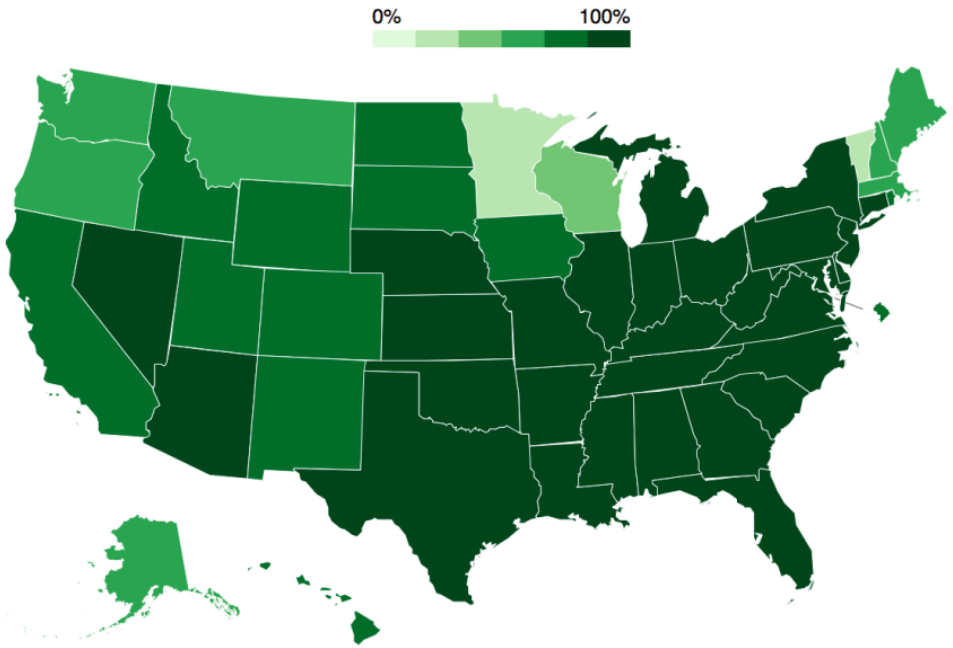
company, thanks to the Physician Payment Sunshine Act, a part of the 2010 Affordable Care Act. The law required all drug and device companies to publicly report their payments. The first reports became public in 2014, covering the last five months of 2013; 2014 payments were released last year.

The payments in our analysis include promotional speaking, consulting, business travel, meals, royalties, and gifts, among others. We did not include research payments, although those are reported in the government's database of industry spending, which it calls Open Payments.

Separately, ProPublica has tracked patterns in Medicare's prescription drug program, known as Part D, which covers more than 39 million people. Medicare pays for at least one in four prescriptions dispensed in the country.

Most Doctors Take Money From Drug, Device Companies

Nationally, about three quarters of doctors across five common medical specialties received at least one payment from a company in 2014. In Nevada, that number was over 90 percent. In Vermont, it was less than 24 percent.



Note: The five specialties are family medicine, internal medicine, cardiovascular disease, psychiatry, and ophthalmology. (Source: Centers for Medicare and Medicaid Services)

This analysis matches the two data sets, looking at doctors in five large medical specialties: family medicine, internal medicine, cardiology, psychiatry, and ophthalmology. We only looked at doctors who wrote at least 1,000 prescriptions in Medicare Part D.

Senator Charles Grassley (R-Iowa), who pushed for the Physician Payment Sunshine Act, said in a statement that "it's gratifying to see" ProPublica's analysis. "Since brand name drugs generally cost more than generic drugs, what doctors prescribe has major effects on Medicare and other payers in the health-care system," he said.

"I look forward to more data, more analysis, and to hearing from doctors about what influences their decision to prescribe brand name drugs versus generic drugs."

Dr. David W. Parke II, chief executive of the American Academy of Ophthalmology, suggested that many payments made to ophthalmologists don't relate to drugs they prescribe in Medicare Part D, and instead may be related to drugs administered in doctors' offices or devices and implants used in eye procedures. As a result, he said, it may be unfair to presume that industry payments are associated with prescribing in Part D.

Still, he said, ProPublica's analysis points to areas that specialty societies may want to look at. "In some cases, there are very appropriate and clinically valid reasons" for doctors who are outliers in their prescribing. "For others, education may very easily result in prescribing change leading to substantive savings for patients, employers, and society."

