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How we discovered 840 minor planets beyond Neptune – and what they can tell us

We have discovered 840 small worlds in the distant and hard-to-explore region beyond Neptune

May 25, 2018 by Michele Bannister, The Conversation

Our solar system is a tiny but wonderfully familiar corner of the vast, dark universe – we have even been able to land spacecraft on our celestial neighbours. Yet its outer reaches are still remarkably unmapped. Now we have discovered 840 small worlds in the distant and hard-to-explore region beyond Neptune. This is the largest set of discoveries ever made, increasing the number of distant objects with well known paths around the sun by 50%.

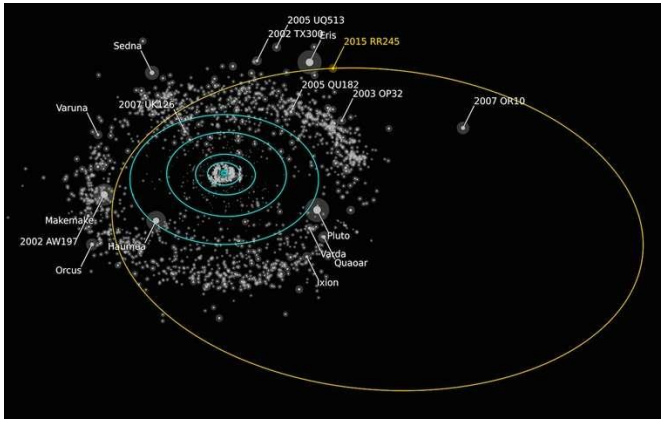
These little icy worlds are important as they help us tell the solar system's history. They can also help us test the idea that there's a yet unseen planet lurking in the outer solar system.

Our planetary system as we see it today is not as it formed. When the sun was newborn, it was surrounded by a massive disk of material. Encounters with tiny, growing planets – including some of the worlds we've just discovered – moved the giant planets outward from the sun until they settled into their present locations. The growing planets, on the other hand, went everywhere, scattering both inward and outward.

Planetary migration also happened in far away systems around many other stars. Fortunately, the celestial bodies in our own planetary system are comparatively close by, making it the only place where we can see the intricate details of how migration happened. Mapping the minor planet populations that are left over from the disk lets us reconstruct the history of how the big planets were pushed into place.

Mapping the sky

The new discoveries were made as part of a five year project called the Outer Solar System Origins Survey (OSSOS). The observations, conducted in 2013-2017, used the imaging camera of one of the world's major telescopes – the Canada-France-Hawaii Telescope on Maunakea in Hawaii. The survey looked for faint, slow-moving points of light within eight big patches of sky near the plane of the planets and away from the dense star fields of the Milky Way.



The dwarf planet candidate 2015 RR245 is on an exceptionally distant orbit, but is one of the few dwarf planets that could one day be reached by a spacecraft mission. **Alex Parker/OSSOS, CC BY-SA**

With 840 discoveries made at distances between six and 83 astronomical units (au) – one such unit is the distance between the sun and the Earth – the survey gives us a very good overview of the many sorts of orbits these "trans-Neptunian objects" have.

Earlier surveys have suffered from losing some of their distant discoveries – when too few observations occur, the predicted path of a minor planet in the sky will be so uncertain that a telescope can't spot it again, and it is considered "lost". This happens more to objects with highly tilted and elongated orbits, producing a bias in what's currently known about these populations.

Our new survey successfully tracked all its distant discoveries. The frequent snapshots we made of the 840 objects over several years meant that each little world's orbit could be determined very precisely.

In total, more than 37,000 hand-checked measurements of the hundreds of discoveries precisely pinned down their arcs across the sky. We also created an accompanying software "simulator" (a

computer model), which provides a powerful tool for testing the inventory and history of our solar system. This lets theorists test out their models of how the solar system came to be in the shape we see it today, comparing them with our real discoveries.

Strange new worlds

The new icy and rocky objects fall into two main groups. One includes those that reside on roundish orbits in the Kuiper belt, which extends from 37au to approximately 50au from the sun. The other consists of worlds that orbit in a careful dance of avoidance with Neptune as it travels around the sun. These "resonant" trans-Neptunian objects, which include Pluto, were pushed into their current elongated orbits during Neptune's migration outwards.

In the Kuiper belt, we found 436 small worlds. Their orbits confirm that a concentrated "kernel" of the population nestles on almost perfectly round, flat orbits at 43 to 45au. These quiet orbits may have been undisturbed since the dawn of the solar system, a leftover fraction of the original disk. Soon, we will see a member of this group up close: the New Horizons spacecraft, which visited Pluto in 2015, will be flying by a world that's about the size of London on New Year's Day 2019.

We found 313 resonant trans-Neptunian objects, with the survey showing that they exist as far out as an incredible 130au – and are far more abundant than previously thought. Among these discoveries is the dwarf planet 2015 RR245, which is about half the size of Britain. It may have hopped onto its current orbit at 82au after an encounter with Neptune hundreds of millions of years ago. It was once among the 90,000 scattered objects of smaller size that we estimate currently exist.

Are there more planets?

Among the most unusual of the discoveries are nine little worlds on incredibly distant orbits, never coming closer to the sun than Neptune's orbit, and taking as long as 20,000 years to travel around our star. Their existence implies an unseen population of hundreds of thousands of trans-Neptunian objects on similar orbits.

How these objects got on their present paths is unclear—some orbit so far out that, even at their closest approach, they are barely tugged by Neptune's gravity. One explanation that has been put forward is that a yet unseen large planet, sometimes called "Planet Nine", could be causing them to cluster in space. However, our nine minor planets all seem to be spread out smoothly, rather than clustering. Perhaps the shepherding of such a large planet is more subtle – or these orbits instead formed in a different way.

The history of our solar system is just beginning to be told. We hope this new set of discoveries will help piece together the story.

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Dodging dementia: more of us get at least a dozen good, happy years after 65

Breathe a little: Most seniors don't have cognitive impairment or dementia

Judith Graham

You've turned 65 and exited middle age. What are the chances you'll develop cognitive impairment or dementia in the years ahead?

New research about "cognitive life expectancy" — how long older adults live with good versus declining brain health — shows that after age 65 men and women spend more than a dozen years in good cognitive health, on average. And, over the past decade, that time span has been expanding.

By contrast, cognitive challenges arise in a more compressed time frame in later life, with mild cognitive impairment (problems with memory, decision-making or thinking skills) lasting about four years, on average, and dementia (Alzheimer's disease or other related conditions) occurring over 1½ to two years.

Even when these conditions surface, many seniors retain an overall sense of well-being, according to new research presented last month

at the Population Association of America's annual meeting. "The majority of cognitively impaired years are happy ones, not unhappy ones," said Anthony Bardo, a co-author of that study and assistant professor of sociology at the University of Kentucky-Lexington.

Recent research finds that:

Most seniors don't have cognitive impairment or dementia. Of Americans 65 and older, about 20 to 25 percent have mild cognitive impairment while about 10 percent have dementia, according to Dr. Kenneth Langa, an expert in the demography of aging and a professor of medicine at the University of Michigan. Risks rise with advanced age, and the portion of the population affected is significantly higher for people over 85.

Langa's research shows that the prevalence of dementia has fallen in the U.S. — a trend observed in developed countries across the globe.

A new study from researchers at the Rand Corp. and the National Bureau of Economic Research finds that 10.5 percent of U.S. adults age 65 and older had dementia in 2012, compared with 12 percent in 2000.

Because the population of older adults is expanding, the number of people affected by dementia is increasing nonetheless: an estimated 4.5 million in 2012, compared with 4.1 million in 2000.

More years of education, which is associated with better physical and brain health, appears to be contributing to this phenomenon.

But gains are unequally distributed. Notably, college graduates can expect to spend more than 80 percent of their lifetime after age 65 with good cognition, according to a new study from researchers at the University of Southern California and the University of Texas at Austin. For people who didn't complete high school, that drops to less than 50 percent.

This research looks at the older population as a whole and can't predict what will happen to any given individual. Still, it's helpful in getting a general sense of what people can expect.

An expanding period of good brain health. With longer lives and lower rates of dementia, most seniors are enjoying more years of life with good cognition — a welcome trend.

Two years ago, Eileen Crimmins, AARP chair of gerontology at the University of Southern California's Leonard Davis School of Gerontology, and colleagues documented this shift in the United States in research using data about adults 65 and older from the Health and Retirement Study.

In 2000, she found, a 65-year-old woman could expect to live 12.5 years with good cognition, four years with mild cognitive impairment and 2.6 years with dementia, on average. A decade later, in 2010, the period in good cognition had expanded to 14.1 years, with 3.9 years spent with mild cognitive impairment and 2.3 years spent with dementia.

For men, the 2010 figures are different: 12.5 years with good cognition after age 65 (compared with 10.7 in 2000); 3.7 years with mild cognitive impairment (the same as in 2000); and 1.4 years with dementia (compared with 1.8 years in 2010).

Improvements in education and nutrition, better control of hypertension and cholesterol, cognitively demanding jobs in middle age, and social engagement in later life may all contribute to this expanded period of good brain health, the study noted.

Well-being often coexists with impairment. Bardo's research adds another dimension to this literature by addressing two questions: Do older adults with cognitive impairment feel they have a good quality of life and, if so, for how long?

