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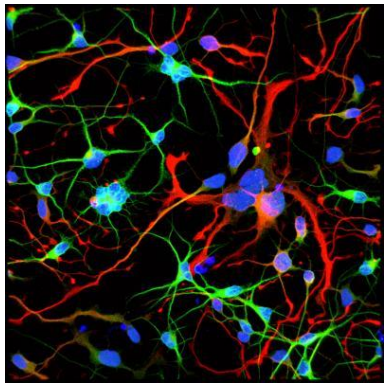
Uncovering the early origins of Huntington's disease

With new findings, scientists may be poised to break a long impasse in research on Huntington's disease, a fatal hereditary disorder for which there is currently no treatment.



One in 10,000 Americans suffer from the disease, and most begin to show symptoms in middle age as they develop jerky movements--and as these patients increasingly lose brain neurons, they slide into dementia. But the new research suggests that these symptoms may be a late manifestation of a disease that originates much earlier, in the first steps of embryonic development.

Huntington's neurons show signs of trouble, like multiple nuclei (blue) within the same cell, long before symptoms emerge. **Laboratory of Stem Cell Biology and Molecular Embryology at The Rockefeller University**

A team at Rockefeller led by Ali Brivanlou, the Robert and Harriet Heilbrunn Professor, developed a system to model Huntington's in human embryonic stem cells for the first time. In a report published in Development, they describe early abnormalities in the way Huntington's neurons look, and how these cells form larger structures that had not previously been associated with the disease.

"Our research supports the idea that the first domino is pushed soon after fertilization," Brivanlou says, "and that has consequences down the line. The final domino falls decades after birth, when the symptoms are observable."

The findings have implications for how to best approach treating the disorder, and could ultimately lead to effective therapies.

A new tool

Huntington's is one of the few diseases with a straightforward genetic culprit: One hundred percent of people with a mutated form of the Huntingtin (HTT) gene develop the disease. The mutation takes the form of extra DNA, and causes the gene to produce a longer-than-normal protein. The DNA itself appears in the form of a repeating sequence, and the more repeats there are, the earlier the disease sets in.

Research on Huntington's has thus far relied heavily on animal models of the disease, and has left many key questions unanswered. For example, scientists have not been able to resolve what function the HTT gene serves normally, or how its mutation creates problems in the brain.

Suspecting that the disease works differently in humans, whose brains are much bigger and more complex than those of lab animals, Brivanlou, along with research associates Albert Ruzo and Gist Croft, developed a cell-based human system for their research. They used the gene editing technology CRISPR to engineer a series of human embryonic stem cell lines, which were identical apart from the number of DNA repeats that occurred at the ends of their HTT genes.

"We started seeing things that were completely unexpected," says Brivanlou. "In cell lines with mutated HTT, we saw giant cells. It looked like a jungle of disorganization."

When cells divide, they typically each retain one nuclei. However, some of these enlarged, mutated cells flaunted up to 12 nuclei--suggesting that neurogenesis, or the generation of new neurons, was affected. The disruption was directly proportional to how many repeats were present in the mutation: The more repeats there were, the more multinucleated neurons appeared.

"Our work adds to the evidence that there is an unrecognized developmental aspect to the pathology," Brivanlou says. "Huntington's may not be just a neurodegenerative disease, but also a neurodevelopmental disease."

Toxic or essential?

Treatments for Huntington's have typically focused on blocking the activity of the mutant HTT protein, the assumption being that the altered form of the protein was more active than normal, and therefore

toxic to neurons. However, Brivanlou's work shows that the brain disruption may actually be due to a lack of HTT protein activity.

To test its function, the researchers created cell lines that completely lacked the HTT protein. These cells turned out to be very similar to those with Huntington's pathology, corroborating the idea that a lack of the protein--not an excess of it--is driving the disease.

The findings are significant, Brivanlou notes, since they indicate that existing treatments that were designed to block HTT activity may actually do more harm than good.

"We should rethink our approach to treating Huntington's," he says. "Both the role of the HTT protein and the timing of treatment need to be reconsidered; by the time a patient is displaying symptoms, it may be too late to medicate. We need to go back to the earliest events that trigger the chain reaction that ultimately results in disease so we can focus new therapies on the cause, not the consequences."

The researchers hope their new cell lines will be a useful resource for studying the cellular and molecular intricacies of Huntington's further, and suggest they may provide a model for examining other diseases of the brain that are specific to humans.

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New evidence shows might of Pharaoh Ramses is fake news

Archaeological evidence from an Egyptian excavation 200 miles east of the Libyan border has helped bust the fearsome reputation of one of the country's most famous pharaohs.

by Mike Addelman, University of Manchester

Dr. Nicky Nielsen, from the University of Manchester, says the Egyptians who lived in the late Bronze Age fortress at of Zawiyet Umm el-Rakham were at peace with their Libyan neighbours. Dr. Nielsen's findings—published in the journal *Antiquity* – contradict the commonly held view that Ramses the Great was waging—and winning- fierce war with his neighbours, in Libya, Nubia and the Near East.

The excavation is directed by Dr. Steven Snape, from the University of Liverpool.

CC0 Public Domain

The evidence—which included 3,300-year-old sickle blades, handstones, querns and cow bones—showed the Egyptians harvested crops and raised cattle herds up to 8 km away from the protection of the fort, located deep in Libyan territory.

According to Dr. Nielsen, the finding adds to the body of evidence that Ramses had limited pedigree as a soldier.

Ramses' famous monuments heralding his prowess as a warrior were nothing more than ancient propaganda, says Dr. Nielsen.

"This evidence demonstrates the degree to which the Egyptian occupants of Zawiyet Umm el-Rakham relied on local Libyans not just for trade, but also for their knowledge of the local environment and effective farming methods," he said.

"It is another strong indication that the widely held belief that Ramses was one of history's greatest generals – is completely wrong.

"How on earth could Ramses have been fiercely at war with Libyan nomads- when his soldiers were living in peace with them deep in their territory? It just doesn't add up.

"In fact, the most significant battle Ramses ever fought was at Kadesh: though one of the most famous in the ancient world –it was disastrously executed by the pharaoh."

According to Dr. Nielsen, the Hittites—the Egyptians' foes- tricked the young king into fighting them, which led him to impetuously imperil a division of his army.

It was only when the three other divisions of his army eventually rescued him was he able to escape, but with no territory gained. In fact he lost control of a great part of modern-day Syria after the battle.

He added: "When you realise that Ramses re-inscribed monuments dedicated to others – so that it appeared they were celebrating his achievements, you realise what a peddler of fake news he was.

"His name was often carved so deeply, it was impossible to remove it – thus preserving his legacy.

"And as he fathered 162 children and ruled Egypt for 69 years, his propaganda had plenty of opportunity to take root."

More information: *Nicky Nielsen. Cereal cultivation and nomad-sedentary interactions at the Late Bronze Age settlement of Zawiyet Umm el-Rakham, Antiquity (2017). DOI: 10.15184/aqy.2017.174*

http://bit.ly/2DU9XYw

What happens to language as populations grow? It simplifies, say researchers

Why does the size of a population of speakers have opposite effects on vocabulary and grammar?

ITHACA, N.Y. - Languages have an intriguing paradox. Languages with lots of speakers, such as English and Mandarin, have large vocabularies with relatively simple grammar. Yet the opposite is also true: Languages with fewer speakers have fewer words but complex grammars.

Why does the size of a population of speakers have opposite effects on vocabulary and grammar?

Through computer simulations, a Cornell University cognitive scientist and his colleagues have shown that ease of learning may explain the paradox. Their work suggests that language, and other aspects of culture, may become simpler as our world becomes more interconnected.

Their study was published in the *Proceedings of the Royal Society B: Biological Sciences*.

"We were able to show that whether something is easy to learn - like words - or hard to learn - like complex grammar - can explain these opposing tendencies," said co-author Morten Christiansen, professor of psychology at Cornell University and co-director of the Cognitive Science Program.

The researchers hypothesized that words are easier to learn than aspects of morphology or grammar. "You only need a few exposures to a word to learn it, so it's easier for words to propagate," he said.

But learning a new grammatical innovation requires a lengthier learning process. And that's going to happen more readily in a smaller speech community, because each person is likely to interact with a large proportion of the community, he said. "If you have to have multiple exposures to, say, a complex syntactic rule, in smaller communities it's easier for it to spread and be maintained in the population."

Conversely, in a large community, like a big city, one person will talk only to a small proportion the population. This means that only a few people might be exposed to that complex grammar rule, making it harder for it to survive, he said.

This mechanism can explain why all sorts of complex cultural conventions emerge in small communities. For example, bebop developed in the intimate jazz world of 1940s New York City, and the Lindy Hop came out of the close-knit community of 1930s Harlem.

The simulations suggest that language, and possibly other aspects of culture, may become simpler as our world becomes increasingly interconnected, Christiansen said. "This doesn't necessarily mean that all culture will become overly simple. But perhaps the mainstream parts will become simpler over time."

Not all hope is lost for those who want to maintain complex cultural traditions, he said: "People can self-organize into smaller communities to counteract that drive toward simplification."

His co-authors on the study, "Simpler Grammar, Larger Vocabulary: How Population Size Affects Language," are Florencia Reali of Universidad de los Andes, Colombia, and Nick Chater of University of Warwick, England.

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This Is Why You Trust Some Strangers and Not Others

A new study suggests the choice seems obvious will likely depend on your prior experience

By Brandon Specktor, Senior Writer | January 29, 2018 03:50pm ET

Imagine you're sitting in a coffee shop, fiddling with your laptop, when nature calls. You decide to ask one of the people sitting near you to watch your computer while you use the bathroom. To your surprise, the person sitting to your left looks suspiciously like Emmy Award-winning nonagenarian Betty White, and the person on your right is a dead ringer for Al Capone. Whom do you ask to watch your property — the Golden Girl, or the gangster?

There is no right or wrong answer, but whether the choice seems obvious will likely depend on your prior experience, a new study suggests. Researchers found that your ability to trust strangers is dependent on the stranger's resemblance to other people you know to be trustworthy or untrustworthy.

In the study, published today (Jan. 29) in the journal Proceedings of the National Academy of Sciences, researchers describe this appearance-bias phenomenon as a "Pavlovian" response by the emotional learning regions of your brain. In other words, certain parts of your brain are conditioned to trust others thanks to their resemblance to friendly faces.

"Our study reveals that strangers are distrusted even when they only minimally resemble someone previously associated with immoral behavior," lead study author Oriel FeldmanHall, an assistant professor in Brown University's Department of Cognitive, Linguistic and Psychological Sciences, said in a statement.

"Like Pavlov's dog — who, despite being conditioned on a single bell, continues to salivate to bells that have similar tones — we use information about a person's moral character … as a basic Pavlovian learning mechanism in order to make judgments about strangers."

For the study, FeldmanHall and her colleagues recruited 91 participants to play a basic computerized trust game. The participants were given $10 to invest with three potential "partners," each of whom was represented by a different headshot on a computer screen. Any money invested with a partner was automatically quadrupled (a $2.50 investment with any partner would yield a $10 return, for example), at which point the partner could either split the profit with the player or keep it all.

As each participant discovered, one partner was always highly trustworthy (split the profits 93 percent of the time), one was somewhat trustworthy (reciprocated 60 percent of the time) and one was untrustworthy (reciprocated 7 percent of the time). Over several rounds of play, the participants quickly learned which partners could be trusted and which could not, the researchers said.