Dr. Kim Allan Williams Sr., president of the American College of Cardiology, said he believes relationships between companies and doctors are circular. The more physicians learn about a new drug's "differentiating characteristics," he said, the more likely they are to prescribe it. And the more they prescribe it, the more likely they are to be selected as speakers and consultants for the company.

"That dovetails with improving your practice, and, yes, you are getting paid to do it," he said.

Williams said new drugs are, at least in part, responsible for a significant decrease in cardiovascular mortality in the past three decades.

"If you're not making strides in this highly competitive area, if you don't have a product that's better, it's not going to fly," he said. "So the fact that there's this high relationship in cardiology [between doctors and companies] may in fact be driving the progress that we're making."

http://bit.ly/1q7RaS6

Saturn's Moons and Rings May Be Younger Than the Dinosaurs

The planet's rings and many of its moons may be only about 100 million years old.

By Elizabeth Howell, Space.com Contributor | March 25, 2016 12:00pm ET

Some of Saturn's icy moons may have been formed after many dinosaurs roamed the Earth. New computer modeling of the Saturnian system suggests the rings and moons may be no more than 100 million years old.

Saturn hosts 62 known moons. All of them are influenced not only by the gravity of the planet, but also by each other's gravities. A new computer model suggests that the Saturnian moons Tethys, Dione and Rhea haven't seen the kinds of changes in their orbital tilts that are typical for moons that have lived in the system and interacted with other moons over long periods of time. In other words, these appear to be very young moons.

"Moons are always changing their orbits. That's inevitable," Matija Cuk, principal investigator at the SETI Institute and one of the authors of the new research, said in a statement. "But that fact allows us to use computer simulations to tease out the history of Saturn's inner moons. Doing so, we find that they were most likely born during the most recent 2 percent of the planet's history."

The age of Saturn's rings has come under considerable debate since their discovery in the 1600s. In 2012, however, French astronomers suggested that some of the inner moons and the planet's well-known rings may have recent origins. The researchers showed that tidal effects — which refer to "the gravitational interaction of the inner moons with fluids deep in Saturn's interior," according to the statement — should cause the moons to move to larger orbits in a very short time.

"Saturn has dozens of moons that are slowly increasing their orbital size due to tidal effects. In addition, pairs of moons may occasionally move into orbital resonances. This occurs when one moon's orbital period becomes a simple fraction of another. For example, one moon could orbit twice as fast as another moon, or three times as fast.

Once an orbital resonance takes place, the moons can affect each other's gravity, even if they are very small. This will eventually elongate their orbits and tilt them from their original orbital plane.

By looking at computer models that predict how extended a moon's orbit should become over time, and comparing that with the actual position of the moon today, the researchers found that the orbits of Tethys, Dione and Rhea are "less dramatically altered than previously thought," the statement said. The moons don't appear to have moved very far from where they were born.

To get a more specific value for the ages of these moons, Cuk used ice geysers on Saturn's moon Enceladus. The researchers assumed that the energy powering those geysers comes from tidal interactions with Saturn and that the level of geothermal activity on Enceladus has been constant, and from there, inferred the strength of the tidal forces from Saturn.

Using the computer simulations, the researchers concluded that Enceladus would have moved from its original orbital position to its current one in just 100 million years — meaning it likely formed during the Cretaceous period. The larger implication is that the inner moons of Saturn and its gorgeous rings are all relatively young. (The more distant moons Titan and Iapetus would not have been formed at the same time.)

"So the question arises — what caused the recent birth of the inner moons?" Cuk said in the statement. "Our best guess is that Saturn had a similar collection of moons before, but their orbits were disturbed by a special kind of orbital resonance involving Saturn's motion around the sun. Eventually, the orbits of neighboring moons crossed, and these objects collided. From this rubble, the present set of moons and rings formed."

The research is being published in the Astrophysical Journal.

http://nyti.ms/1qaJcYA

Who Will Become a Terrorist? Research Yields Few Clues

Terrorist's backgrounds are so diverse that they defy a single profile

By MATT APUZZO MARCH 27, 2016

WASHINGTON — The brothers who carried out suicide bombings in Brussels last week had long, violent criminal records and had been regarded internationally as potential terrorists. But in San Bernardino, Calif., last year, one of the attackers was a county health inspector who lived a life of apparent suburban normality.

And then there are the dozens of other young American men and women who have been arrested over the past year for trying to help the Islamic State. Their backgrounds are so diverse that they defy a single profile.