His study, which has not yet been published, focuses on happiness as an important indicator of quality of life. The data come from thousands of adults 65 and older who participated in the Health and Retirement Study between 1998 and 2012 and who were asked if they were happy "all/most of the time" or "some/none of the time" during the past week.

These answers were combined with information about cognitive impairment derived from tests that examined seniors' ability to recall words and to count backward, among other tasks.

Findings suggest that cognitive impairment is not a deterrent to happiness. Of the period that seniors spent cognitively impaired, about 5.5 years on average, they reported being happy for 4.8 years — about 85 percent of the time. Of the 12.5 years that older adults spent in good cognitive health, they reported being happy nearly 90 percent of the time.

The bottom line: "Cognitive impairment doesn't equate with unhappiness," Bardo said. Still, he cautioned that his study didn't look at how happiness correlates with the extent of impairment. Certainly, people with moderate to severe dementia experience serious difficulties in their lives, as do their caregivers, he noted.

Amal Harrati, an instructor at Stanford University Medical School, said Bardo's paper appears sound, methodologically, but wondered whether older adults with cognitive impairment can be trusted to report reliably on their happiness.

Langa of the University of Michigan said the findings "fit my general experience and sense of treating older patients in my clinical work." In the early stages of cognitive impairment, people often start focusing on enjoying family and being in the "here-and-now" while paying less attention to "small frustrations that can get us down in our daily lives," he wrote in an email response to questions.

"As cognitive decline worsens, I think it is more likely that one can become unhappy, possibly due to the advancing pathology that can affect specific brain regions" and behavioral issues such as hallucinations and paranoia, he added.

Jennifer Ailshire, an assistant professor of gerontology and sociology at USC's Leonard Davis School of Gerontology, noted that happiness is often tied to an individual's personality characteristics. This measure "doesn't necessarily reflect how individuals with cognitive impairment are interacting with other people or their environment," she commented.

Laura Gitlin, dean of the college of nursing and health professions at Drexel University in Philadelphia, observed that happiness is only one element of living well with cognitive impairment and dementia. Going forward, she suggested, "there is much work to do" to identify what contributes more broadly to well-being and a positive quality of life in older adults with these conditions.

This article originally appeared on Kaiser Health News.

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Mechanics of pesticide-Parkinson's link revealed

A genetic mutation massively increases risk for agrochemical exposure.

Andrew Masterson reports.

Even very low levels of exposure to some common agricultural chemicals can boost the risk of Parkinson's disease, according to new research.

A paper published in the journal *Federation of American Societies for Experimental Biology* reveals that exposure to pesticides known as paraquat and maneb dramatically affects the function of dopamine-producing neurons – the cells primarily targeted by Parkinson's – in people carrying a particular genetic mutation.

Separate lines of research kicked off two decades ago identified the chemicals and the mutation – in a gene known as alpha-synuclein, located on chromosome four – as risk factors for developing Parkinson's, but the latest study is the first to uncover what happens on a cellular level when the two combine.

"People exposed to these chemicals are at about a 250% higher risk of developing Parkinson's disease than the rest of the population," says Scott Ryan from the University of Guelph in Ontario, Canada, lead author of the new study.

"We wanted to investigate what is happening in this susceptible population that results in some people developing the disease."

The role of chemical exposure in influencing risk for Parkinson's was first identified in epidemiological studies, starting in 1998.

A separate line of investigation around the same time focussed on a large Italian family group prone to developing the disease, many members of which carried the alpha-synuclein mutation.

Ryan and his colleagues set out to determine what happens to human cell function when both risk factors are combined.

To do so researchers established two cohorts of stem cells. The first used cells derived from Parkinson's patients known to be carrying the mutation. The second derived from standard embryonic stem cells into which the mutation was edited.

Both sets were induced to form the target neurons, which were then exposed to varying levels of paraquat and maneb.

In cells containing the mutation even very low levels of exposure prevented the mitochondria from functioning correctly, depriving the neurons of essential energy and causing them to fail.

Cells that did not carry the mutation needed higher doses before function was impaired.

"Until now, the link between pesticides and Parkinson's disease was based primarily on animal studies as well as epidemiological research that demonstrated an increased risk among farmers and others exposed to agricultural chemicals," explains Ryan.

"We are one of the first to investigate what is happening inside human cells."

Critical exposure levels for the mutation-carrying cells were lower than the maximum safe levels contained in Canadian Environmental Protection Authority regulations.

Ryan says that the results indicate that current one-level-fits-all advice for chemical exposure needs to be ditched.

"This study shows that everyone is not equal, and these safety standards need to be updated in order to protect those who are more susceptible and may not even know it," he says.

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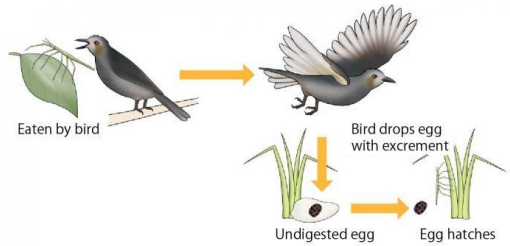
The stick insects that survive being eaten by birds

It's commonly assumed that when insects are eaten by birds, they and their unborn young have no chance of survival.

However, a team of Japanese researchers hypothesized that the eggs within insect bodies can pass through birds undigested.

They tested this hypothesis with stick insects, known for their hard eggs, and found that some eggs are excreted unharmed and successfully hatch. Stick insects cannot travel very far by themselves, so being eaten by birds could even contribute to expanding their habitat.



This is an image of the new mechanism for stick insect habitat expansion suggested by these findings. For insects with very low mobility, such as stick insects, bird predators could be helping them to expand their habitats. **Kobe University**

The research team was led by Associate Professor Kenji Suetsugu (Kobe University Graduate School of Science), Associate Professor Katsuro Ito (Kochi University), and Associate Professor Takeshi Yokoyama (Tokyo University of Agriculture and Technology). The findings were published in the online edition of *Ecology* on May 28.

Plants cannot move around, so they have developed various ways to distribute their seeds. The most common is seed dispersal by animals, who eat the fruits and excrete the seeds whole. For many birds, insects are also one of their main food sources. If insect eggs can pass through birds unharmed, we could say that insects, just like plants, are using the birds as a means of long-distance transport.

To achieve this, several conditions must be met: the eggs must be strong enough to pass through digestive tracts unharmed, the insect young born from these eggs must be able to fend for themselves, and the eggs must be viable without fertilization. Stick insects fulfil these conditions. The insect eggs are only fertilized just before the eggs are laid, using sperm stored within the seminal vesicle. However, females of many stick insect species are parthenogenic, enabling them to produce viable eggs without fertilization. In addition, like plant seeds, stick insect eggs have a very hard shell. They lay these eggs by scattering them on the surface of the ground, and after hatching the young locate suitable plants for food by themselves.

The research team fed eggs from three species of stick insects to brown-eared bulbul (one of the main bird predators for stick insects). For all three species, between 5 and 20% of the eggs were excreted unharmed. They also confirmed that for one species, eggs retrieved from the bird's excrement successfully hatched. Despite being eaten by birds, the unborn insects survived. Adult stick insects are frequently eaten by birds, and the stomachs of adult female stick insects are always filled with eggs, so this route is a potential way to widen stick insect distribution.

Many plants have evolved eye-catching, nutritious fruit as a strategy to appeal to animals, while stick insects are plain and hard to spot. But even though they do not actively seek to be eaten, for insects with low mobility like stick insects, consumption by birds is one way to expand their habitat. Many relatives of stick insects have dispersed across islands unconnected to the mainland. The ability of animals with low mobility to successfully travel long distances is a topic that puzzled Darwin.

"Our next step is analyzing the genetic structure of stick insects" comments team leader Professor Suetsugu. "Based on this we'd like to investigate whether similar genetic structure of stick insects can be found along birds' migration flight paths, and whether there are genetic similarities between stick insects and plants that rely on birds for seed distribution". These investigations will reveal that the dispersal of stick insect eggs by birds could affect the distribution and gene flow of stick insects.

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Genes, environment and schizophrenia: new study finds the placenta is the missing link

Placenta may also hold the key to why developmental brain disorders are more common in males

Baltimore, MD - Hiding in plain sight, new research shines a spotlight on the placenta's critical role in the nature versus nurture debate and how it confers risk for schizophrenia and likely other neurodevelopmental disorders including ADHD, autism, and Tourette syndrome. This new scientific frontier, with far-reaching implications for maternal and child health, creates the possibility that scientists can more accurately predict who is at risk of mental illness, and develop strategies to prevent or lessen their occurrence by increasing the resiliency and health of the placenta.

The study, "Convergence of placenta biology and genetic risk for schizophrenia," was led by researchers at the Lieber Institute for Brain Development and published in *Nature Medicine*. "For the first time, we have found an explanation for the connection between early life complications, genetic risk, and their impact on mental illness and it all converges on the placenta," said Daniel R. Weinberger, who led the team of investigators on the study and is CEO of the Lieber Institute for Brain Development (LIBD).

In contrast to prior studies that focused on how genes related to behavioral disorders directly alter prenatal brain development, this novel research found that many genes associated with risk for schizophrenia appear to alter early brain development indirectly, by influencing the health of the placenta. The research showed that these

genes are "turned on" in the placenta during complicated pregnancies and signal a placenta under duress.