After being conditioned with these trustworthy and untrustworthy faces, each participant played a second game with a new group of potential investment partners. Unbeknownst to the players, many of the new faces they saw were morphed versions of their same partners from the initial game. When the players were again asked to pick an investment partner, they consistently chose the faces that most closely resembled the trustworthy partner from the previous game and rejected the faces that most resembled the untrustworthy partner.

Neural scans of the participants also revealed that the same regions of their brains were at work when initially learning whether to trust a partner in the first experiment and when deciding whether to trust a stranger in the second experiment. Brain activity looked strikingly similar when participants learned that a partner was untrustworthy and when they subsequently decided not to trust a stranger.

"We make decisions about a stranger's reputation without any direct or explicit information about them based on their similarity to others we've encountered, even when we're unaware of this resemblance," senior study author Elizabeth Phelps, a professor in New York University's Department of Psychology, said in a statement. "This shows our brains deploy a learning mechanism in which moral information encoded from past experiences guides future choices."

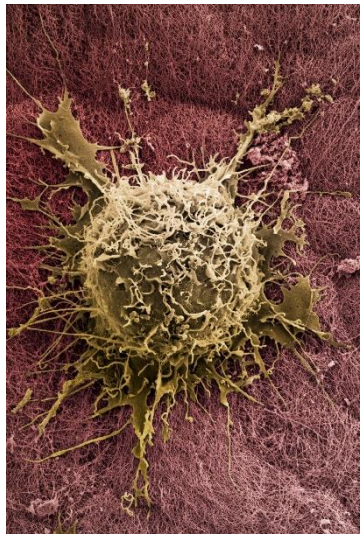
http://nyti.ms/2BOtW9i

Scientists Discover a Bone-Deep Risk for Heart Disease

Few doctors, and even fewer patients, have heard of CHIP. But it is emerging as a major cause of heart attacks and stroke, as deadly as high blood pressure or cholesterol.

By GINA KOLATA JAN. 29, 2018

It's been one of the vexing questions in medicine: Why is it that most people who have heart attacks or strokes have few or no conventional risk factors?



These are patients with normal levels of cholesterol and blood pressure, no history of smoking or diabetes, and no family history of cardiovascular disease. Why aren't they spared?

To some researchers, this hidden risk is the dark matter of cardiology: an invisible but omnipresent force that lands tens of thousands of patients in the hospital each year. But now scientists may have gotten a glimpse of part of it.

A colored scanning electron micrograph of a bone marrow stem cell. Scientists have learned that an accumulation of mutated stem cells in bone marrow dramatically increases a person's risk of dying from a heart attack or stroke.
SPL/Science Source

They have learned that a bizarre accumulation of mutated stem cells in bone marrow increases a person's risk of dying within a decade, usually from a heart attack or stroke, by 40 or 50 percent. They named the condition with medical jargon: clonal hematopoiesis of indeterminate potential.

CHIP has emerged as a risk for heart attack and stroke that is as powerful as high LDL or high blood pressure but it acts independently of them. And CHIP is not uncommon.

The condition becomes more likely with age. Up to 20 percent of people in their 60s have it, and perhaps 50 percent of those in their 80s.

"It is beginning to appear that there are only two types of people in the world: those that exhibit clonal hematopoiesis and those that are going to develop clonal hematopoiesis," said Kenneth Walsh, who directs the hematovascular biology center at the University of Virginia School of Medicine.

Brian Gear, of Braintree, Mass., has clonal hematopoiesis of indeterminate potential, or C.H.I.P., which greatly increases his odds of heart attack or stroke.
Kayana Szymczak for The New York Times

The growing evidence has taken heart researchers aback. Dr. Peter Libby, a cardiologist at Brigham and Women's Hospital and professor of medicine at Harvard Medical School, calls CHIP the most important discovery in cardiology since statins.

"I'm turning part of my lab to work on this full time," Dr. Libby said. "It's really exciting."

The mutations are acquired, not inherited — most likely by bad luck or exposure to toxins like cigarette smoke. But there is little that patients can do.

Brian Gear, a project manager at a Boston company that analyzes health care data, was given genetic testing by doctors at Dana-Farber Cancer Institute because his mother had had a blood cancer that can be inherited. The diagnosis was CHIP, something he had never heard of. And because it dramatically increased his risk of heart disease, it was life-changing.

"It is almost like a Ph.D. in letting go of control," said Mr. Gear, who said he was in his mid-30s. "As much as you want to have a plan and a destiny, you also have this thing. It's scary and it's terrifying."

"I don't want to use the word time-bomb, but that's how it feels," he added.

CHIP was discovered independently by several groups of researchers who were not even investigating heart disease. Mostly, they were looking at the genes of patients who might develop leukemia or, in one research project, schizophrenia.

The scientists searched databases from genetic studies involving tens of thousands of people whose DNA had been obtained from their white blood cells.

To their great surprise, the teams converged on the same phenomenon. Unexpectedly large numbers of study participants had blood cells with mutations linked to leukemia — but they did not have the cancer. Instead, they had just one or two of the cluster of mutations.

“This clearly wasn’t happening by chance,” said Steven McCarroll, a geneticist at the Broad Institute and Harvard Medical School. “We knew we were onto something, but what were we onto?”

The investigators quickly guessed the broad outlines.

White blood cells, the attack dogs of the immune system, arise from stem cells in the bone marrow. Every day, a few hundred such stem cells spew out blood cells that begin dividing rapidly into the 10 billion needed to replace those that have died.

Sometimes, by chance, one of those marrow stem cells acquires a mutation, and the white blood cells it produces carry the same mutation. “Some mutations are just markers of past events without any lasting consequence,” said Dr. David Steensma, a blood cancer specialist at Harvard Medical School and Dana-Farber Cancer Institute.

But others, especially those linked to leukemia, seem to give stem cells a new ability to accumulate in the marrow. The result is a sort of survival of the fittest, or fastest growing, stem cells in the marrow.

“Some mutations may alter the growth properties of the stem cell,” said Dr. Steensma. “Some may just make the stem cell better at surviving in certain less hospitable parts of the bone marrow where other stem cells can’t thrive.” The mutated stem cells outlast normal stem cells in the marrow, and their progeny — an increasing percentage of white blood cells — show up in the blood with mutations.

Perhaps the most extreme example of how this can play out was reported in 2014, when researchers described a 115-year-old woman. Nearly her entire supply of white blood cells was generated by mutated stem cells in her bone marrow.

Before being diagnosed with C.H.I.P., Mr. Gear had run eight marathons. Determined not to let the diagnosis overshadow his life, he hopes to complete a triathlon soon. **Kayana Szymczak for The New York Times**

At the first she had developed just two mutated stem cells. But over time their progeny came to dominate her bone marrow. She lived about as long as a human can, nonetheless, and died of a tumor.

But the big surprise came when researchers looked at the medical records of people with these white blood cell mutations. They had 54 percent increase in the odds of dying within the next decade, compared to people without CHIP And the cause: heart attacks and strokes.

Dr. Benjamin Ebert, chair of medical oncology a the Dana-Farber Cancer Institute, was the first to see the link. He turned for help to Dr. Sekar Kathiresan, a cardiologist and genetics researcher at the Massachusetts General Hospital and the Broad Institute, who had genetic data from four more large studies.

They confirmed that CHIP doubled the risk of a heart attack in typical patients — and increased the risk fourfold in those who had heart attacks early in life. But how might mutated white blood cells cause heart disease? One clue intrigued scientists.

Artery-obstructing plaque is filled with white blood cells, smoldering with inflammation and subject to rupture. Perhaps mutated white cells were causing atherosclerosis or accelerating its development.

In separate studies, Dr. Ebert and Dr. Walsh gave mice a bone-marrow transplant containing stem cells with a CHIP mutation, along with stem cells that were not mutated. Mutated blood cells began proliferating in the mice, and they developed rapidly growing plaques that were

burning with inflammation. “For decades people have worked on inflammation as a cause of atherosclerosis,” Dr. Ebert said. “But it was not clear what initiated the inflammation.”

Now there is a possible explanation — and, Dr. Ebert said, it raises the possibility that CHIP may be involved in other inflammatory diseases, like arthritis.

For now, doctors advise against testing for CHIP, since there is nothing specific to be done to reduce the increased risks of cancer or heart disease that it confers. But, he said, if people really want to know if they have CHIP, they can get a blood test that costs a few thousand dollars. (If there is no particular reason for the test, insurance may not pay.)

Dr. Steensma said that if he had CHIP, he would make sure he did his best to control all of his heart disease risks, like cholesterol and blood pressure, and that he had a healthy diet and exercised. Drugs may be developed to help stem the inflammation in arteries, he added.

As for the cancer risk, Dr. Ross Levine at Memorial Sloan Kettering Cancer Center just opened a C.H.I.P clinic in part to explore whether some patients with CHIP have a greater risk of blood cancers, and if so, what to do about it.

At the moment, CHIP is mostly found accidentally in patients who are genetically tested for other reasons — like Brian Gear. The diagnosis stunned him, but it also has brought into focus the important things in his life. “There are things I love in life and people I love,” he said. “You try to live that life.”

http://bbc.in/2nDqPvF

Handheld device sequences human genome

Scientists have used a device that fits in the palm of the hand to sequence the human genome.

By James Gallagher Health and science correspondent, BBC News

They say the feat, detailed in the journal Nature Biotechnology, opens up exciting possibilities for using genetics in routine medicine.

It is a far cry from the effort to sequence the first human genome which started in 1990.

The Human Genome Project took 13 years, laboratories around the world and hundreds of millions of dollars.

Since then there has been a revolution in cracking the code of life.

Prof Nicholas Loman, one of the researchers and from the University of Birmingham, UK, told the BBC:

"We've gone from a situation where you can only do genome sequencing for a huge amount of money in well equipped labs to one where we can have genome sequencing literally in your pocket just like a mobile phone.

Image copyright Oxford Nanopore

"That gives us a really exciting opportunity to start having genome sequencing as a routine tool, perhaps something people can do in their own home."

Sequencing technology has the potential to change the way we do medicine. Analysing the mutated DNA of cancers could be used to pick the best treatment. Or inspecting the genetic code of bacteria could spot antibiotic resistance early. Prof Loman used the handheld device to track the spread of Ebola during the outbreak in West Africa.

Image copyright Oxford Nanopore

Many companies are racing to sequence DNA faster and cheaper.

The handheld device used in the study was developed by the company Oxford Nanopore. The technology works by passing long strands of DNA through a tiny hole (the eponymous nanopore).

The building blocks of DNA are four bases known by their letters A, C, G and T. As each passes through the pore it creates a unique electrical signal that allows researchers to determine the DNA sequence.

The research group say the approach was around 99.5% accurate, but also allowed them to look at parts of human DNA that had been poorly studied.

The commonly used "short read" method of sequencing DNA involved breaking it up into short fragments, sequencing those and piecing it all back together like a jigsaw. But the challenge is that some fragments of the genetic code look incredibly similar, so it becomes a near impossible puzzle made of identical pieces.

Prof Matthew Loose, from the University of Nottingham, UK, said the nanopore tech analysed longer strands of DNA so "we can read parts of the genome not seen before". This includes the tips of chromosomes - called telomeres.

Prof Loose told the BBC: "Telomere length can be quite important in cancer and ageing, it's difficult in short reads because of the repeats, but we can see and start to map those things."