What turns people toward violence — and whether they can be steered away from it — are questions that have bedeviled governments around the world for generations. Those questions have taken on fresh urgency with the rise of the Islamic State and the string of attacks in Europe and the United States. Despite millions of dollars of government-sponsored research, and a much-publicized White House pledge to find answers, there is still nothing close to a consensus on why someone becomes a terrorist.

"After all this funding and this flurry of publications, with each new terrorist incident we realize that we are no closer to answering our original question about what leads people to turn to political violence," Marc Sageman, a psychologist

and a longtime government consultant, wrote in the journal Terrorism and Political Violence in 2014. “The same worn-out questions are raised over and over again, and we still have no compelling answers.”

More than a decade later, law enforcement officials and government-funded community groups still regard money problems as an indicator of radicalization.

When President Obama announced plans in 2011 to prevent homegrown terrorism, the details were sketchy, but the promise was clear. The White House would provide warning signs to help parents and community leaders.

“It’s going to be communities that recognize abnormal behavior,” Denis McDonough, the deputy national security adviser at the time, said. As an example, he cited truancy, which he said was an indicator of possible gang activity. “Truancy is also going to be an early warning sign for violent extremism,” he said.

But the years that followed have done little to narrow the list of likely precursors. Rather, the murky science seems to imply that nearly anyone is a potential terrorist. Some studies suggest that terrorists are likely to be educated or extroverted; others say uneducated recluses are at risk. Many studies seem to warn of the adolescent condition, singling out young, impatient men with a sense of adventure who are “struggling to achieve a sense of selfhood.”

Such generalizations are why civil libertarians see only danger in government efforts to identify people at risk of committing crimes. Researchers, too, say they have been frustrated by both the Bush and Obama administrations because of what they say is a preoccupation with research that can be distilled into simple checklists, even at the risk of casting unnecessary suspicion on innocent people.

“They want to be able to do things right now,” said Clark R. McCauley Jr., a professor of psychology at Bryn Mawr College who has conducted government-funded terrorism research for years. “Anybody who offers them something right now, like to go around with a checklist — right now — is going to have their attention.

“It’s demand driven,” he continued. “The people with guns and badges are so eager to have something. The fact that they could actually do harm? This doesn’t deter them.”

Europe, too, is grappling with these questions, but there is no clear answer. Hans Bonte, the mayor of the Belgian town of Vilvoorde, attended a White House summit meeting on radicalization last year and described efforts to stem a steady tide of angry young men leaving to join the Islamic State. In Britain, the government encourages or requires people to alert the authorities about people who could become risks. That has spurred debate abroad, and has raised questions in the United States about whether the Constitution would allow the government to keep tabs on lawful political or religious speech.

“I understand, from an American standpoint, that can be troubling,” said Lorenzo Vidino, the director of the Program on Extremism at the Center for Cyber and Homeland Security at George Washington University. “But the European model, for most countries, is to intervene early, as soon as you see the first sign of extremism.”

Researching terrorism is admittedly difficult. It involves tough questions about who qualifies as a terrorist, or as a rebel or a soldier. Nelson Mandela? Palestinian suicide bombers? The Taliban of today? The Afghan mujahedeen when the C.I.A. supported them?

Researchers seldom have access to terrorists, and scientific methods, such as control groups, are rare. In 2005, Jeff Victoroff, a University of Southern California psychologist, concluded that the leading terrorism research was mostly just political theory and anecdotes. “A lack of systematic scholarly investigation has left policy makers to design counterterrorism strategies without the benefit of facts,” he wrote in The Journal of Conflict Resolution.

When the government does give advice about what to look for, the origin of that information is often impossible to know. A 2012 National Counterterrorism Center report, for instance, declared that anxiety, unmet personal needs, frustration and trauma helped drive radicalization. “Not all individuals who become radicalized have unmet personal needs, but those who do are more vulnerable to radicalization,” the document said, citing no sources.

Finding terrorism’s roots was supposed to help turn people away from violence. But even when someone comes to the government’s attention, there is no policy on what the response should be. The Obama administration envisions a network of counselors, religious figures and experts who can step in to help. With rare exceptions, such a network has not materialized.

The White House recently put the Department of Homeland Security in charge of a task force to coordinate those efforts, an acknowledgment that the loose alliance of the past several years had suffered from a lack of goals and coordination. George Selim, the Homeland Security official leading the effort, said the administration had never intended to dictate policies. The government, Mr. Selim said, has successfully started conversations and fostered relationships between communities and law enforcement groups.