While the subject of myth and ritual in many cultures, the placenta remains a scientifically neglected human organ, despite its essential role for supplying nutrients and chemicals critical for normal prenatal development. Indeed, the placenta is the only organ removed from a human body that is not routinely sent to the laboratory for examination.

For over a quarter of a century, brain development during pregnancy and shortly after birth has remained central to a hypothesis that schizophrenia is a neurodevelopment disorder. However, the biological mechanisms involved were poorly understood. Previous studies have shown that genetic variants alone increase the odds of developing schizophrenia by only a fraction, while early life complications during pregnancy and labor can increase risk by up to 2-fold. The Lieber Institute investigators studied over 2800 adult individuals, 2038 of whom had schizophrenia, of various ethnic backgrounds from four countries, including the USA, Europe and Asia. All had undergone genetic testing and were surveyed for obstetrical history information.

Researchers found a prominent interaction between genes associated with risk for schizophrenia and a history of a potentially serious pregnancy complication. Individuals having high genetic risk and serious early life complications have at least a fivefold greater likelihood of developing schizophrenia in comparison to individuals with similarly high genetic risk but no history of serious obstetrical complications. This led to a series of analyses of gene expression in multiple placenta tissue samples, including samples of placenta from complicated pregnancies that include preeclampsia and intrauterine growth restriction. The results showed a striking and consistent turning on of the schizophrenia genes in these placentae and the more they were turned on, the more the placenta showed other signs of being under stress, for example, being more inflamed.

A Clue to Higher Male Risk for Schizophrenia

One of the many mysteries of developmental behavioral disorders, including schizophrenia, autism, ADHD, dyslexia, and Tourette Syndrome is why their incidence is 2-4 times greater in males than in females. The Lieber Institute team findings may shed light on this mystery. They found that the schizophrenia genes turned on in the placenta from complicated pregnancies were dramatically more abundant in placentas from male compared with female offspring. The placenta appears to be at least part of the explanation for the sex bias associated with these disorders.

"The surprising results of this study make the placenta the centerpiece of a new realm of biological investigation related to how genes and the environment interact to alter the trajectory of human brain development," said Weinberger.

Further research into this emerging frontier of clinical medicine will advance the understanding of the biological interplay between placental health and neurodevelopment. There is a potential to discover novel approaches to therapeutic treatments and prevention strategies, and ultimately reduce the incidence of neurodevelopmental behavior disorders.

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Small study suggests a new way to treat fluid buildup in heart failure

Duke team challenges the paradigm about fluid as a symptom of heart failure

DURHAM, N.C. - One of the key features of heart failure is an accumulation of fluid in the heart and lungs that causes life-threatening symptoms, including shortness of breath, lightheadedness and an elevated heart rate. This fluid buildup has long been considered a symptom of heart failure, but researchers at

Duke University Medical School have explored a new theory: It might be a key contributor, and a fairly treatable one, at that.

Led by cardiology fellow Marat Fudim, M.D., the researchers performed a small proof-of-concept study among five acute heart failure patients at Duke University Hospital. The researchers performed a simple procedure essentially shutting off the spigot causing the fluid buildup, immediately improving other heart failure symptoms.

The study is being presented May 26 at the European Society of Cardiology's Heart Failure 2018 meeting and is also published in the journal Circulation.

"Obviously, this is a small study, but the results from these five patients suggest that this approach has potential for one of the most common heart conditions in the world," Fudim said, noting that more than five million people in the United States have heart failure and it is one of the leading causes of hospitalizations and death.

Fudim and colleagues, including Manesh Patel, M.D., chief of Duke's Division of Cardiology and member of the Duke Clinical Research Institute, designed the study to address a curious observation around the fluid buildup that accompanies heart failure: If the buildup were the result of a person simply retaining water, patients would see weight gain in the days and weeks before an acute episode. This isn't the case.

Instead, Fudim said, the fluid is a spilling of the natural stockpile that the body stores in the belly region for emergencies such as stress or trauma. The release of this extra blood, driven by an activation of nerves by hormones, is a welcome boost to the organs in fight-or-flight events.

With heart failure, however, the body appears to be stuck on alert, flooding the heart and lungs with fluid beyond the organs' capacity to manage it. Controlling this process is a bundle called the splanchnic nerves.

What if, Fudim and colleagues surmised, they could turn off the portion of the splanchnic nerve bundle that controls the flood of fluid to the heart and lungs? The procedure is actually relatively simple and is not uncommon -- a similar procedure has been used for decades to ease abdominal pain among cancer patients.

One side effect of the procedure among cancer patients was lower blood pressure as blood shifts into the belly region -- "which is exactly what we want to achieve for heart failure patients," Fudim said.

The Duke study only briefly numbed the over-active area of the nerve bundle using a temporary anesthetic that lasted 90 minutes. Among the five heart failure patients who underwent the procedure at Duke, all showed a marked reduction of pressures inside the heart and increases in cardiac output. This was primarily driven by a significant reduction in vascular resistance and improved arterial vascular storage space.

"The splanchnic vascular compartment may be a key player in the fluid imbalance that is a hallmark of acute and chronic heart failure" Patel said. "These findings suggest that continued research into therapeutic use of splanchnic nerve block for the treatment of acute and potentially also chronic heart failure is of interest."

Patel and Fudim said larger studies are already planned and will include a control group to compare outcomes, which was not part of the current study.

In addition to Patel and Fudim, study authors include W. Schuyler Jones, Richard L. Boortz-Marx, Arun Ganesh, Cynthia L. Green and Adrian F. Hernandez.

The study received funding support from the American Heart Association (17MCPRP3346022

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Researchers identify the electrophysiological sign of cerebral infarction

A massive and extremely slow change in electrical potential is evidence of irreparable damage

Researchers from Charité - Universitätsmedizin Berlin have analyzed the underlying electrophysiological indicators of subarachnoid hemorrhage, the second most common type of brain hemorrhage that can lead to ischemic stroke within a matter of days. Their findings, which have been published in the journal *Brain**, may lay the foundations for new stroke treatments.

Subarachnoid hemorrhage is a type of brain bleed that occurs in the area between the membranes surrounding the brain. Patients with subarachnoid hemorrhage can develop complications within approximately one week. Between one in three and one in four patients will develop symptoms of ischemic stroke, a type of stroke caused by an inadequate blood supply. This phenomenon occurs as the result of mechanisms triggered by the molecular breakdown products of the patient's earlier hemorrhagic stroke. It sets off a wave of electrochemical depolarization, or 'spreading depolarization', within the brain tissue. Affected areas of the brain require large amounts of energy in order to restore normal conditions.

In healthy brains, this depolarization of nerve cells is linked to blood supply, meaning blood vessels widen in areas of the brain that are active. However, a subarachnoid hemorrhage may disrupt the signaling cascades between nerve cells and blood vessels, so that the depolarization of nerve cells causes extreme constriction of the blood vessels, which leads to spreading ischemia. Deprived of energy, the nerve cells are incapable of restoring normal electrochemical gradients. If depolarization persists for too long, affected nerve cells will begin to die off. Measurements of the electrical brain potential will then show an extreme and very gradual change , a process known as 'negative ultraslow potential', which is indicative of 'terminal spreading depolarization'.

"Two months ago, we were able to show for the first time that terminal spreading polarization occurs in humans - namely in patients who had suffered cardiac arrest. Now we have been able to show that it also occurs in patients with cerebral infarctions after subarachnoid hemorrhage," explains Prof. Dr. Jens Dreier of Charité's Center for Stroke Research Berlin (CSB). Prof. Dreier and his team analyzed data from 11 patients, comparing their findings with results obtained from animal experiments. The waves of depolarization observed indicate disturbances of energy metabolism. The 'negative ultraslow potential' constitutes the electrophysiological correlate of infarction, and of tissue death due to an inadequate supply of blood.

Prof. Dreier emphasizes: "Measurements of spreading depolarization may prove as important to the development of interventions for patients with stroke, global ischemia and traumatic brain injury, as similar electrophysiological tools have proved in the past, in the areas of epilepsy or cardiology - because they make the underlying causes visible."

*Lückl J, Lemale CL, Kola V, Horst V, Khojasteh U, Oliveira-Ferreira AI, Major S, Winkler MKL, Kang EJ, Schoknecht K, Martus P, Hartings JA, Woitzik J, Dreier JP. *The negative ultraslow potential, electrophysiological correlate of infarction in the human cortex.* Brain, *Volume 141, Issue 6, 1 June 2018, Pages 1734-1752, DOI: 10.1093/brain/awy102.*

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Wars and clan structure may explain a strange biological event 7,000 years ago

7,000 years ago it seems as if male population dropped precipitously

Starting about 7,000 years ago, something weird seems to have happened to men: Over the next two millennia, recent studies suggest, their genetic diversity -specifically, the diversity of their Y chromosomes - collapsed. So extreme was that collapse that it was as if there was only one man left to mate for every 17 women.

Anthropologists and biologists were perplexed, but Stanford researchers now believe they've found a simple - if revealing - explanation. The collapse, they argue, was the result of generations

of war between patrilineal clans, whose membership is determined by male ancestors.