But while the cost of the sequencing is tumbling, there remains a big barrier - being able to rapidly read the genetic code is not the same as understanding what it says.

Dr Sobia Raza, the head of science at the PHG Foundation genomics think tank, told the BBC: "Our ability to sequence whole genomes quickly and cheaply continues to improve. "But short-term patient benefits also depend on how well and how fast we can analyse and make sense of the genomic data, and that is still quite a challenge."

http://bit.ly/2DXMK7V

Berserk leprosy bacteria are wildly mutating to become extremely drug resistant

New method to study the bacteria's genetics reveals grim situation.

Beth Mole - 1/30/2018, 5:00 AM

An ancient bacterium known for devastating and disfiguring its victims has turned to frantically ravaging its own genome to maintain its killer status, according to a new study.

Strains of *Mycobacterium leprae*—the main bacterium behind leprosy*—are hypermutating and becoming extremely drug resistant.

Researchers made the alarming discovery in a survey of 154 *M. leprae* genomes collected from 25 countries. The survey, published recently in *Nature Communications*, offers a rare genetic glimpse of the ancient, yet cryptic, bacterium, which still manages to cause 200,000 new cases worldwide each year.

Enlarge / "Brah, sloweth thy roll!" From a manuscript by early medical writer Roger of Salerno (c.1200). Getty | Hulton Archive

The international team of researchers, led by Stewart Cole of the Ecole Polytechnique Fédérale de Lausanne in Switzerland, noted that the hypermutating state "likely favors the emergence of drug resistance." But, there's a catch. Because *M. leprae* already has a concise genome, it also "could be detrimental and ultimately lethal," he and his team write. Basically, the revved-up mutation rate could haphazardly damage genes essential for survival.

Enlarge / Arran Reeve, suffering from leprosy, circa 1886. Pierre Arents

The genetic peek into what *M. leprae* strains are up to globally is a rare opportunity, despite the bacterium's long history with humans. Leprosy likely arose all the way back in the Iron Age (1200-600 BC) and has plagued us ever since.

In 1873, physician Gerhard Henrik Armauer Hansen was the first to link bacteria to the disease. He reported that when he dropped water on human cells scraped from a leprous nodule, "rod-shaped bodies" burst out. Those rod-shaped bodies were *M. leprae*, and the observation was the first time in history that a bacterium was linked to a chronic disease. Hansen's discovery provided the other name for leprosy, Hansen's disease.

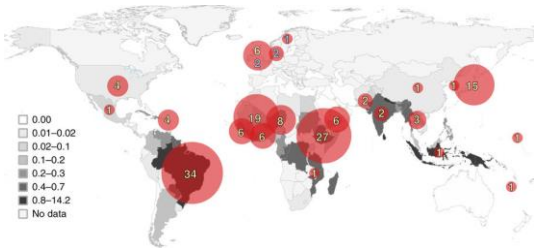
Perplexing plague

Still, more than a century later, relatively little is known about leprosy. The bacterium is extremely difficult to study because of its unique biology: it grows frustratingly slowly, lives within cells, and transmits cryptically. As such, scientists have yet to figure out how to grow *M. leprae* alone in labs, how exactly it causes disease, why it is killed by some antibiotics, and how it moves around. It remains a public health threat in South America, Africa, South and Southeast Asia, and Micronesia, where it infects about 200,000 each year.

When it does infect people, researchers know that it usually takes up residence in peripheral nerve cells. Some evidence suggests *M. leprae* reprograms the cells into a "stem-cell like" state to do its bidding. Infection leads to the inflammation, granulomas, and systemic bacterial spread within the patient. Eventually, patients also suffer sensory loss, disability, and deformations. Left untreated, the infection can be fatal.

So far, researchers still aren't sure how the bacterium pulls that off or how it arrives in its victims. Direct transmission between people is thought to be the most likely case, but some experts have suggested spread by insects and animals. *M. leprae* is known to infect mice, armadillos, red squirrels, and some non-human primates.

In the past, the only way researchers could get enough *M. leprae* for genetic studies was to infect mice and armadillos in lab—then wait a year. *M. leprae* takes 14 days to go through one generation. By contrast, *E. coli* can do this in 20 minutes. The slow growth, together with its intracellular residence, make extracting *M. leprae* from human tissue incredibly difficult.

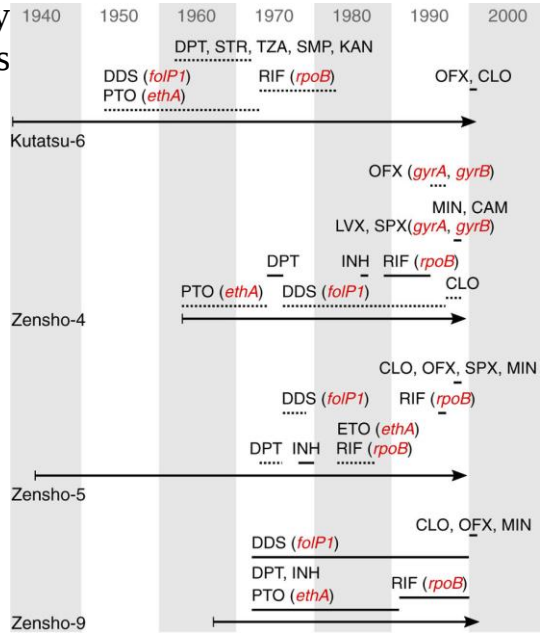


***Geographic distribution of the M. leprae samples used in this study. World map shows the number of registered cases of leprosy per 10,000 population (prevalence rates) in 2015 as reported by the World Health Organization.* A. Benjak et al.**

But, for the new study, Cole and colleagues got around the problem. They worked out and optimized a way to isolate *M. leprae* from punch biopsies of human tissue. The trick was to disrupt the human cells first, degrade the human DNA, then try to rupture the bacteria and collect as much bacterial DNA as possible.

Deformed DNA

The team analyzed *M. leprae* genomes from 147 human samples, six red squirrels, and one armadillo from across the globe (see diagram). All samples were from natural infections. The researchers looked at how the strains related to each other, how they appeared to be evolving, and mutations related to drug resistance.



***Timeline of the leprosy treatment and emergence of drug resistance in the XDR strains. Mutated genes conferring resistance to the corresponding drugs are shown in red. Arrows spa from the onset of disease to the end of treatment. Horizontal lines show the period when a drug was given. Dotted lines mean irregular treatment. CAM chloramphenicol, CLO clofazimine, DDS dapsone, DPT thiambutosine (diphenylthiourea), ETO ethionamide, INH isoniazid, KAN kanamycin, LVX levofloxacin, MIN minocycline, OFX ofloxacin, PTO protionamide, RIF rifampicin, SMP sulfamethoxypyridazine, SPX sparfloxacin, STR streptomycin, and TZA thiozamin.* A. Benjak et al.**

From their relatedness analysis, the researchers found that the strains belonging to the most ancient lineage in their collections were from East Asia. This lines up with previous work suggesting leprosy originated in Eurasia and spread along human migration routes into Africa and the Americas.

But the researchers noted eight strains that were hypermutated, which came from five different subtypes of the bacterium. These

hypermutants contained large numbers of mutations throughout their genome. They also all had broken versions of a gene that normally would allow the bacteria to proofread and fix DNA sequence errors, which explains the hypermutation.

The team also noted step-wise development of antibiotic resistance, particularly in some of the hypermutants. Since the 1980s, leprosy has been treated with a combination of two to three antibiotics, typically rifampicin, dapsone, and clofazimine, though it's unclear how clofazimine kills *M. leprae*. Prior to that, doctors sometimes prescribed single antibiotics.

For several strains that were resistant to three or more drugs (extensively drug resistant or XDR strains), the researchers looked back at the medical records of the patients from which doctors isolated the strains. The researchers noted that, in several cases, the XDR strains infected patients over decades, with resistance to individual drugs developing one by one as new drugs were tried.

"Drug resistance is alarming for leprosy control," the authors note. And their new study dug up completely new mutations that may make bacteria resistant to drugs in never-before-seen ways.

"Our discovery of these mutations... should encourage further experimentation in order to establish their true role and contribution to antimicrobial resistance," the authors conclude.

***A second leprosy bacterium, *Mycobacterium lepromatosis,* was discovered in 2008 and has been found infecting red squirrels and humans.**

Nature Communications, *2018*. *DOI:* 10.1038/s41467-017-02576-z (About DOIs).

http://bit.ly/2FEUiq2

Ohio State study of brain pacemaker shows promise in slowing decline of Alzheimer's

Patients with surgical implant retain functionality longer, improve quality of life

COLUMBUS, Ohio - While most treatments for Alzheimer's disease focus on improving memory, researchers at The Ohio State University Wexner Medical Center conducted a study aimed at slowing the decline of problem-solving and decision-making skills in these patients.

For the first time ever, thin electrical wires were surgically implanted into the frontal lobes of the brains of patients with Alzheimer's disease to determine if using a brain pacemaker could improve cognitive, behavioral, and functional abilities in patients with this form of dementia.

The deep brain stimulation (DBS) implant is similar to a cardiac pacemaker device, except that the pacemaker wires are implanted in the brain rather than the heart.

Findings of the study are published online in the Journal of Alzheimer's Disease.

"We have many memory aides, tools and pharmaceutical treatments to help Alzheimer's patients with memory, but we don't have anything to help with improving their judgments, making good decisions, or increasing their ability to selectively focus attention on the task at hand and avoid distractions. These skills are necessary in performing daily tasks such as making the bed, choosing what to eat and having meaningful socializing with friends and family," said Dr. Douglas Scharre, co-author of the study and director of the Division of Cognitive Neurology at Ohio State's Wexner Medical Center's Neurological Institute.

"The frontal lobes are responsible for our abilities to solve problems, organize and plan, and utilize good judgments. By stimulating this region of the brain, the Alzheimer's subjects cognitive and daily functional abilities as a whole declined more slowly than Alzheimer's patients in a matched comparison group not being treated with DBS," he said.

The pilot study found that DBS targeting frontal brain regions can reduce the overall performance decline typically seen in people with mild or early stage Alzheimer's, Scharre said.

Scharre is a neurologist who focuses on treating patients with Alzheimer's and other dementias. He collaborated with Dr. Ali Rezai, a

neurosurgeon who specializes in neuromodulation, to conduct this clinical trial.

"This same technology has been successfully used to treat more than 135,000 patients worldwide with Parkinson's disease. Our findings suggest that frontal network modulation to improve executive and behavioral deficits should be further studied in patients with Alzheimer's disease," said Rezai, the former director of Ohio State's Neurological Institute who is now leading the Rockefeller Neuroscience Institute at West Virginia University.

All three study participants showed improvement, including LaVonne Moore, 85, of Delaware, Ohio. When she entered the study in 2013, she was not doing any meal preparation. After two years of deep-brain stimulation, she could independently initiate preparations of a simple meal, assemble ingredients and cook the meal.

She was able to organize an outing, including arranging transportation and destination, planning for the weather and bringing the needed money. She also regained independence to select her clothing attire, researchers noted.

Her 89-year-old husband, Tom Moore, said her Alzheimer's disease has progressed, but more slowly than he expected. "LaVonne has had Alzheimer's disease longer than anybody I know, and that sounds negative, but it's really a positive thing because it shows that we're doing something right," Moore said. She didn't hesitate to volunteer for the study, he added.

He said she told him: "I will do anything to help others not go through what I'm going through."