In Minneapolis, one of the pilot cities for the administration’s counter-radicalization efforts, Andrew M. Luger, the United States attorney for Minnesota, has built relationships with the Somali community. He said that a prevention program was coming soon, and that interventions were farther off.

“It’s taken a lot of time,” he said. “We’re at a point where a lot of it is beginning to come to fruition.”

Though the government plays down its use of checklists, the Justice Department offers grants for the development of “a rapid assessment” tool to help the authorities “gauge the potential” for extremism. Last year, the Intercept news organization revealed a government checklist to score people in terrorism investigations based on factors, including whether they feel mistreated by the government, distrust law enforcement or suffer from discrimination.

Mr. McCauley said many of his colleagues and peers conducted smart research and drew narrow conclusions. The problem, he said, is that studies get the most attention when they suggest warning signs. Research linking terrorism to American policies, meanwhile, is ignored.

As a practical matter, scientists note, checklists are mathematically certain to fail. Even a test with 99 percent accuracy would be wrong far more often than right. It is a counterintuitive thought, but in a country with a huge population and a tiny number of terrorists, even a nearly perfect test would flag many more innocent people than actual terrorists.

In social services, this problem all but disappears. There are few consequences for seeking help for someone who appears to be suicidal but is not. When the F.B.I. is the only option, the ramifications can be severe.

“We talk a very good game,” said John Horgan, a professor at Georgia State University who has conducted numerous government-funded studies. “But from the national security standpoint, we still have a scorecard mentality of early identifications and sting operations.”

In Montgomery County, Md., a Washington suburb, a Muslim-led interfaith organization called Worde thinks it may have a solution. Organizers have provided families and faith leaders with lists of warning signs: depression, trauma, economic stress and political grievances. Anyone who spots these indicators signs can call Worde, which will arrange mental health or religious counseling.

Police officers become involved only when there is a threat of imminent danger, said Hedieh Mirahmadi, the group’s president. Ideally, she said, people get help without being stigmatized or placed on government watch lists.

The program is unproven; a nearly complete study on its effectiveness gives it high marks for building community relationships but does not assess whether the group reduces violent extremism. And while Ms. Mirahmadi said “nobody would disagree” with her warning signs, researchers are far less certain that they are indicators of potential radicalization. Still, the Obama administration believes Worde could be a model and has awarded it $500,000 in grants.

Faiza Patel, a lawyer with the Brennan Center for Justice, remains skeptical. Worde has not released its intervention protocols or its method for assessing things like political grievances. Ms. Mirahmadi said such tools would be too easily misunderstood.

But, she said, it is a start. She said her group had counseled about 20 people, providing help that otherwise did not exist. Whether any of these people would have become violent, she said, is impossible to know.

http://bit.ly/1UWqfnN

Japan: Trouble reaching innovative new space satellite

Japan's space agency says communication has failed with a newly launched, innovative satellite with X-ray telescopes meant to study black holes and other space mysteries.

TOKYO (AP) — Japan Aerospace Exploration Agency spokeswoman Izumi Yoshizaki said Monday that efforts to restore communication links since the problem began Saturday afternoon have been unsuccessful, and it was investigating what might have happened to the satellite, which is called Hitomi and was launched Feb. 17.

"We are really doing our best," she said by telephone in Tokyo.

She said the agency was looking into a statement from the Joint Space Operations Center, or JSpOC, the U.S. military organization that tracks and identifies objects in space, that Hitomi may have splintered into several pieces.

Whether that had happened or not is unclear, Yoshizaki said.

Jonathan McDowell, an astronomer at the Harvard-Smithsonian Center for Astrophysics, said he suspected the satellite had suffered an "energetic event," possibly a gas leak or a battery explosion, that sent it tumbling end-over-end. That would mean its antenna isn't pointing where it needs to, which is why the satellite can't communicate with the space agency, he said.

The danger is that in that state, the satellite may not be able to draw the solar energy it needs to its panels and its battery will run down before the space agency can reconnect with the satellite and try to fix it, he said.

"Everyone's just gutted," said McDowell, who works with another high-tech space X-ray telescope, Chandra. "To hear that they've run into this piece of bad luck, it's so very sad. I know enough about how the sausage was made to know that this could have easily have happened to us. Space is very unforgiving."