The outlines of that idea came to Tian Chen Zeng, a Stanford undergraduate in sociology, after spending hours reading blog posts that speculated - unconvincingly, Zeng thought - on the origins of the "Neolithic Y-chromosome bottleneck," as the event is known. He soon shared his ideas with his high school classmate Alan Aw, also a Stanford undergraduate in mathematical and computational science. "He was really waxing lyrical about it," Aw said, so the pair took their idea to Marcus Feldman, a professor of biology in Stanford's School of Humanities and Sciences. Zeng, Aw and Feldman published their results May 25 in Nature Communications.

A cultural culprit

It's not unprecedented for human genetic diversity to take a nosedive once in a while, but the Y-chromosome bottleneck, which was inferred from genetic patterns in modern humans, was an odd one. First, it was observed only in men - more precisely, it was detected only through genes on the Y chromosome, which fathers pass to their sons. Second, the bottleneck is much more recent than other biologically similar events, hinting that its origins might have something to do with changing social structures.

Certainly, the researchers point out, social structures were changing. After the onset of farming and herding around 12,000 years ago, societies grew increasingly organized around extended kinship groups, many of them patrilineal clans - a cultural fact with potentially significant biological consequences. The key is how clan members are related to each other. While women may have married into a clan, men in such clans are all related through male ancestors and therefore tend to have the same Y chromosomes. From the point of view of those chromosomes at least, it's almost as if everyone in a clan has the same father.

That only applies within one clan, however, and there could still be considerable variation between clans. To explain why even between-clan variation might have declined during the bottleneck, the researchers hypothesized that wars, if they repeatedly wiped out entire clans over time, would also wipe out a good many male lineages and their unique Y chromosomes in the process.

Computing clans

To test their ideas, the researchers turned to mathematical models and computer simulations in which men fought - and died - for the resources their clans needed to survive. As the team expected, wars between patrilineal clans drastically reduced Y chromosome diversity over time, while conflict between non-patrilineal clans - groups where both men and women could move between clans - did not.

Zeng, Aw and Feldman's model also accounted for the observation that among the male lineages that survived the Y-chromosome bottleneck, a few lineages underwent dramatic expansions, consistent with the patrilineal clan model, but not others.

Now the researchers are looking at applying the framework in other areas - anywhere "historical and geographical patterns of cultural interactions could explain the patterns you see in genetics," said Feldman, who is also the Burnet C. and Mildred Finley Wohlford Professor.

Feldman said the work was a unusual example of undergraduates driving research that was broad both in terms of the academic disciplines spanned - in this case, sociology, mathematics and biology - and in terms of its potential implications for understanding the role of culture in shaping human evolution. And, he said, "Working with these talented guys is a lot of fun."

Feldman is co-director of Stanford's Center for Computational, Evolutionary and Human Genomics, and a member of Stanford Bio-X, the Stanford Cancer Institute, the Stanford Neurosciences Institute and the Stanford Woods Institute for the Environment. Aw was a 2016 participant in the Bio-X Undergraduate Summer Research Program.

The research was supported by the Center for Computational, Evolutionary and Human Genomics, the Morrison Institute for Population and Resource Studies and a grant from the National Science Foundation.

http://bit.ly/2kL7PdM

Woulda, coulda, shoulda: The haunting regret of failing our ideal selves

Forsaken dreams. Romantic interests not pursued. Securing a job near home rather than an adventurous position overseas.

ITHACA, N.Y. - Our most enduring regrets are the ones that stem from our failure to live up to our ideal selves, according to new Cornell University research.

Psychologist Tom Gilovich and former Cornell graduate student Shai Davidai have found people are haunted more by regrets about failing to fulfill their hopes, goals and aspirations than by regrets about failing to fulfill their duties, obligations and responsibilities.

The research, "The Ideal Road Not Taken," was published in the journal Emotion. It builds on the idea that three elements make up a person's sense of self: the actual, ideal and the ought selves. The actual self is made up of the attributes a person believes they possess. The ideal self is the attributes they would ideally like to possess, such as hopes, goals, aspirations or wishes. The ought self is the person they feel they should have been based on duties, obligations and responsibilities.

Gilovich and Davidai surveyed hundreds of participants through the course of six studies, describing the differences between the ought and ideal selves, and asking them to list and categorize their regrets based on these descriptions.

The participants said they experienced regrets about their ideal self far more often (72 percent versus 28 percent). More than half mentioned more ideal-self regrets than ought-self regrets when asked to list their regrets in life so far. And when asked to name their single biggest regret in life, 76 percent of participants mentioned a regret about not fulfilling their ideal self.

Why do ideal-self failures spark such enduring regret? The expectations of the ought self are usually more concrete and involve specific rules - such as how to behave at a funeral - and so are easier to fulfill. But ideal-related regrets tend to be more general: Be a good parent, be a good mentor. "Well, what does that mean, really?" Gilovich said. "There aren't clear guideposts. And you can always do more."

The research has practical implications, he said. First, we often assume we first need inspiration before we can strive to achieve our ideals. But a significant amount of psychological research shows that's not true, Gilovich said.

"As the Nike slogan says: 'Just do it,'" he said. "Don't wait around for inspiration, just plunge in. Waiting around for inspiration is an excuse. Inspiration arises from engaging in the activity."

And people often fail to achieve their ideal goals because they're worried about how it will look to others. For example, a person might want to learn how to sing but feel they could never let others hear how bad they are.

Again, Gilovich says, just do it.

"People are more charitable than we think and also don't notice us nearly as much as we think," he said. "If that's what holding you back - the fear of what other people will think and notice - then think a little more about just doing it."

http://bit.ly/2srmBe0

Mathematical model explains why metastasis can occur even when cancer is caught early

Cells within tumors compete with one another, some thriving, some failing

The concept of survival of the fittest most often applies to the competition that occurs within and between animal species, but

evolutionary pressures can be found elsewhere--even in a cancerous tumor.

Cancer researchers have come to understand tumors not as lumps of identical cells, but rather as diverse, dynamic populations unto themselves. And, like individuals within animal populations, cells within tumors compete with one another, some thriving, some failing. In a new study, researchers from the University of Pennsylvania have crafted a mathematical model to understand the dynamics at play as cancerous tumors grow and spread. Setting their model into action, Jimmy Qian, a rising senior in the Vagelos Scholars Program in the Molecular Life Sciences, and Erol Akçay, an assistant professor of biology in the School of Arts and Sciences, were able to explain a somewhat paradoxical observation, that mutations that lead to metastasis--the spread of cancer to sites distant from the primary tumor--often arise early, rather than late, in a tumor history.

Reporting in the journal *PLOS ONE*, Qian and Akçay suggest that incorporating evolutionary and ecological theory into cancer biology may help guide more effective treatment plans.

"In the public consciousness it often seems like cancer is this big, unitary disease that we need to beat somehow, like polio, which it isn't," says Akçay. "Each cancerous tumor is a community of essentially different 'species' doing different things."

"Understanding how cancer evolves," adds Qian, "may help us to predict which lineage will come to dominate in a tumor and, possibly, preemptively treat that to minimize the chance for drug resistance. Or, if we can predict what sort of evolutionary mechanisms cause metastasis, we can try to tackle that before metastasis even starts."

Cancer cells don't simply dwell and reproduce amidst normal cells; they actively modify the environment around them to make it more conducive to their own growth. This process may entail enhancing blood-vessel formation or altering the structure and metabolism of nearby cells. Cultivation of the so-called tumor microenvironment, or tumor niche, isn't limited to neighboring tissues, however. Metastasis arises when malignant cells secrete factors through the bloodstream to distant sites in the body as a way of readying new spaces for cancer to grow.

"It's like humans. We prepare our kids by creating college funds and things like that," Qian says. "Cancer is doing the same thing. It's preparing a distant site that its kids will one day migrate to."

To Qian and Akçay, steeped in theoretical evolutionary biology and ecology theory, this feature of cancer's spread presented interesting questions: Assuming that cancer cells must sacrifice some of their own resources to prepare these distant areas of the body, how would such a lineage compete with others that cultivated areas closer to the primary tumor? And what about "cheating" lineages that didn't contribute to constructing the tumor niche, and therefore used fewer resources?

Imagining a primary tumor, the researchers crafted a model tumor composed of four types of cancer cells: producers that help construct the tumor's immediate microenvironment; producers that help construct distant, pre-metastatic sites by secreting various molecules; producers that do both of these tasks (and bear twice the cost in resources); and cheaters, which do not contribute to niche construction (and thus sacrifice fewer resources).

Setting up competitive interactions among these various cancer cell subsets and running simulations, the researchers observed that, when tumors were small, producers that contributed to the formation of pre-metastatic niches were more likely to "win" because there were fewer competitors around to overtake them. But once the tumors grew in size, more mutations arose, and thus the pool of competitors increased.

"The mutants that contribute to pre-metastatic niches are more likely to arise in bigger tumors, but are less likely to establish themselves in those tumors," Akçay says. "That's the tradeoff."

"This would predict that some smaller tumors are actually more likely to lead to metastasis," Qian says, a finding supported by recent observations showing that, indeed, cancer-cell mutations that arise early are more likely to be the source of metastatic disease.