Next, Ohio State researchers want to explore non-surgical methods to stimulate the frontal lobe, which would be a less invasive treatment option to slow down the symptoms of Alzheimer's disease.

Alzheimer's disease is the most common form of degenerative dementia, affecting more than 5 million Americans. By 2050, this number could rise as high as 16 million, according to the Alzheimer's Association. The disease - which has no cure and is not easily managed - becomes progressively disabling with loss of memory, cognition and worsening behavioral function, in addition to a gradual loss of independent functioning, Scharre said.

Funding for this study was provided by The Ohio State University Center for Neuromodulation, the Wright Center of Innovation in Biomedical Imaging, OTF-TECH-11-044 and philanthropic donations.

Other Ohio State researchers involved in this study include Emily Weichart, Dylan Nielson, Jun Zhang, Punit Agrawal, Per B. Sederberg and Michael V. Knopp. The authors have no conflicts of interest to report except Rezai, who declares that a patent (US 8,538,536) was issued.

http://bit.ly/2FDoUyD

It Looks Like the Flu, But Isn't: What Is Adenovirus?

The flu isn't the only virus that could leave you feeling feverish and generally miserable this winter — another virus, called adenovirus, can cause similar symptoms, although doctors don't routinely test for it.

By Rachael Rettner, Senior Writer | January 30, 2018 05:21pm ET

Adenoviruses are prolific viruses that can cause a variety of illnesses, including upper respiratory infections — such as colds — as well as pneumonia, gastrointestinal illness, conjunctivitis (pink eye) and even urinary tract infections, said Dr. Amesh Adalja, a senior scholar at the Johns Hopkins Center for Health Security. (There are 52 strains of adenovirus, and different strains cause different illnesses.)

When a person has a respiratory infection caused by an adenovirus, "it would be really hard to tell it apart from influenza" just by looking at the patient, Adalja said. Symptoms can include fever, sore throat, cough and runny nose, according to the Centers for Disease Control and Prevention (CDC). [The 9 Deadliest Viruses on Earth]

However, unlike the flu, adenovirus doesn't have a "striking seasonality," Adalja told Live Science. Although outbreaks of adenovirus infections are most common in the late winter, spring and early summer, they can occur year-round, the CDC said.

In some cases, adenoviruses can cause severe respiratory symptoms, including pneumonia, particularly in patients whose immune systems are compromised, Adalja said. In 2007, an outbreak of adenovirus sickened about 140 people in four states, killing 10 patients, according to the CDC. But that fatality rate doesn't compare to that of the flu, which can cause between 12,000 and 56,000 deaths per year, according to the CDC.

Outbreaks of adenovirus in the military led the U.S. Department of Defense to begin vaccinating military recruits against two strains of the virus in 1971, according to Medscape. When vaccine production stopped in 1996, cases of adenovirus in the military increased, as the disease spreads easily in close quarters.

This re-emergence of the disease led to the reintroduction of the vaccine among recruits in 2011, Medscape reported. It's estimated that the vaccine prevents about 15,000 cases of adenovirus infections in U.S. military recruits, according to the U.S. Army Medical Material Development Activity.

A recent study, published in the journal Emerging Infectious Diseases, looked at adenovirus respiratory infections in nonmilitary members and concluded that the vaccine should also be considered for susceptible groups outside the military, such as those living in long-term-care facilities or college dorms.

Adalja agreed that "because [adenovirus] does cause a considerable burden of illness, we want to explore" the ability to use the vaccine outside of the military context.

For example, the vaccine may benefit people at high risk of contracting the virus, such as patients with lung disease and others with compromised immune systems, but it may even benefit the general population, Adalja said.

However, future studies would be needed to examine which segments of the population would benefit most, and whether vaccination would be cost-effective, he said.

http://bit.ly/2DXZdq5

Chlorinated lipids predict lung injury and death in sepsis patients

SLU research explores collateral damage as the body fights infection

ST. LOUIS -- In a study published in the Journal of Clinical Investigation Insight, Saint Louis University scientists have found that elevated levels of chlorinated lipids are linked to sepsis, lung injury and death. The finding may offer a way to diagnosis and treat sepsis earlier, saving lives and avoiding serious side effects.

Sepsis is a dangerous immune response to an infection in which the whole body becomes inflamed. Most of the body's infections are local, sealed off and kept within the boundaries of an organ or part of the body, like the lungs or sinuses. In some cases, however, an untreated infection spreads and causes overwhelming systemic inflammation throughout the body.

Adults and children of every age can develop sepsis. It carries a high mortality rate as well as high risk of complications from massive drops in blood pressure and organ failure. The key challenge in treating sepsis is to diagnosis it and begin antibiotics quickly; as organs begin to shut down, treating sepsis becomes a matter of beating the clock.

In 2002, David Ford, Ph.D., professor of biochemistry and molecular biology at Saint Louis University, made a discovery of a type of lipid that had not previously been identified in humans.

"My lab discovered chlorinated lipids," Ford said. "They are made in the body under conditions where there is inflammation."

Ford's team, together with Jane McHowat, Ph.D., professor of pathology at SLU, have continued their study of chlorinated lipids and inflammation to better understand the link between the two.

In the study described in the Journal of Clinical Investigation Insight paper, researchers examined blood samples taken soon after admission to the hospital from patients who were eventually diagnosed with sepsis.

They found that chlorinated lipids not only were present in the blood but that they also predicted whether a patient would go on to suffer acute respiratory distress symptom (ARDS) and predicted whether patients would die within 30 days from a lung injury.

"Chlorinated lipids appear to serve as a very early warning sign that a patient is on track for a severe lung injury that could be fatal," Ford said.

Investigators had learned that elevated levels of chlorinated lipids could serve as a biomarker, a sign post that appeared when the body became inflamed. But, they also wondered if chlorinated lipids were the culprit causing the inflammation.

"There is another layer to this research: Are chlorinated lipids a causative agent?

"We examined this at a basic science level," Ford said. "Our research suggests that they do cause injury in the microcirculation of the lung. The data in this paper suggests chlorinated lipids have a causative role."

Researchers found that chlorinated lipids are generated by enzymes in neutrophils, a type of white blood cell. When the body is fighting an infection, neutrophils kill microbes. In the process of fighting off the intruder, chlorinated lipids are generated as a by-product. They are the collateral damage that occurs to a patient's own tissue by its immune system.

In a second paper, published in the Journal of Lipid Research, Ford and his collaborators explored the mechanisms of how this process works.

Celine Hartman, a SLU graduate student, made an analog (similar form) of a chlorinated lipid. That allowed the research team to track where the lipid travels within the endothelial cells in the linings of blood and lymph vessels.

"What Celine found was that the analog goes very specifically to a granule within an endothelial cell, called a Weibel-Palade body," Ford said. "That is significant because Weibel-Palade bodies contain proteins that are responsible for inflammation at the site where blood interfaces with the small blood vessels of an organ, the microcirculation, which is associated with organ injury and edema."

The findings in these papers set the stage for two strategies against sepsis.

First, if researchers can develop a rapid test for chlorinated fatty acids in the clinic, they could begin treatment sooner and buy time for patients.

"Right now, the only treatment for sepsis is antibiotics," Ford said. "The faster a patient is put on them, the greater survival and fewer side effects. There have been studies showing that the faster antibiotics are administered after hospital admission, the better the patient's outcome."

Second, if chlorinated lipids are indeed causative as Ford's data suggests, then molecules could be developed to block their action, leading to a potential new therapy to stop sepsis-caused organ injury and death.

Researchers on the Journal of Clinical Investigation Insight paper include Nuala J. Meyer, John P. Reilly, Rui Feng, Jason D. Christie, Stanley L. Hazen, Carolyn J. Albert, Jacob D. Franke, Celine L. Hartman, Jane McHowat, and David A. Ford.

Researchers on the Journal of Lipid Research paper include Celine L. Hartman, Mark A. Duerr, Carolyn J. Albert, William L. Neumann, Jane McHowat, and David A. Ford.

The research was funded by the National Institutes of Health (grants R01GM115553, R01HL122474, P01HL076491, and R01GM115552) and the American Heart Association Grant-in-Aid 15GRNT25750022.

http://bit.ly/2nBV3QC

Body movements just need a 'puff' of dopamine to get started

A new study in mice suggests that a burst of dopamine levels at the beginning of a movement only, as opposed to all the time, is what gets us going; this may have important implications for treating Parkinson's disease

NEW YORK and Lisbon, Portugal -- From morning til night, we never stop executing movements at the right time and speed. But patients suffering from Parkinson's disease lose this natural control over their voluntary movements.

Parkinson's is caused by the death of the neurons that make a neurotransmitter, dopamine, in a region of the brain called the substantia nigra. Now a new study, published by scientists from the Champalimaud Centre for the Unknown (Portugal) and Columbia

University's Mortimer B. Zuckerman Mind Brain Behavior Institute in the journal Nature, represents an important step towards better understanding the precise normal function of these neurons.

Experts have long worked to understand why the absence of these so-called dopaminergic neurons (and therefore, the lack of dopamine) leads to the motor dysfunctions that are the hallmarks Parkinson's, such as stiffness, slow movements and tremors. The more widely accepted explanation has been that, in order to move normally, our brain constantly needs a certain level of dopamine - something that Parkinson's patients progressively lose.

However, as psychiatrist and neuroscientist Joaquim Alves da Silva, first author of the new study, explains, people with Parkinson's disease actually "do not have a global motor problem." As incredible as it may seem, they can even ride a bicycle -- a rather complex motor task -- if pushed at the right time.

The motor problems that Parkinson's patients experience are more specific, and this was the observation that motivated the new study. "The patients' problem is in the difficulty to initiate movement and in the slowness of movement," adds Alves da Silva.

In fact, as these authors now showed in mice not afflicted by Parkinson's disease, for a movement to unfold correctly it only takes a "puff" of dopamine -- or more precisely, a peak of dopaminergic cell activity -- right before the movements starts. In other words, dopamine (or, in this case, the activity of the cells that produce it) is just a "trigger" for voluntary movements.

"Our most important result is that we showed, for the first time, that the change in neural activity is necessary to promote movement," says Alves da Silva. "And also for the first time, we showed that the dopamine peak that precedes movement initiation does not only regulate initiation, but also regulates movement vigor."

Previous results already pointed in this direction. "Our laboratory and others had shown that, in normal conditions, there is a transient increase in the activity of dopamine-producing neurons, and that this increase seems to precede movement initiation," says Alves da Silva. "But we still had to determine whether that neural activity was mostly important to initiate movement or if it was also important during movement execution," he adds.

The scientists performed their experiments by using optogenetics, a technique that allowed them to turn neurons on and off very quickly with laser light.

"In this way, we were certain that we were only recording the activity of the animals' dopaminergic cells" in the substantia nigra, explains Alves da Silva.

The mice were placed in an "arena" where they could roam freely. By using motion sensors, the authors then measured whether the animals were moving or not at any given moment. They recorded identified dopamine neurons and were able to observe a transient peak of activity in many of these cells before the movements.

In the next phase, the scientists activated or inhibited the dopamine cells with a laser. And they could then see that when the mice were not moving, "activating the neurons for half a second was enough to promote movement -- and with more vigor -- than without these neurons' activity," says Alves da Silva.

However, if the neurons were activated when the mice were already moving, the animals "just went on doing whatever they were doing" in terms of movement and movement vigor, as measured by acceleration. Moreover, inhibiting the neurons' activity during an ongoing movement did not have any effect on its normal execution.