"It happens a lot," Qian notes, "that by the time a lot of patients identify the primary tumor, there are already the seeds of metastasis elsewhere in the body. So even if you successfully treat the primary tumor, the metastases could take more years to grow and well up later." While concerning, the study does suggest that cancer therapies may benefit from considering a tumor as an ecosystem, one with clashing and cooperating populations of cells that could be manipulated to a patient's benefit.

"I think you can bring a lot of ecological and evolutionary theory to bear in designing treatments," Akçay says. "There are people who are looking at optimal treatment schedules for controlling the expansions of cell populations and trying to disrupt the dynamics that would allow cancerous and metastatic tumors to grow.

"We're not there yet--our model is still trying to understand the basic idea--but I think ideas like that can eventually find their way into treatment design."

Qian was supported by the Roy and Diana Vagelos Scholars Program in the Molecular Life Sciences.

https://wb.md/2Leif0H

Anticholinergics and Dementia: It's the Drugs

It is well known that anticholinergic medications affect cognition, with long-term exposure linked to dementia

Charles P. Vega, MD

Hello. I'm Dr Charles Vega, and I am a clinical professor of family medicine at the University of California at Irvine. Welcome to Medscape Morning Report, our 1-minute news story for primary care.

It is well known that anticholinergic medications affect cognition, with long-term exposure linked to dementia. Guidelines indicate that they are to be avoided in frail, elderly patients. However, it has been unclear whether the increased risk is specific to the anticholinergic or to the underlying conditions being treated.

A case-control study involving over 300,000 patients suggests that it is the drugs. Antidepressants, drugs for Parkinson's, and urologic meds increase the risk of developing dementia for up to 20 years after exposure.

The data are observational and the associations were moderate, with an odds ratio ranging from 1.1 to 1.6 for exposure to drugs with a known risk for short-term cognitive dysfunction. However, given the high incidence of dementia, the investigators contend that this represents an appreciable risk to patients.

This study reinforces the need for a thorough drug history in our older patients because drugs with anticholinergic properties are out there in many forms.

https://nyti.ms/2Lht3eo

Boulder-Size Clues to How Humans Settled the Americas

Scientists have discovered what they say is “direct evidence” supporting the theory that Ice Age migrants from Asia traveled down the Pacific Coast, rather than through North America’s interior.

By Nicholas St. Fleur

How did early humans first enter the Americas?

After crossing into Alaska, the Ice Age adventurers may have trekked along two routes: either by foot through the interior of present-day Canada through a grassy passageway between two large ice sheets, or they moved south along the Pacific Coast.

Scientists have debated the two theories, and in recent years support for the coastal route has grown from archaeological finds, such as 13,000-year-old footprints on an island in British Columbia. Now, geologists studying boulders and bedrock on Alaska’s southeastern

islands have found evidence of an ice-free route some 17,000 years ago down the coast that would have allowed human travel.

"We're not definitively saying they took the coastal route," said Alia Lesnek, a graduate student at the University at Buffalo and lead author of the study. "We have some of the first direct evidence that that was something that could be done."

Infographic showing study sites. **Bob Wilder/University at Buffalo**

The finding, published Wednesday in the journal Science Advances, supports the theory that the first people to populate the Americas were seafarers traveling from island to island.

In the summer of 2015, Ms. Lesnek hopped out of a helicopter into a grassy valley on Baker Island in southeastern Alaska. There, she spotted a large gray boulder, that to most people may have appeared unremarkable. But to Ms. Lesnek, the rock's smooth surface and rounded edges were clues to its ancient past: it had been plopped onto the landscape thousands of years earlier by giant glaciers.

She took out a power saw with a blade as wide as a grapefruit and with two hands cut into the rock. "It's exciting, but a little bit nerve-racking because it spins really fast and makes a loud noise like 'Reeeiiiinnnn'," Ms. Lesnek said.

After making a chip a few centimeters deep, she used a sledgehammer and chisel to knock the surface piece loose. It was one of the many boulder and bedrock samples she and her colleagues collected from four different islands in the Alexander Archipelago of southeastern Alaska.

Back at the lab, the team determined how long ago the rock samples had been trapped by ice sheets. Glaciers are like slow-moving rivers that pick up rocks and move them. When the ice melts, the boulders are dropped. As they sit on the Earth's surface, they are exposed to cosmic radiation, which the scientists can analyze.

"It's kind of like a rock sunburn," said Ms. Lesnek.

The researchers also dated seal bones from a coastal cave, suggesting that coastal travelers would have had a reliable food source. **Jason Briner**

The team concluded the islands had been covered by ice sheets up until about 15,000 to 17,000 years ago. The finding suggests that the glaciers covering that part of the Pacific Coast melted and possibly created a pathway for humans at the right time.

The dating coincides with recently discovered archaeological and genetic evidence that suggests the first pulse of human migration into the Americas was around 16,000 years ago, the team said. The ice sheets covering Canada's inland corridor did not melt until 13,000 to 14,000 years ago, according to Jason Briner, a geologist at the University at Buffalo and an author on the study.

"Our data suggest the coastal route became available 17,000 years ago," Dr. Briner said. "That's like 4,000 to 3,000 years earlier than when the inland route opened."

The team also dated some seal bones that had been previously discovered in a coastal cave and found that the animals were present around 17,000 years ago. The bones suggested that if people had taken the coastal route they would have found food.

Dr. Briner said their study only looked at about 10 percent of the entire coastal corridor, and that future work will aim to apply the same dating methods on other parts of the route.

"The dates are concordant with other lines of evidence and reliably interpreted," said E. James Dixon, an anthropologist and emeritus

professor at the University of New Mexico who was not involved in the paper. “Although the research does not prove the coastal migration hypothesis, it certainly strengthens it.”

http://bit.ly/2Lk3vNX

One in four intensive care patients return to hospital, study shows

A quarter of intensive care patients are readmitted to hospital shortly after returning home and some of these readmissions are avoidable, research suggests.

High levels of carer stress, difficulty understanding health and social care packages and psychological trauma all contribute to high rates of return, the findings show.

Pinpointing the reasons for unplanned readmissions is key to developing care packages that support patients at home and could save vital funds, researchers say.

After-hospital care packages vary between hospitals but unplanned hospital readmissions are thought to cost the NHS in England £2 billion per year.

The study refers to patients who have had stays in intensive care units (ICU) - specialised wards that look after people who are extremely ill and need close monitoring, including patients with sepsis, car crash victims and those recovering from heart attack.

Findings from more than 55,000 anonymised records from ICU patients in Scotland showed that one in four patients experienced unplanned readmissions within three months of leaving hospital.

Researchers led by the University of Edinburgh interviewed 58 ICU patient volunteers and unpaid carers about their wellbeing, care services and other issues that they felt contributed to their return to hospital.

Findings showed that in some cases, readmission was medically unavoidable and linked to acute illness.

However, around half of the patients felt that their readmission was linked to a 'perfect storm' of factors, including carers stress, psychological trauma after facing near-death and poor understanding of health and social care systems.

Contributing factors that were commonly mentioned by patients and carers were grouped into ten categories including poor communications between acute and community based care and inadequate psychological care.

One patient who took part in the study, said: "I've suffered with depression for 20 years on and off. It's reactive depression and this whole thing has been so traumatic. When I got out of hospital it was a downward spiral..."

Another patient who was interviewed, said: "I have good support from my husband but totally rely on him. Then he wasn't here. He had two weeks work... I was on my own. Not eating properly. I think that's how I ended up in hospital."

Researchers say the findings highlight the need for services to take into account complex psychological and social needs and for patients to be better supported in the months leaving ICU.

The study, published in the journals Thorax and BMJ Quality and Safety, was funded by the Chief Scientist Office, part of the Scottish Government Health Directorates.

Lead researcher, Professor Tim Walsh, Director of the Edinburgh Critical Care Research Group at the University of Edinburgh, said: "This is a fascinating chance to learn from patients and understand avoidable reasons why they might be readmitted to hospital, so that we might spot those most at risk. Our findings show that we have some way to go to improve quality of life for intensive care survivors. "We have launched a further project to improve the care of the most vulnerable patients by bringing together staff and charities working in hospitals, community health and social care."

http://bit.ly/2JbmVnm

Study finds two ancient populations that diverged later 'reconverged' in the Americas

Challenges previous research suggesting that the first people in the Americas split into northern and southern branches

CHAMPAIGN, Ill. -- A new genetic study of ancient individuals in the Americas and their contemporary descendants finds that two populations that diverged from one another 18,000 to 15,000 years ago remained apart for millennia before mixing again. This historic "reconvergence" occurred before or during their expansion to the southern continent.

The study, reported in the journal Science, challenges previous research suggesting that the first people in the Americas split into northern and southern branches, and that the southern branch alone gave rise to all ancient populations in Central and South America.

The study shows for the first time that, deep in their genetic history, many Indigenous people in the southern continent retain at least some DNA from the "northerners" who are the direct ancestors of many Native communities living today in the Canadian east.

"It was previously thought that Indigenous South Americans, and indeed most Native Americans, derived from one ancestry related to the Clovis people, who lived about 13,000 years ago," said Cambridge University archaeology professor Toomas Kivisild, who co-led the research with University of Illinois anthropology professor Ripan Malhi

"We now find that all Native populations in North, Central and South America also draw genetic ancestry from a northern branch most closely related to Indigenous peoples of eastern Canada," Kivisild said. "This cannot be explained by activity in the last few thousand years. It is something altogether more ancient." "We are starting to see that previous models of ancient populations were unrealistically simple," Malhi said.