"These results show that the activity of dopamine neurons can act as a gate to permit or not the initiation of movements," says Rui Costa, DVM, PhD, associate director of Columbia's Zuckerman Institute who led the study. "They explain why dopamine is so important in motivation, and also why lack of dopamine in Parkinson's disease leads to the symptoms that it does."

The authors say the new study could pave the way for the development of treatments for Parkinson's disease with fewer side-effects.

Currently, Parkinson's is usually treated with the drug levodopa, which works by boosting dopamine in the body and alleviating symptoms. "But levodopa elevates dopamine all the time, not just when we want to move" says Costa, who is also professor of neuroscience and neurology at Columbia University Irving Medical Center. And indeed, the long-term use of levodopa often causes other motor disorders -- mainly, erratic and involuntary body movements known as dyskinesia. "Our study suggests that strategies that would boost dopamine when there is a desire to move would work better," adds Costa.

When patients do not respond to or cannot take the drug, there is an alternative treatment, called "deep brain stimulation" (DBS). For this, patients are implanted with a high-frequency pacemaker that blocks the abnormal electric signals generated in the brain areas that control movement and make it difficult for the patients to initiate movement.

It is known that DBS substantially improves parkinsonian symptoms -- but it can also have adverse effects. This study suggests that it may be better to stimulate the brain only when patients want to initiate movement, promoting not only initiation but also controlling the vigor of the movement. If this possibility were to be confirmed, it could render DBS more physiological, more natural, so decreasing unwanted side-effects.

This paper is titled: "Dopamine neuron activity before action initiation gates and invigorates future movements." Additional contributors include Fatuel Tecuapetla and Vitor Paixão.

This research was supported by the Gulbenkian Foundation, Funcação para a Ciencia e Tecnologica, ERA-NET, European Research Council (COG 617142) and the Howard Hughes Medical Institute (IEC 55007415).

The authors report no financial or other conflicts of interest.

http://bit.ly/2EFI1J1

Cancer 'vaccine' eliminates tumors in mice, Stanford researchers find

Injecting minute amounts of two immune-stimulating agents directly into solid tumors in mice can eliminate all traces of cancer in the animals, including distant, untreated metastases, according to a study by researchers at the Stanford University School of Medicine.

The approach works for many different types of cancers, including those that arise spontaneously, the study found.

The researchers believe the local application of very small amounts of the agents could serve as a rapid and relatively inexpensive cancer therapy that is unlikely to cause the adverse side effects often seen with bodywide immune stimulation.

"When we use these two agents together, we see the elimination of tumors all over the body," said Ronald Levy, MD, professor of oncology. "This approach bypasses the need to identify tumor-specific immune targets and doesn't require wholesale activation of the immune system or customization of a patient's immune cells."

One agent is currently already approved for use in humans; the other has been tested for human use in several unrelated clinical trials. A clinical trial was launched in January to test the effect of the treatment in patients with lymphoma.

Levy, who holds the Robert K. and Helen K. Summy Professorship in the School of Medicine, is the senior author of the study, which will be published Jan. 31 in Science Translational Medicine. Instructor of medicine Idit Sagiv-Barfi, PhD, is the lead author.

'Amazing, bodywide effects'

Levy is a pioneer in the field of cancer immunotherapy, in which researchers try to harness the immune system to combat cancer. Research in his laboratory led to the development of rituximab, one of the first monoclonal antibodies approved for use as an anticancer treatment in humans.

Some immunotherapy approaches rely on stimulating the immune system throughout the body. Others target naturally occurring checkpoints that limit the anti-cancer activity of immune cells. Still others, like the CAR T-cell therapy recently approved to treat some types of leukemia and lymphomas, require a patient's immune cells to be removed from the body and genetically engineered to attack the tumor cells. Many of these approaches have been successful, but they

each have downsides -- from difficult-to-handle side effects to high-cost and lengthy preparation or treatment times.

"All of these immunotherapy advances are changing medical practice," Levy said. "Our approach uses a one-time application of very small amounts of two agents to stimulate the immune cells only within the tumor itself. In the mice, we saw amazing, bodywide effects, including the elimination of tumors all over the animal."

Cancers often exist in a strange kind of limbo with regard to the immune system. Immune cells like T cells recognize the abnormal proteins often present on cancer cells and infiltrate to attack the tumor. However, as the tumor grows, it often devises ways to suppress the activity of the T cells.

Levy's method works to reactivate the cancer-specific T cells by injecting microgram amounts of two agents directly into the tumor site. (A microgram is one-millionth of a gram). One, a short stretch of DNA called a CpG oligonucleotide, works with other nearby immune cells to amplify the expression of an activating receptor called OX40 on the surface of the T cells. The other, an antibody that binds to OX40, activates the T cells to lead the charge against the cancer cells. Because the two agents are injected directly into the tumor, only T cells that have infiltrated it are activated. In effect, these T cells are "prescreened" by the body to recognize only cancer-specific proteins.

Cancer-destroying rangers

Some of these tumor-specific, activated T cells then leave the original tumor to find and destroy other identical tumors throughout the body.

The approach worked startlingly well in laboratory mice with transplanted mouse lymphoma tumors in two sites on their bodies. Injecting one tumor site with the two agents caused the regression not just of the treated tumor, but also of the second, untreated tumor. In this way, 87 of 90 mice were cured of the cancer. Although the cancer recurred in three of the mice, the tumors again regressed after a second treatment. The researchers saw similar results in mice bearing breast, colon and melanoma tumors.

Mice genetically engineered to spontaneously develop breast cancers in all 10 of their mammary pads also responded to the treatment. Treating the first tumor that arose often prevented the occurrence of future tumors and significantly increased the animals' life span, the researchers found.

Finally, Sagiv-Barfi explored the specificity of the T cells by transplanting two types of tumors into the mice. She transplanted the same lymphoma cancer cells in two locations, and she transplanted a colon cancer cell line in a third location. Treatment of one of the lymphoma sites caused the regression of both lymphoma tumors but did not affect the growth of the colon cancer cells.

"This is a very targeted approach," Levy said. "Only the tumor that shares the protein targets displayed by the treated site is affected. We're attacking specific targets without having to identify exactly what proteins the T cells are recognizing."

The current clinical trial is expected to recruit about 15 patients with low-grade lymphoma. If successful, Levy believes the treatment could be useful for many tumor types. He envisions a future in which clinicians inject the two agents into solid tumors in humans prior to surgical removal of the cancer as a way to prevent recurrence due to unidentified metastases or lingering cancer cells, or even to head off the development of future tumors that arise due to genetic mutations like BRCA1 and 2.

"I don't think there's a limit to the type of tumor we could potentially treat, as long as it has been infiltrated by the immune system," Levy said.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The study's other Stanford co-authors are senior research assistant and lab manager Debra Czerwinski; professor of medicine Shoshana Levy, PhD; postdoctoral scholar Israt Alam, PhD; graduate student Aaron Mayer; and professor of radiology Sanjiv Gambhir, MD, PhD.

Gambhir is the founder and equity holder in CellSight Inc., which develops and translates multimodality strategies to image cell trafficking and transplantation.

The research was supported by the National Institutes of Health (grant CA188005), the Leukemia and Lymphoma Society, the Boaz and Varda Dotan Foundation and the Phil N. Allen Foundation.
Stanford's Department of Medicine also supported the work.

http://bit.ly/2BW86R9

Ancient Ale: Oldest Beer in Greece Dates to Bronze Age

The ancient Greeks may have liberally indulged in wine, but that's not the only alcoholic beverage they imbibed, according to a new study that describes the discovery of two potential Bronze Age breweries.

By Laura Geggel, Senior Writer

The "stout" discoveries mark what may be the oldest beer-making facilities in Greece and upend the notion that the region's ancient go-to drink was only wine, the researchers said.

"It is an unexpected find for Greece, because until now all evidence pointed to wine," study researcher Tania Valamoti, an associate professor of archaeology at Aristotle University of Thessaloniki, in Greece, told Live Science.

A handful of sprouted cereal grains discovered at a Bronze Age site in Argissa, Greece. The scale bar is 0.04 inches (1 millimeter). **Copyright Springer-Verlag GmbH Germany, part of Springer Nature 2017**

The finding hints that prehistoric Greeks were "using alcoholic drinks for feasts all year-round, instead of just on a seasonal basis," when grapes were ripe, Brian Hayden, a professor of archaeology at Simon Fraser University, in British Columbia, Canada, who wasn't involved with the study, told Live Science.

Beer time

Archaeologists found the remains of several buildings that may have been used for beer making: some at Archondiko in northern Greece, and another at Agrissa, a site south of Archondiko on the eastern side of Greece. Both sites had been wrecked by fire, which turned them into time capsules of sorts, Valamoti said. After the fire, the prehistoric people appear to have moved out, leaving countless burned artifacts behind, including the remains of sprouted cereal grains.

At Archondiko, archaeologists found about 100 individual sprouted cereal grains dating to the early Bronze Age, from about 2100 to 2000 B.C. At Agrissa, they found about 3,500 sprouted cereal grains dating to the middle Bronze Age, from about 2100 to 1700 B.C.

The discovery of sprouted cereal grains is significant: To make beer, a brewer sprouts cereal grains (a process known as malting), which changes the grain's starch into sugars. This sprouting process is then interrupted by roasting the grain. Next, the grains are coarsely ground and mixed with lukewarm water to make wort, which helps convert the remaining starches into sugars. Finally, during alcoholic fermentation, "the sugars in the malt are used by yeast, which is present in the air or introduced with grapes or from other sources," Valamoti wrote in the study.

"I'm 95 percent sure that they were making some form of beer," Valamoti said. "Not the beer we know today, but some form of beer."

To learn more about the beer-making ways of the ancient Greeks, researchers ground malted barley (Hordeum) with the ERC PlantCult Project. **Copyright Springer-Verlag GmbH Germany, part of Springer Nature 2017**

In addition, archaeologists found a two-chambered structure at Archondiko that "seems to have been carefully constructed to maintain low temperatures in the rear chamber, possibly even below 100 degrees Celsius [212 degrees Fahrenheit]," Valamoti wrote in the study. Given that a temperature of 158 degrees F (70 degrees C) is ideal for preparing the mash and wort, it's possible that ancient people used this structure during the beer-making process, she said.

There were even special cups — 30 at Archondiko and 45 in the Agrisso house — near the sprouted grains, suggesting they may have been used

to serve beer. However, the Archondiko cups were difficult to drink from, so it's possible that thirsty people there sipped beer through straws, Valamoti said.

She noted that although the discovery may be the oldest-known evidence of beer in Greece, it's not the oldest in the world, and beer isn't even the oldest alcohol on record. Prehistoric people appear to have discovered wine first, as there is evidence of wine residue on pottery from about 6000 B.C. in Georgia, Live Science previously reported, as well as from the sixth millennium B.C. in Iran and the fifth millennium B.C. in Armenia and Greece, Valamoti said.

As for beer, Egyptian records show that people drank it as early as the mid-fourth millennium B.C., and people in the Near East slurped down the amber liquid as early as 3200 B.C., according to the study.

"Textual evidence from historic periods in Greece clearly shows that beer was considered an alcoholic drink of foreign people, and barley wine a drink consumed by the Egyptians, Thracians, Phrygians and Armenians, in most cases drunk with the aid of a straw," Valamoti wrote in the study.

The finding, which was funded in part by the European Research Council project "PlantCult," was published online Dec. 30, 2017, in the journal Vegetation History and Archaeobotany.

http://bit.ly/2EdmVUP

Alzheimer's blood test developed

Australian and Japanese collaboration concludes three-decade hunt for effective diagnostic method.

Andrew Masterson reports.

A combined Australian-Japanese research project has produced a potentially revolutionary blood test for the detection of Alzheimer's disease – raising hopes of earlier and more precise interventions in the treatment of the devastating condition.

In a paper in the journal *Nature*, scientists from bodies including the Florey Institute in Melbourne, Australia, and the Shimadzu Corporation in Kyoto, Japan, outline a blood test that uses mass spectrometry to detect the presence of the key biomarker for Alzheimer's – a protein called amyloid-beta – with an accuracy of greater than 90%.

The test has so far been trialled on two cohorts – comprising 252 Australian and 121 Japanese volunteers – and has successfully detected low levels of amyloid-beta fragments in the blood.

A simple blood test for Alzheimer's has been shown to work with 90% accuracy.
TEK IMAGE/Getty Images

Although at an early stage, the success of the trial raises the possibility that Alzheimer's could be detected much earlier than is currently possible – well before symptoms become apparent. It may also allow earlier and better distinctions between different types of dementia, and permit ongoing monitoring of the effectiveness of treatments.

Current diagnostics for the disease rely either on positron-emission tomography – known as PET scans – to detect amyloid-beta deposits in the brain or lumbar punctures to measure amyloid-beta concentrations in the cerebrospinal fluid. At a press conference to announce the discovery, Colin Masters from the Florey Institute said the new approach "is as good as, if not better than, the existing tests."

For Masters and his colleagues at Florey, the success of the current work marks an important step in a very long research journey. "We've been working on a blood test since 1989," he said.

Mass spectrometry is an analytical method that is widely used in medicine and industry. It involves ionising chemicals in a sample and then classifying them according to their mass-to-charge ration, enabling precise identification.

Calibrating the specific approach for the Alzheimer's blood test was the responsibility of the Shimadzu Corporation's Koichi Tanaka, who was awarded the Nobel Prize for Chemistry in 2002 for his work on using the technique to analyse biological macro molecules.

The blood tests carried out on the Japanese and Australian volunteers were all conducted in Tanaka's laboratory, and Masters says the next step in the development process is to roll the test out to other researchers. "We need to scale it up next," he said. "The Shimadzu Corporation say they can do that within the next six to 12 months, but that remains to be seen."

For Masters, however, even getting to this stage brings considerable personal satisfaction. "We can finally say that we have a high-performing blood test," he said, "which from my point of view is a major achievement."

http://bit.ly/2E3KDUf

Quantum chemistry solves mystery why there are these 20 amino acids in the genetic code

Publication in PNAS provides an answer to an old and fundamental question of biochemistry

Using quantum chemical methods, a team of researchers led by Dr. Matthias Granold and Professor Bernd Moosmann of the Institute of Pathobiochemistry at Johannes Gutenberg University Mainz solved one of the oldest puzzles of biochemistry. They uncovered why there are 20 amino acids that form the basis of all life today, even though the first 13 amino acids generated over time would have been sufficient to form a comprehensive repertoire of the required functional proteins. The decisive factor is the greater chemical reactivity of the newer amino acids rather than their spatial structure. In their publication in the leading journal PNAS, the Mainz-based researchers also postulate that it was the increase in oxygen in the biosphere that triggered the addition of supplementary amino acids to the protein tool box.

All life on Earth is based on 20 amino acids, which are governed by the DNA to form proteins. In the inherited DNA, it is always three sequential DNA bases, or codons, which combine to "encode" one single of these 20 amino acids. The resultant grid of codons is what is known as the genetic code. "Researchers have been puzzled for decades why evolution has selected these 20 amino acids for genetic encoding," said Professor Bernd Moosmann. "The presence of the last and newest seven amino acids is particularly hard to explain, because suitable and functional proteins can be assembled using just the first and oldest 10 to 13 amino acids."

In a new approach, the researchers compared the quantum chemistry of all amino acids used by life on Earth with the quantum chemistry of amino acids from space, brought in on meteorites, as well as with that of modern reference biomolecules. They found that the newer amino acids had become systematically softer, i.e., more readily reactive or prone to undergo chemical changes. "The transition from the dead chemistry out there in space to our own biochemistry here today was marked by an increase in softness and thus an enhanced reactivity of the building blocks," explained Moosmann. The researchers were able to verify the results of their theoretical calculations in biochemical experiments. Functional aspects also must have played a significant role with regard to the more recent amino acids as these newcomers hardly exhibit particular advantages when it comes to building protein structures.

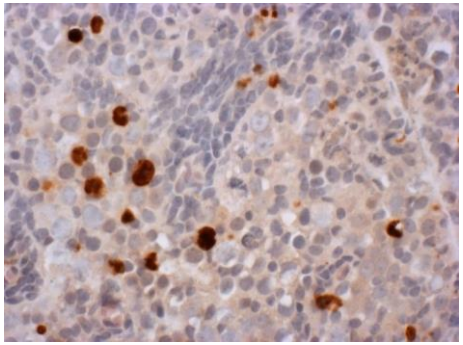
However, the problem remained of why the soft amino acids were added to the tool box in the first place. What exactly were these readily reactive amino acids supposed to react with? On the basis of their results, the researchers conclude that at least some of the new amino acids, especially methionine, tryptophan, and selenocysteine, were added as a consequence of the increase in the levels of oxygen in the biosphere. This oxygen promoted the formation of toxic free radicals, which exposes modern organisms and cells to massive oxidative stress. The new amino acids underwent chemical reactions with the free radicals and thus scavenged them in an efficient manner. The oxidized new amino acids, in turn, were easily repairable after oxidation, but they protected other and more valuable biological structures, which are not repairable, from oxygen-induced damage. Hence, the new amino acids provided the remote ancestors of all living cells with a very real survival advantage that allowed them to be successful in the more oxidizing,

"brave" new world on Earth. "With this in view, we could characterize oxygen as the author adding the very final touch to the genetic code," stated Moosmann.

http://bit.ly/2E64kXr

Ibuprofen in the first three months of pregnancy may harm future fertility of baby girls

Pregnant women who take the pain killer ibuprofen in the first 24 weeks of their pregnancy may be reducing the store of eggs in the ovaries of their daughters.



This is ovarian tissue that has been exposed to ibuprofen for seven days. The big brown cells are dying germ cells and the smaller brown cells are also dying
Severine Mazaud-GuiJot, INSERM

Researchers have found the first evidence in human ovarian tissue that exposure to ibuprofen during the crucial first three months of foetal development results in a "dramatic loss" of the germ cells that go into making the follicles from which female eggs develop. The germ cells either died or failed to grow and multiply at the usual rate.

The authors of the study, which is published today (Friday) in Human Reproduction[1], one of the world's leading reproductive medicine journals, say that their findings raise concerns about the long-term effects of ibuprofen on the future fertility of women exposed to the pain killer when in their mothers' wombs.

"Baby girls are born with a finite number of follicles in their ovaries and this defines their future reproductive capacity as adults," explained Dr Séverine Mazaud-Guittot, a researcher at INSERM in Rennes, France, who led the study. "A poorly stocked initial reserve will result in a shortened reproductive life span, early menopause or infertility - all events that occur decades later in life.

"The development of the follicles in the foetus has not been completed by the end of the first trimester, so if the ibuprofen treatment is short then we can expect the ovarian reserve to recover to some extent. However, we found that two to seven days of exposure to ibuprofen dramatically reduced the germ cell stockpile in human foetal ovaries during the first trimester of pregnancy and the ovaries did not recover fully from this damage. This suggests that prolonged exposure to ibuprofen during foetal life may lead to long-term effects on women's fertility and raises concern about ibuprofen consumption by women during the first 24 weeks of pregnancy. These findings deserve to be considered in light of the present recommendations about ibuprofen consumption during pregnancy."

Around 30% of women are estimated to use ibuprofen in the first three months of pregnancy. Current recommendations are that the pain killer should not be taken after that time as it is known to increase the risks of foetal malformations; however, there is no firm guidance on whether or not it is safe to take in the early weeks.

Dr Mazaud-Guittot and her colleagues obtained human foetuses between 7-12 weeks of development from legally induced terminations of pregnancy and with the mothers' consent. Then they cultured the ovarian tissue in the laboratory; part of the tissue from each foetus was exposed to ibuprofen and a second part (the control) was not. Samples from 185 foetuses were analysed. In addition, the researchers measured the quantity of ibuprofen in the blood in the umbilical cord in order to analyse how much the foetus would have been exposed to.

They found that ibuprofen crosses the placental barrier. "The concentration that we found in the umbilical cords of foetuses from mothers who ingested 800 mg (four pills of 200 mg) two to four hours before surgery is similar to the concentration that can be found in adult's blood for the same treatment. In simple terms, the foetus is exposed to the same concentration as the mother. Therefore, we tested concentrations that were in the range of those that can be found in adult's blood in the ovarian samples in the lab," said Dr Mazaud-Guittot.

In contrast to the foetal tissue that was not exposed to ibuprofen, the tissue that was exposed to concentrations of 10 µM (micromolar) of ibuprofen for a week had approximately half the number of ovarian germ cells[2].

"We found there were fewer cells growing and dividing, more cells dying and a dramatic loss of germ cell numbers, regardless of the gestational age of the foetus," she said. "There were significant effects after seven days of exposure to 10 µM of ibuprofen, and we saw cell death as early as after two days of treatment. Five days after withdrawing ibuprofen, these harmful effects of ibuprofen were not fully reversed.

"This is the first study to look at the effects of ibuprofen on the ovarian tissue of baby girls, and the first to show that ibuprofen can cross the placental barrier during the first trimester of pregnancy, exposing the foetus to the drug. The implications of our findings are that, just as with any drug, ibuprofen use should be restricted to the shortest duration and at the lowest dose necessary to achieve pain or fever relief, especially during pregnancy. The wisest advice would be to follow currently accepted recommendations: paracetamol should be preferred to any anti-inflammatory drug up to 24 gestational weeks, and the latter should not be used thereafter. However, practitioners, midwifes and obstetricians are best placed to give expert advice: every mother and every pregnancy is unique."

The researchers say that further work needs to be carried out into the mechanisms of action of ibuprofen on human ovaries, and on alternative painkillers. In addition, the study does have limitations in that the foetal tissue was studied in the laboratory rather than in a living body. "A further limitation is the duration: in this study we could not address the long-term effect of this drug on the ovary. That's why further research at the population level is required to determine whether ibuprofen exposure during pregnancy will affect the fertility or the reproductive functioning of the daughters," concluded Dr Mazaud-Guittot.

Professor Hans Evers, editor-in-chief of *Human Reproduction*, who was not involved in the research, commented: "The authors are to be commended for investigating the effect of ibuprofen on germ cells and follicles in human ovarian tissue, and these are important findings that require further investigation. However, at this stage it is not possible to say whether the reduced numbers of follicles in tissue samples from baby girls might translate into reduced fertility 30 years later. At present this is speculation and requires long-term follow-up studies of daughters of women who took ibuprofen while in their first three months of pregnancy."