The researchers analyzed 91 ancient genomes from sites in California and Canada, along with 45 mitochondrial genomes from present-day Native individuals. The work adds to the evidence that two populations diverged 18,000 to 15,000 years ago. This would have been during or after their migration across the now-submerged land bridge from Siberia along what is now coastal Alaska, the researchers report.

Ancient genomes from southwest Ontario show that after the split, Indigenous ancestors representing the northern branch migrated to the Great Lakes region. They may have followed the retreating glacial edges as the most recent ice age began to thaw, the researchers said. Populations representing the southern branch likely continued down the Pacific coast, inhabiting islands along the way, the researchers found.

"The ancient Anzick child from Montana also represents the southern branch and is associated with the Clovis culture, which was once thought to be ancestral to all Native Americans," Malhi said. "The analysis of genomes from ancient peoples from Ontario and California allowed us to identify components of the northern and southern branches in contemporary Central and South American genomes. These components were likely the result of a 'reconvergence' of the two branches deep in time."

"The blending of lineages occurred either in North America, prior to the expansion south, or as people migrated deeper into the southern continent, most likely following the western coast," said Christiana Scheib, the first author of the study who conducted the work while at the University of Cambridge. "We don't have ancient DNA to corroborate how early this northern ancestral branch arrived."

Scheib and Kivisild hold dual appointments at the University of Cambridge and the University of Tartu, in Estonia. Malhi also is an affiliate of the Carl R. Woese Institute for Genomic Biology at the U. of I.

http://bit.ly/2kJ0rQ4

Green tea molecule could prevent heart attacks

Compound breaks-up potentially dangerous protein plaques in blood vessels

Green tea could hold the key to preventing deaths from heart attacks and strokes caused by atherosclerosis, according to research funded by the British Heart Foundation and published in the *Journal of Biological Chemistry*.

Scientists from Lancaster University and the University of Leeds have discovered that a compound found in green tea, currently being studied for its ability to reduce amyloid plaques in the brain in Alzheimer's disease, also breaks up and dissolves potentially dangerous protein plaques found in the blood vessels.

Atherosclerosis is the build-up of fatty material inside our arteries that can reduce the flow of blood to the heart and brain. In advanced stages of the condition, a protein called apolipoprotein A-1 (apoA-1) can form amyloid deposits, which are similar in structure to those associated with Alzheimer's disease. These deposits build up within atherosclerotic plaques. Here, they increase the size of the plaques, further restricting blood flow, and may also make the plaques less stable, increasing the risk of a heart attack or stroke.

Researchers found that epigallocatechin-3-gallate (EGCG), most commonly associated with green tea, binds to the amyloid fibres of apoA-1. This converts the fibres to smaller soluble molecules that are less likely to be damaging to blood vessels.

Now, the team are working on finding ways of introducing effective amounts of EGCG into the bloodstream without it being necessary to drink large and potentially harmful quantities of green tea. This could involve modifying the chemical structure of EGCG, making it easier to be absorbed from the stomach and more resistant to metabolism, or developing new methods to deliver the molecule to the plaques - such as via an injection.

David Middleton, Professor in Chemistry at Lancaster University, said:

"The health benefits of green tea have been widely promoted and it has been known for some time that EGCG can alter the structures of amyloid plaques associated with Alzheimer's disease.

"Our results show that this intriguing compound might also be effective against the types of plaques which can cause heart attacks and strokes."

Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation, said: "Our bodies are very good at breaking down EGCG so swapping your cuppa for green tea is unlikely to make a big difference with respect to your heart health. "But by engineering the molecule slightly, we might be able to make new medicines to treat heart attack and stroke."

Professor Sheena Radford, Director of the Astbury Centre for Structural Molecular Biology at the University of Leeds and co-author of the research, said: "The findings of this round of studies are very encouraging. We now need to apply the best scientific techniques to find how we can take the molecular EGCG element from green tea, and turn it into a functioning tool to combat life-limiting health issues."

http://bit.ly/2Jntir8

Aging-Related Diseases May Be a Negative Outcome of Human Evolution

Genetic adaptations for human brain development also make us vulnerable to Alzheimer's disease, according to a new study.

By Sukanya Charuchandra

While granting human species some advantages over our primate cousins, recent genomic adaptations appear to have come at a cost. Research published last week (May 23) in *Cell Systems* proposes that an evolutionary tradeoff, advantageous in early life, contributes to Alzheimer's and possibly other aging-related diseases.

"I find the idea that genes that have been involved in the development of the human brain and in making the human brain different from the brains of great apes might also be genes that have the byproduct of raising the risk of Alzheimer's is one of those ironic twists that seem to be pretty common in evolutionary biology," says evolutionary biologist Stephen Stearns of Yale University who was not involved in this research.

In 1957, evolutionary biologist George Williams proposed a theory: adaptations that made species more fit in the early years of life likely made them more vulnerable to diseases in the post-reproductive years. However, there has been little research to support his theory.

Han Liang of the University of Texas MD Anderson Cancer Center led a team to test this theory. The researchers started by focusing on enhancers, pieces of DNA with the ability to boost the activities of certain genes, and therefore, the levels of resulting proteins. Previous research had identified enhancers as key to as key to human evolution after diverging from the last common ancestor with chimpanzees. Using FANTOM, an annotated database with information on expression levels of human-specific enhancers, Liang's group compared human data with that of primates to find the fastest evolving enhancers. Comparisons with primates including chimpanzee, gorilla, orangutan, and macaque genomes revealed 93 such enhancers expressed within neurons and neuronal stem cells that had evolved rapidly in humans.

Liang's group found that genes lying close to these enhancers, and therefore possibly under their control, were important for brain development. It is plausible that the enhancers were positively selected for during evolution because of their effects on these brain-related genes. However, they also found evidence of proximal associations between the enhancers and genes implicated in Alzheimer's, Parkinson's disease, type 2 diabetes, hypertension, and osteoporosis. According to Williams's theory, these aging-related diseases would manifest later in life and would go unnoticed during the Darwinian selection process because of the advantage they bestowed in the early years. "Because this happened after reproduction, selection will not see those kinds of change," says Liang.

"I think some of this evidence is correlative," and the associations between the enhancers and aging-related diseases is not definitive evidence of cause-and-effect, says João Pedro de Magalhães, who studies aging at the University of Liverpool in the U.K., and was not involved in this research. However, he agrees that patterns are emerging from Liang's data that imply that "something is indeed going on."

In order to see if there is indeed a functional connection between the enhancers and aging-related diseases, Liang's team used The Cancer Genome Atlas and GTEx, both large databases, to draw up gene maps highlighting all the genes coexpressed with each enhancer. The researchers targeted one such enhancer associated with brain development and also with genes known to be linked to brain diseases. When Liang's group used CRISPR to delete the enhancer in human cell lines, protein abundance from its related genes fell. Importantly, some of these genes are usually suppressed by a gene called *REST*, which keeps Alzheimer's at bay. However, in the presence of the functional enhancer, these genes are boosted. Thus, while this enhancer may be important for brain development, it seemingly opposes *REST*'s protective function against Alzheimer's.

Randolph Nesse, who conducts research to understand the evolutionary origins of diseases at Arizona State University, describes the study as "a wonderful example about how evolutionary thinking and medicine is coming together with advances in genomics to open up a whole new area."

H. Chen et al., "Fast-evolving human-specific neural enhancers are associated with aging-related diseases," **Cell Systems**, *doi:10.1016/j.cels.2018.04.002, 2018.*

http://bit.ly/2kOjFE9

Researchers have identified 121 giant planets that may have habitable moons

We've all heard about the search for life on other planets, but what about looking on other moons?

by Sarah Nightingale

In a paper forthcoming in The *Astrophysical Journal*, researchers at the University of California, Riverside and the University of Southern Queensland have identified more than 100 giant planets that potentially host moons capable of supporting life. Their work will guide the design of future telescopes that can detect these potential moons and look for tell-tale signs of life, called biosignatures, in their atmospheres.

An artist's illustration of a potentially habitable exomoon orbiting a giant planet in a distant solar system. **NASA GSFC: JAY FRIEDLANDER AND BRITT GRISWOLD**

Since the 2009 launch of NASA's Kepler telescope, scientists have identified thousands of planets outside our solar system, which are called exoplanets. A primary goal of the Kepler mission is to identify planets that are in the habitable zones of their stars, meaning it's neither too hot nor too cold for liquid water - and potentially life - to exist.

Terrestrial (rocky) planets are prime targets in the quest to find life because some of them might be geologically and atmospherically similar to Earth. Another place to look is the many gas giants identified during the Kepler mission. While not a candidate for life themselves, Jupiter-like planets in the habitable zone may harbor rocky moons, called exomoons, that could sustain life.

"There are currently 175 known moons orbiting the eight planets in our solar system. While most of these moons orbit Saturn and Jupiter, which are outside the Sun's habitable zone, that may not be the case in other solar systems," said Stephen Kane, an associate professor of planetary astrophysics and a member of the UCR's Alternative Earths Astrobiology Center. "Including rocky exomoons in our search for life in space will greatly expand the places we can look."