[1] "Ibuprofen is deleterious for the development of first trimester human fetal ovary ex vivo," by S. Leverrier-Penna et al. Human Reproduction *journal. doi:10.1093/humrep/dex383.*

[2] Micromolar is a unit of concentration corresponding to one millionth molecular weight per litre.

http://bit.ly/2GPlR8b

Experimental therapy could boost stroke recovery

Spinal injection and rehabilitation efforts shown to increase connections between the brain and spinal cord

Edmonton, AB - An experimental therapy being tested by University of Alberta scientists that targets the spinal cord may one day be key to spurring on enhanced recovery for stroke victims.

By injecting a drug called chondroitinase ABC (ChABC) into the spinal cord of rats 28 days after they suffered a stroke, researchers found they were able to enhance recovery by inducing amplified rewiring of circuits connecting the brain to the spinal cord. When they also combined the spinal therapy with rehabilitative training, recovery amplified further.

"This gives us real evidence that there are things we can do for people with a permanent physical disability--such as paralysis or having difficulty controlling movements--after a stroke," said Ian Winship, an associate professor of psychiatry at the U of A. "There is hope that eventually we might have a therapy that can help somebody with a deficit that is really affecting their quality of life, even years after the stroke."

"These are deficits that previously have been thought to be untreatable and people just learned to live with them," added Anna Wiersma, lead author of the study and a recent PhD graduate at the U of A's Neuroscience and Mental Health Institute. "The fact that these might not actually be untreatable and that we have an opportunity to help patients who are in the chronic stages of stroke is really exciting."

Stroke is the most common cause of adult disability in Canada. Currently more than 400,000 Canadians are living with the effects of stroke. The typical path of recovery involves intensive rehabilitation therapy. In the first few weeks following a stroke, patients experience gains as the brain rewires itself, but they will eventually plateau and rarely regain full capacity--even with ongoing rehabilitation.

In the study, the scientists explored the impact of injecting ChABC into the spinal cord. The drug acts on components that surround the cells of the nervous system and prevent growth of new connections. It also removed the inhibition of growth, allowing for new connections between the unaffected motor areas in the brain and the spinal networks that control movement.

The researchers found that injecting ChABC a month after suffering a stroke and without rehabilitative training led to moderate improvements of sensorimotor deficits. When combining both spinal therapy and rehabilitative therapy, they found that their subjects recovered better and were able to perform some sensorimotor tasks at pre-stroke levels.

"The idea here is there is still something we can potentially do for people that would give them a second wave of recovery," said Winship. "That's pretty exciting because (rehabilitation efforts) have a ceiling effect. You can only achieve so much recovery. This drug could remove that ceiling."

The researchers acknowledge there are barriers to overcome before the work could be tested and applied in humans. The major drawback is that injected ChABC only extends a small distance and acts for a finite period of time--both of which would be challenging in a human spinal cord, which is much larger than that of a rat. Time of recovery in a human is also much longer, meaning multiple injections would likely be needed, increasing the risk of infection or injury.

Winship and Wiersma speculate one solution may be to introduce the drug through another way than through injection. They believe using a viral vector could make cells genetically express ChABC instead of having it injected directly. The solution would allow for longer-lasting expression and greater spread within the spinal cord.

"The potential is there but at this point we need a lot more evidence that this is going to be something that is truly effective," said Winship. "This approach is still a long way from the clinic, but this gives us real evidence that there are things we can do for people with permanent disability after a stroke."

The research was funded by the Heart and Stroke Foundation and Alberta Innovates. The study was published in the Journal of Neuroscience.

http://bit.ly/2GRfVeO

Practical hair regeneration technology

Researchers at YNU develop a method for large-scale preparation of hair producing tissues

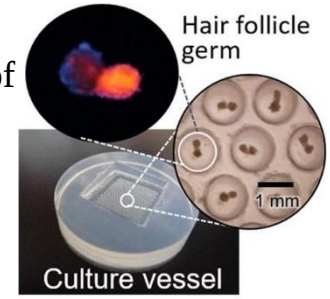
マウス毛包原基の大量培養法の開発と、移植による毛の再生に成功

毛髪再生医療の実用化へ大きく前進

Researchers have developed a method for the mass preparation of cellular aggregates, also known as 'hair follicle germs (HFGs)', that may lead to a new treatment for hair loss.

Although hair loss is not life-threatening, it troubles a substantial number of individuals all over the world, particularly in aging societies. Hair regenerative medicine has emerged as a new therapy to combat the problem. The therapy involves regenerating hair follicles, the tiny organs that grow and sustain hair. One of the more challenging obstacles to hair regenerative medicine has been the preparation of hair follicle germs, the reproductive source of hair follicles, on a large scale. The paper, published in the journal Biomaterials, reports the successful preparation of up to 5000 HFGs simultaneously, and reports new hair growth from the HFGs after transplantation into mice.

"The key for the mass production of HFGs was a choice of substrate materials for culture vessel," says the corresponding author Junji Fukuda, Professor, Yokohama National University. "We used oxygen-permeable dimethylpolysiloxane (PDMS) at the bottom of culture vessel, and it worked very well."



The research group further evaluated the feasibility of this method by transferring the prepared HFGs from a fabricated approximately 300-microwell array, called "HFG chip", to generate hair follicles and hairs on the mouse body. The group confirmed black hair generation at both the back and scalp transplantation sites. The regenerated hair exhibited the typical hair cycle of murine hair.

Culture vessel for the mass preparation of hair follicle germs (above). Generated hairs on the back of a mouse (below). **Yokohama National University**

"This simple method is very robust and promising. We hope that this technique will improve human hair regenerative therapy to treat hair loss such as androgenic alopecia," adds Fukuda. "In fact, we have preliminary data that suggests human HFG formation using human keratinocytes and dermal papilla cells."

The paper "Spontaneous hair follicle germ (HFG) formation in vitro, enabling the large-scale production of HFGs for regenerative medicine" is available online from 6 November 2017 Biomaterials, with doi: 10.1016/j.biomaterials.2017.10.056

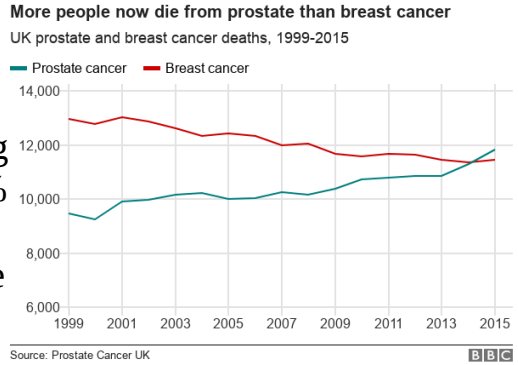
http://bbc.in/2nJYzYB

Prostate cancer deaths overtake those from breast cancer

The number of men dying from prostate cancer has overtaken female deaths from breast cancer for the first time in the UK, figures show.

An ageing population means more men are developing and dying from the disease. Prostate Cancer UK says advances in the diagnosis and treatment of breast cancer are paying off, and increased funding could benefit prostate cancer. The biggest cancer killers in the UK remain lung and bowel cancer, with prostate now in third place.

The latest figures from 2015 show there were 11,819 deaths from prostate cancer compared with 11,442 from breast cancer.



Although deaths from prostate cancer have been rising over the past 10 years or so, the mortality rate or the proportion of men dying from the disease has fallen - by 6% - between 2010 and 2015.

For breast cancer the mortality rate has come down by 10%, meaning deaths in women are declining more quickly.

Gary Pettit was 43 when he was diagnosed with prostate cancer, five years ago, after a routine medical through work.

He had no symptoms - only an abnormally high PSA (prostate-specific antigen) blood test, which led to further tests and biopsies.

Within weeks, he had a seven-hour operation at the Royal Marsden in London to remove the cancer. "I'm a lucky boy. I stored my sperm before the op and now we've got a little seven-month-old miracle baby, called Teddy. I can't say how lucky I've been."

Gary says recovering from the surgery took quite a while and there were some side-effects which he is still getting used to - but he is clear of cancer and keen to raise awareness among other men.

"It is still a taboo subject with men. They get shy and embarrassed, but it's so important to get checked out."

'Tremendous progress'

Angela Culhane, chief executive of the charity Prostate Cancer UK, said the disease currently received half the funding and half the research that is devoted to breast cancer.

She said developing better diagnostic tests that could be used as part of a nationwide screening programme would be a priority.

At present, there is no single, reliable test for prostate cancer - the PSA test, biopsies and physical examinations are all used.

Men with prostate cancer can also live for decades without symptoms or needing treatment because the disease often progresses very slowly.

What are the symptoms?

There can be few symptoms of prostate cancer in the early stages, and because of its location most symptoms are linked to urination:

- ***needing to urinate more often, especially at night***
- ***needing to run to the toilet***
- ***difficulty in starting to urinate***
- ***weak urine flow or taking a long time while urinating***
- ***feeling your bladder has not emptied fully***

Men with male relatives who have had prostate cancer, black men and men over 50 are at higher risk of getting the disease.

Ms Culhane said: "It's incredibly encouraging to see the tremendous progress that has been made in breast cancer over recent years.

"The introduction of precision medicine, a screening programme and a weighty research boost has no doubt played an important role in reducing the number of women who die from the disease.

"The good news is that many of these developments could be applied to prostate cancer and we're confident that with the right funding, we can dramatically reduce deaths within the next decade."

Living longer

Michael Chapman, director of information and involvement at Cancer Research UK, said: "The number of men getting and dying from prostate cancer is increasing mostly because of population growth and because we are living longer.

"We're dedicated to improving diagnosis and treatments for all cancers which is why we're investing in research to help develop more treatments to give more people more time this World Cancer Day on Sunday."

http://bit.ly/2BYveOY

Mini-primaquine does help stop people infecting mosquitoes with malaria

Mini-primaquine does help stop people infecting mosquitoes with malaria, but impact on transmission in the community remains unclear

A single dose of primaquine is thought to stop people with P. falciparum malaria infecting mosquitoes, which could help bring down malaria transmission. In this Cochrane Review update prepared by an international team of researchers and co-ordinated through the Cochrane infectious Diseases Group(link is external) (CIDG) based at LSTM, the researchers added recent data to examine this question. Their findings are relevant to the global recommendation by the World Health Organization that mini-primaquine be given to all people unwell with malaria in areas where transmission is low to reduce transmission further.

In these new trials, researchers test infectivity of people by getting mosquitoes to feed on people or their blood and then measuring whether the mosquitoes become infected with malaria. For the currently recommended dose of 0.25 mg/kg, the calculations across 3 trials with 105 participants show the percentage of people infectious 2 to 3 days after treatment is reduced from 14% of people in the control group to 2% in the primaquine group. A little later, a week after the treatment had been started, the absolute effect was smaller- with 4% infectious in the control group and 1% in the primaquine group. This shows that primaquine does reduce transmission-but it may not be to the extent that people had hoped for.

Many potentially infectious people with malaria are asymptomatic, so few would seek treatment. The question of whether a partial reduction in infectiousness for a few days would materially affect the community malaria burden is still unanswered, although malaria modelers have generally concluded that the increased impact would be marginal.

Dr Patricia Graves from James Cook University in Cairns, Australia is first author on the review. She said: "The trials show infectiousness is reduced with low dose primaquine, but the effects were relatively modest and short lived. We also do not know if this then would have any effect on malaria transmission at community level. Given the current evidence, it might be better for policy makers to concentrate on other approaches to help reduce transmission".