The researchers identified 121 giant planets that have orbits within the habitable zones of their stars. At more than three times the radii of the Earth, these gaseous planets are less common than terrestrial planets, but each is expected to host several large moons.

Scientists have speculated that exomoons might provide a favorable environment for life, perhaps even better than Earth. That's because they receive energy not only from their star, but also from radiation reflected from their planet. Until now, no exomoons have been confirmed.

"Now that we have created a database of the known giant planets in the habitable zone of their star, observations of the best candidates for hosting potential exomoons will be made to help refine the expected exomoon properties. Our follow-up studies will help inform future telescope design so that we can detect these moons, study their properties, and look for signs of life," said Michelle Hill, an undergraduate student at the University of Southern Queensland who is working with Kane and will join UCR's graduate program in the fall.

The title of the paper is "Exploring Kepler Giant Planets in the Habitable Zone." In addition to Hill, who is the is lead author, and Kane, other contributors are: Eduardo Seperuelo Duarte from Instituto Federal do Rio de Janeiro in Brazil; Ravi K. Kopparapu from the NASA Goddard Flight Center in Maryland; Dawn M. Gelino from the NASA Exoplanet Science Institute at Caltech; and Robert A. Wittenmyer from University of Southern Queensland.

http://bit.ly/2st2fkq

Walking faster could make you live longer: research

Increased walking pace associated with reduced mortality risk

Speeding up your walking pace could extend your life, research led by the University of Sydney suggests.

Walking at an average pace was found to be associated with a 20 percent risk reduction for all-cause mortality compared with walking at a slow pace, while walking at a brisk or fast pace was associated with a risk reduction of 24 percent.

A similar result was found for risk of cardiovascular disease mortality, with a reduction of 24 percent walking at an average pace and 21 percent walking at a brisk or fast pace, compared to walking at a slow pace.

The protective effects of walking pace were also found to be more pronounced in older age groups.

Average pace walkers aged 60 years or over experienced a 46 percent reduction in risk of death from cardiovascular causes, and fast pace walkers a 53 percent reduction.

Published today, the findings appear in a special issue of the *British Journal of Sports Medicine* (from the BMJ Journals group) dedicated to Walking and Health, edited by lead author Professor Emmanuel Stamatakis from the University of Sydney's Charles Perkins Centre and School of Public Health.

"A fast pace is generally five to seven kilometres per hour, but it really depends on a walker's fitness levels; an alternative indicator is to walk at a pace that makes you slightly out of breath or sweaty when sustained," Professor Stamatakis explained.

A collaboration between the University of Sydney's Charles Perkins Centre and Faculty of Medicine and Health, the University of Cambridge, University of Edinburgh, University of Limerick and University of Ulster, the researchers sought to determine the associations between walking pace with all-cause, cardiovascular disease and cancer mortality.

Linking mortality records with the results of 11 population-based surveys in England and Scotland between 1994 and 2008 - in which participants self-reported their walking pace - the research team then adjusted for factors such as total amount and intensity of all physical activity taken, age, sex and body mass index.

"Walking pace is associated with all-cause mortality risk, but its specific role - independent from the total physical activity a person undertakes - has received little attention until now," Professor Stamatakis said.

"While sex and body mass index did not appear to influence outcomes, walking at an average or fast pace was associated with a significantly reduced risk of all-cause mortality and cardiovascular disease. There was no evidence to suggest pace had a significant influence on cancer mortality however."

In light of the findings, the research team is calling for walking pace to be emphasised in public health messages.

"Separating the effect of one specific aspect of physical activity and understanding its potentially causal association with risk of premature death is complex," Professor Stamatakis said.

"Assuming our results reflect cause and effect, these analyses suggest that increasing walking pace may be a straightforward way for people to improve heart health and risk for premature mortality - providing a simple message for public health campaigns to promote.

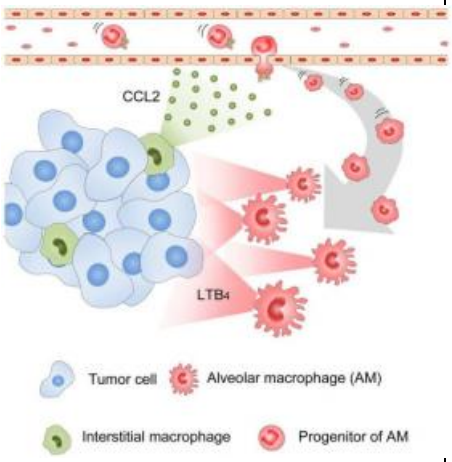
"Especially in situations when walking more isn't possible due to time pressures or a less walking-friendly environment, walking faster may be a good option to get the heart rate up - one that most people can easily incorporate into their lives."

http://bit.ly/2szyGwV

When push comes to shove: Airway cells propel liver cancer spread to lungs

Kanazawa University-led Japanese researchers reveal lung scavenger cells as the driving force behind liver cancer metastasis to the lungs

Kanazawa, Japan - Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and the third biggest cause of death from cancer worldwide. Although HCC patients have benefited from recent improvements in diagnoses and various therapies, their average survival time is still only 16.2 months, falling to just under 6 months in those whose cancer has spread to their lungs.



This is a schematic representation of the presumed dynamics and roles of alveolar macrophages (AMs) in lung metastasis. Interstitial macrophages (IMs) in lung metastatic foci can produce an inflammatory chemokine, CCL2, thereby recruiting blood-borne, CCR2-expressing AMs into lungs. The AMs abundantly produced LTB4, a potent inducer of tumor cell proliferation, and eventually promote the growth of tumor cells in the lung.

Kanazawa University

Lung metastasis occurs when tumor cells from the liver enter the bloodstream. This process involves a range of tumor-host cell interactions, but the exact details have not been known.

Now, a Japanese team of researchers led by Kanazawa University has undertaken a detailed investigation of the role of two different scavenger white blood cells (macrophages) of the lung, and a myriad of molecules associated with inflammation in a mouse model of metastasis. The study was reported in the *Journal of Immunology*.

The animal model was produced by injecting a mouse HCC cell line into the veins of mice, which resulted in the growth of small metastatic lung nodules that resembled HCC lung metastasis in humans.

By monitoring the metastasis, the team detected an accumulation of two types of macrophages in the lungs: interstitial macrophages (IMs) and alveolar macrophages (AMs).

"IMs derive from the circulation, and were already known to aid the survival and growth of lung tumors," study first author Takuto Nosaka says.

"Conversely, AMs come from tissue lining the inside of air sacs (alveoli) in the lungs, and were only recently shown to be involved in metastasis. Their function in lung metastasis was unclear, but their observed increase in this model is the first evidence that they must play an important role."

Indeed, AMs around the mouse lung nodules produced more of the inflammatory lipid leukotriene B4 (LTB4) than IMs.

LTB4 activates immune cells, and directly boosts the proliferation and invasiveness of both human and mouse cancer cells, including HCC cells.

AMs were also shown to directly promote tumor cell growth at metastatic lung nodules through LTB4 secretion.

"We next focused on AM recruitment from the bloodstream into the lungs, and showed that this was controlled by IMs which express the signaling molecule CCL2," corresponding author Naofumi Mukaida explains.

"The CCL2 receptor, CCR2, is expressed by AMs, and binding of the two molecules controls AM accumulation."

This AM-IM interaction contributes to the progression of lung metastasis through the production of LTB4, suggesting the potential for developing a novel treatment approach that targets these molecules.

http://bit.ly/2JsoGzZ

Cell Transplant Trial for Spinal Injury Is Safe

The first human experiment with neural precursor cells implanted to treat chronic spinal cord injury suggests the procedure is safe, and hints at a small benefit.

By Ruth Williams

Four patients with chronic spinal damage and a complete loss of motor and sensory functions below their waists have received transplants of human neural stem cells in a first-of-its-kind clinical trial. A report in *Cell Stem Cell* today (June 1) documents the procedure and the subsequent clinical follow up of the patients, who exhibit no signs of untoward effects but rather tiny hints of improvement.

"It's an extremely interesting and important piece of work," says neurologist Eva Feldman of the University of Michigan who was not involved with the work. "The rodent model results were very compelling and . . . laid the groundwork for this very small, proof-of-concept safety trial."

While these results seem tantalizing, "the numbers [of patients] are extremely small," says Feldman, and "the patients themselves notice no change in function or quality of life."

Three of the four patients were deemed by examiners to have very slight improvements in sensation and muscle movement.

Severe spinal injuries can have devastating consequences, often leaving patients with complete paralysis below the injury site and with little hope of recovery. While there is currently no therapy that can promote neuronal repair in such patients, evidence from animal studies, including those carried out in primates, has indicated that transplantation of human-derived neural stem cells to the site of injury can promote some functional recovery of downstream musculature.

Previous work by Joseph Ciacci and Martin Marsala of the University of California, San Diego, and colleagues has shown that the human neural stem cell line NSI-566, which is approved by the US Food and Drug Administration for use in patients, can improve motor and sensory neuronal function in rat models of spinal cord injury. In their new study, the researchers show that these cells survive long-term in the rats and produce extensive new nerve endings. They also show that the cells cause no adverse reactions in pigs. Based on these and other preclinical studies, the team decided to proceed with a small trial in humans.