Access the full-text open access article here(link is external):

Graves PM, Choi L, Gelband H, Garner P. Primaquine or other 8-aminoquinolines for reducing Plasmodium falciparum transmission. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD008152. DOI: 10.1002/14651858.CD008152.pub5.

http://bit.ly/2nNOQAz

Testosterone may protect men from autoimmune diseases

A new explanation for why males are less susceptible to these disorders than women.

Diana Gitig - 2/3/2018, 12:00 AM

Testosterone. Source of prostates and testes, muscles and machismo, chest hair, and according to some, even math skills. Its levels are only one of the biological differences between males and females, but they may help to explain another: the discrepancies in the incidence of autoimmune diseases.

Women are three to nine times more likely than men to suffer from autoimmune diseases, including multiple sclerosis (MS), Grave's disease, celiac disease, systemic lupus erythematous, and rheumatoid arthritis. Not only do women get these diseases at higher rates, they usually get them at younger ages.

Men's higher testosterone levels—about seven to eight times higher than women's—have been shown to be protective for MS in both mice and men. But it was not clear exactly how this worked. Recent work in a mouse model of MS has filled in the downstream effectors that mediate testosterone's protective effects. These effectors might be useful as therapeutics, whereas testosterone use really isn't, especially for women, who are the ones who need it most.

The work focused on a type of immune cell called a mast cell. Mast cells get a bad rap because they release histamine during allergic reactions, but they're generally involved in inflammation. In the mice that recapitulate MS, testosterone influences the behavior of mast cells in the lymph nodes, central nervous system, and lining of the brain. In female mice, which don't have as much testosterone, mast cells instead produce pro-inflammatory signaling molecules called cytokines.

When mast cells in these areas are exposed to testosterone, however, researchers found that they produce a cytokine with the opposite effect: one that tones down inflammation. In male mice that lack mast cells, MS progresses much like it does in female mice. This suggests that the anti-inflammatory signaling is the key, rather than the promotion of inflammation that happens in females.

Two drugs currently approved for the treatment of MS act by shifting the population of T cells in patients to look more like those seen in male mice, to the kinds of T cells that mitigate inflammation rather than those that promote it. Perhaps the cytokine that testosterone induces mast cells to make, interleukin-33, might one day join them.

PNAS, *2018. DOI: 10.1073.pnas.1710401115 (About DOIs).*

http://wb.md/2GRN0Hy

Avoid These Antibiotics in the First Trimester of Pregnancy

We all know to be cautious when prescribing antibiotics to women who are pregnant.

Arefa Cassoobhoy, MD, MPH

Hello. I'm Dr Arefa Cassoobhoy, a practicing internist, Medscape advisor, and senior medical director for WebMD. Welcome to Morning Report, our 1-minute news story for primary care.

We all know to be cautious when prescribing antibiotics to women who are pregnant. A new CDC analysis looked at a commercial insurance database to assess this further.

Among almost 35,000 pregnant women treated for urinary tract infections (UTIs) in their first trimester, nearly 35% received

nitrofurantoin and about 8% received trimethoprim-sulfamethoxazole (TMP/SMX).

This is despite recommendations that these antibiotics should be avoided during the first trimester unless there are no alternatives. Options thought to be safe during pregnancy are amoxicillin-clavulanate, cephalosporins, and fosfomycin.

Given that almost 50% of pregnancies in the United States are unintended, we should always consider the possibility of pregnancy when treating women of reproductive age.

http://bit.ly/2E4b3Bh

An Ancient Virus May Be Responsible for Human Consciousness

You've got an ancient virus in your brain. In fact, you've got an ancient virus at the very root of your conscious thought.

By Rafi Letzter, Staff Writer | February 2, 2018 12:18pm ET

According to two papers published in the journal Cell in January, long ago, a virus bound its genetic code to the genome of four-limbed animals. That snippet of code is still very much alive in humans' brains today, where it does the very viral task of packaging up genetic information and sending it from nerve cells to their neighbors in little capsules that look a whole lot like viruses themselves.

And these little packages of information might be critical elements of how nerves communicate and reorganize over time — tasks thought to be necessary for higher-order thinking, the researchers said.

Though it may sound surprising that bits of human genetic code come from viruses, it's actually more common than you might think: A review published in Cell in 2016 found that between 40 and 80 percent of the human genome arrived from some archaic viral invasion.

That's because viruses aren't just critters that try to make a home in a body, the way bacteria do. Instead, as Live Science has previously reported, a virus is a genetic parasite. It injects its genetic code into its host's cells and hijacks them, turning them to its own purposes — typically, that means as factories for making more viruses. This process is usually either useless or harmful to the host, but every once in a while, the injected viral genes are benign or even useful enough to hang around.

The 2016 review found that viral genes seem to play important roles in the immune system, as well as in the early days of embryo development. But the new papers take things a step further. Not only is an ancient virus still very much active in the cells of human and animal brains, but it seems to be so important to how they function that processes of thought as we know them likely never would have arisen without it, the researchers said.

The Arc gene

Shortly after a synapse fires, the viral gene known as Arc comes to life, writing its instructions down as bits of mobile genetic code known as RNA, the researchers found. (A synapse is the junction between two neurons.)

RNA is DNA's messenger and agent in the world outside the cell's nucleus. A single-strand copy of code from DNA's double helix, it carries genetic instructions to places they can be useful. (And, interestingly, viruses tend to store their genetic code in RNA, rather than in DNA.)

Following the Arc RNA's instructions, the nerve cell builds "capsids" — virus-like envelopes — around it. Those envelopes let it travel safely between cells, and it does just that, entering neighboring neurons and passing its packet of genetic information along to them, according to the studies.

It's still unclear what that information does when it arrives in a new cell, but the researchers found that without the process functioning properly, synapses wither away. And problems with the Arc gene tend to show up in people with autism and other atypical neural conditions, the researchers said.

In a companion article, two experts who were not involved in the 2018 papers (the same two experts, in fact, behind the 2016 review) wrote that this process offers the best explanation yet for how nerve cells

exchange the information necessary to reorganize themselves in the brain over time.

"These processes underlie brain functions ranging from classical operant conditioning to human cognition and the concept of 'self,'" they wrote. (Classical and operant conditioning are simple forms of reward and punishment-based learning in animals and humans.)

Bizarrely, Arc seems to have made the jump from virus to animal more than once. The researchers found that Arc genes in humans and other four-limbed creatures seem to be closely related to one another. The Arc genes in fruit flies and worms, however, seem to have arrived separately.

The next step for this research, the outside experts wrote in the companion article, is to bring experts in neuroscience and ancient viruses together to work out the mechanisms for just how Arc arrived in the genome, and exactly what information it's passing between our cells today.

http://theatln.tc/2nD9ST6

Your Dog Feels No Shame

The myth of canine guilt

William Brennan

In 2011, a Maryland dog owner named Mali Vujanic uploaded a video to YouTube confidently titled "Guilty!" He'd come home to find his two retrievers near an empty bag of cat treats. The first dog, a golden retriever, lounged calmly, her conscience seemingly clean.

Esther Aarts

But the second dog, a yellow Labrador named Denver, sat quaking in a corner, her eyes downcast, making what Vujanic called "her signature 'I done it' face." Vujanic gasped at the apparent admission of guilt: "You did this!" Denver beat her tail nervously and grimaced. "You know the routine. In the kennel." Obediently, the dog impounded herself.

The video quickly garnered a flood of comments. Since then, "dog shaming" has become popular on Twitter and Instagram, as owners around the world post shots of their trembling pets beside notes in which the dogs seem to cop to bad behavior. "0 days since the last toilet paper massacre," a Weimaraner confesses; "I ate an extra large pepperoni pizza," admits a chocolate Lab. Human enthusiasm for guilty dogs seems boundless: A 2013 collection of dog-shaming photos landed on the *New York Times* best-seller list; Denver's video has been viewed more than 50 million times.

But according to Alexandra Horowitz, a dog-cognition expert at Barnard College, what we perceive as a dog's guilty look is no sign of guilt at all. In a 2009 study, she had owners forbid their dogs to eat a tempting treat, then asked the owners to leave the room. While each owner was gone, she either removed the treat or fed it to the dog. When the owners returned, they were told—regardless of the truth—that their dog either had or had not eaten it. If owners thought their dogs had indulged, reprimands followed, and guilty looks abounded. Yet dogs who hadn't eaten the treat were *more* likely to appear guilty than dogs who had—so long as their owners lashed out. Far from signaling remorse, one group of researchers wrote in a 2012 paper, the guilty look is likely a submissive response that has proved advantageous because it reduces conflict between dog and human.

History reveals the most-extreme consequences of that conflict. The Avesta, an ancient Zoroastrian religious text, deemed dogs capable of "willful" offenses and ordered that transgressors be punished with mutilation. In medieval Europe, misbehaving mutts were routinely tried in court on criminal charges such as assault and murder; punishments ranged from jail to death.

By comparison, it's easy to see harsh words and corny tweets as benign responses to bad behavior. But some experts worry that our

assumptions of canine guilt may be self-fulfilling. Julie Hecht, a doctoral student who studies animal behavior at the Graduate Center of the City University of New York, cites research showing that the more dogs are punished, the more they tend to act in ways that drive their owners mad. Scolding, Hecht believes, may confuse dogs, resulting in "an anxious cycle of destruction and appeasement" that could ultimately "harm the dog–human bond."

To keep that bond strong, Horowitz suggests that dog owners "take away the temptation": Put a lid on the trash can, keep your shoes in the closet, hide the kitty snacks. And if you must blame someone when your dog misbehaves, look inward. As one commenter put it after watching Denver shake in submission, "Let's face it, *somebody* left the treats out."

http://bit.ly/2EhJ5oR

Rats help each other out just as humans do

Rats demonstrate cooperative behaviour similar to human beings, researchers at the University of St Andrews have discovered.

When offered food by a partner rat, the common Norway rat was more inclined to engage in grooming with this rat than when no food was received from it and vice versa, according to the research published in *Current Biology* (February 1).

Dr. Manon Schweinfurth of the School of Psychology and Neuroscience at the University of St Andrews, and Professor Michael Taborksy of the Institute of Ecology and Evolution at the University of Bern, applied saltwater to a rat's neck – a place hard for the rat to reach – to create a situation where help was needed.

To induce food provisioning, partner rats could pull food items towards the other rat. Afterwards, the rats had the opportunity to reciprocate the favour by either grooming the rat which had given them food, or offering food to the rat which had groomed them.

Rats were found to groom cooperative food-providers more often than partners who had refused to help. In addition, rats provided more food to cooperative groomers.

Dr. Schweinfurth said: "We found the rats traded these two services among each other according to the decision rules of direct reciprocity e.g. 'I help you because you helped me'.

http://bit.ly/2nAvqji

A 100-million-year-old flower

An ancient flower perfectly preserved in amber.

The tiny flower above – around 4 mm in diameter – belonged to a tree that lived 100 million years ago in what was then the island of Greater India. The tree was a member of a species dubbed *Tropidogyne pentaptera*, which scientists believe was a rainforest tree related to the Ceropetalum genus found today in Australian and Papua New Guinea.

The specimen was found in Myanmar with six others, preserved in amber.

A specimen of the 100-million-year-old flower Tropidogyne pentaptera. **George Poinar Jr. / Oregon State University**

Georges Poinar, the scientists who described the flowers, speculates that a passing dinosaur may have knocked the flowers into a pool of resin from an araucaria tree that fossilised over time into amber.