Ciacci, Marsala and their team performed cell transplantation on one woman and three men between 24 and 35 years old who had suffered mid-thoracic spinal injuries as a result of motor vehicle accidents. In all cases, the severity of spinal damage was enough to cause a complete loss of motor and sensory functions below the injury site and, after a year, it was deemed that the patients "had essentially no chance of any type of spontaneous recovery," says Ciacci.

Each patient received six intraspinal injections of 200,000 cells per injection, and was assessed for motor and sensory function at regular intervals postoperatively—at two weeks, every month for six months, and every six months thereafter, up to at least 18 months.

None of the patients at any of the follow-up time points reported feeling that they had an improved quality of life. Three of the four patients, however, were deemed by examiners to have very slight improvements in sensation and muscle movement. That is, the patients could feel or move muscles further downstream from the injury than they could prior to treatment.

"The only conclusion one can draw from the results in patients is that the procedure was probably safe," neuroscientist Mark Tuszynski of the Center for Neural Repair at the University of California, San Diego, writes to *The Scientist* in an email.

Tuszynski argues that it might have been premature to do the study because the existing preclinical animal models are not representative of patients with chronic injuries. In the animal studies, he explains, cells were transplanted just one or two weeks after injury, while the patients in the trial had been suffering paralysis for more than a year. “There was never an animal study done to show that this approach could be useful in chronic spinal cord injury, which I think is essential if one is treating chronically injured patients,” Tuszynski writes. “I am not sure why this clinical trial was done when such data was lacking.”

In response, Marsala says that, after a week, “with respect to pathology, [the rats] show a very similar level of injury development” to that of the patients, “so we feel quite confident that it is reflecting the chronic state.”

In conclusion, says Feldman, “the important take-home message of this paper is that there is more work that should be done because clearly the surgery is safe, and maybe or maybe not there is an efficacy signal.”

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https://wb.md/2J7KSjw

The Chinese Cough Syrup That's All the Rage

Question

An increasingly popular traditional medicine remedy, Nin Jiom* pei pa koa *seems to have all the right ingredients to help relieve cough—but does scientific support exist for using this product?

Response from Expert Philip J. Gregory, PharmD
Drug Information Consultant

Nin Jiom *pei pa koa* is a combination product used in traditional Chinese medicine. Although it has been available for decades, it has suddenly achieved stardom as a trendy natural remedy for cough. The remedy also goes by the abbreviated name *pei pa koa*, which is its original traditional Chinese medicine name. When it began to be commercially manufactured by the Nin Jiom Medicine Manufactory in 1946, the words "Nin Jiom" were added to the name, which means "remembrance of the mother."[1,2]

Available as a lozenge or as syrup, the product contains 16 different ingredients, with honey, Sichuan fritillary, Chinese licorice, apricot seed extract, and loquat present in the largest quantities (Table).

Honey, the largest-quantity ingredient, provides about 800 mg per 15-mL dose. Of all the ingredients, honey has the best evidence supporting its use for cough. A Cochrane review of clinical trials that evaluated honey for cough in children found that it was more effective than diphenhydramine or placebo but not as effective as dextromethorphan for reducing cough frequency.[3] Largely on the basis of these findings, a recent expert panel report also suggested honey as an option for cough in pediatric patients older than 1 year.[4]

Sichuan fritillary (*Fritillaria verticillata*), also known as *chuan bei mu*, has a long history of traditional use as an antitussive and expectorant agent. Multiple isolated constituents have been found to have antitussive and anti-inflammatory effects in animal models.[5] However, clinical research has not confirmed these effects in humans.

Chinese licorice (*Glycyrrhiza uralensis*), also known as *gan coa*, is also traditionally used as an antitussive and expectorant. Licorice constituents are thought to reduce inflammation of the laryngeal mucosa, thereby reducing cough. Clinical research shows that preoperative use of licorice lozenges or a licorice-containing gargle can significantly reduce postoperative sore throat and related cough compared with placebo.[6,7]

Apricot seed (*Prunus armeniaca*), also known as *xing ren*, is commonly used in traditional Chinese medicine as an antitussive. The seed contains amygdalin, which can be hydrolyzed in the gut to produce small amounts of cyanic acid. The cyanic acid constituent is thought to produce the antitussive effect. This constituent can

produce cyanide toxicity, especially in children. Several cases have been documented of serious cyanide toxicity in children consuming apricot seeds.[8] Because of this safety hazard, parents should be advised against using this product for their children.

Loquat (*Eriobotrya japonica*), like many of the other ingredients in the product, has traditionally been used for cough and other respiratory conditions, such as bronchitis and asthma. Extracts of the loquat leaf have been found to have anti-inflammatory and analgesic effects, possibly owing to weak opioid agonist action, in animal models.[9,10] However, these effects have not been documented clinically.

The other ingredients in the product are present in relatively small quantities. Historically, most have been used for cough or as an expectorant in traditional Chinese medicine formulations. However, clinical evidence supporting these ingredients for such uses is lacking.

Table. Labeled Ingredients in 1 Tablespoon (15 mL) of Nin Jiom Pei Pa Koa

Ingredient	Amount	Comment
Honey	***813 mg***	***Reduces cough frequency, but not as effective dextromethorphan[3]***
Sichuan fritillary (bulb)	***179 mg***	***Antitussive and anti-inflammatory effects in animal models[5]***
Chinese licorice (root)	***164 mg***	***Clinical research shows that it can lower postoperative sore throat and cough[6,7]***
Apricot seed extract	***45 mg***	***Concerns about cyanide toxicity[8]***
Loquat (leaf)	***41 mg***	***Anti-inflammatory and analgesic effects in animal models[9,10]***
Coltsfoot (flower bud)	***25 mg***	***Traditional use as an expectorant and antitussive[11]***
Polygala (root)	***25 mg***	***Traditional use as an expectorant[11]***
Pummelo (peel)	***25 mg***	***Traditional use as an expectorant and antitussive[11]***
Platycodon (root)	***15 mg***	***Traditional use as an expectorant and for sore throat[11]***
Menthol	***7 mg***	***Counterirritant effects[11,12]***
Adenophora (root)	***6 mg***	***Traditional use as an expectorant for bronchitis and whooping cough[11]***
Ginger (fresh rhizome)	***6 mg***	***Traditional use as an anti-inflammatory and antipyretic[11]***
Poria (sclerotium)	***6 mg***	***Traditional use as an antitussive; some evidence of anti-inflammatory effects[12]***
Tricosanthes (seed)	***6 mg***	***Traditional use as an expectorant and antitussive[11]***
Apricot (seed)	***4 mg***	***Concerns about cyanide toxicity[8]***
Schisandra (fruit)	***1 mg***	***Traditional use as an expectorant and for influenza[11]***

From a traditional medicine perspective, Nin Jiom *pei pa koa* has all the right ingredients to help relieve cough—but from an evidence-based medicine perspective, very little scientific support exists for using this product. Two primary ingredients, honey and Chinese licorice, have some evidentiary support for relieving cough; evidence for most other ingredients is speculative at best.

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http://bit.ly/2JeMW5h

New Liquid Biopsy Detects Cancer at Earlier Stages Than Currently Possible

The test can pick up several types of cancer, including pancreatic and ovarian, years before symptoms appear.

By Jim Daley | June 1, 2018

A new liquid biopsy test could detect cancer years before symptoms are apparent, according to research presented today (June 1) at the American Society of Clinical Oncologists (ASCO) meeting in Chicago. The test—a noninvasive blood draw followed by DNA screening—could lead to dramatic changes in cancer treatment, say researchers.

“This is potentially the holy grail of cancer research, to find cancers that are currently hard to cure at an earlier stage when they are easier to cure, and we hope this test could save many lives,” lead author Eric Klein, an oncologist at the Cleveland Clinic in Ohio, tells *The Telegraph*. The test “gives us the opportunity to find them months or years before someone would develop symptoms and be diagnosed.”

Klein’s research team collected 1,627 blood draws from 878 patients with untreated, newly diagnosed cancer and 749 healthy controls. Three DNA tests were used to screen the samples. Of them, the most sensitive was able to spot cancers 90 percent of the time.

Together, the three tests were able to detect 10 different types of cancer, including colorectal, esophageal, lung, pancreatic, and ovarian. They were less effective at detecting stomach, uterine, and early-stage prostate cancer, according to the ASCO abstract.

The liquid biopsy is not yet ready for the clinic, according to the researchers, but its development marks a significant advance in the fight against cancer, says Simon Stevens, the chief executive of NHS England who was not involved in the study. Stevens tells *The Guardian* “new techniques” such as cancer blood tests could “unlock enormous survival gains,” for cancer patients. “[W]e stand on the cusp of a new era of personalized medicine that will dramatically transform care for cancer and for inherited and rare diseases.”

https://bbc.in/2st3JLM

Prostate cancer immune system drug results could be 'spectacular'

Drugs that boost the immune system have saved the lives of some men with terminal prostate cancer, say doctors in the UK.

By James Gallagher Health and science correspondent, BBC News

The team at the Institute of Cancer Research and the Royal Marsden Hospital in London said the results were "spectacular" and a "big deal". However, the therapy will not work for most patients. Cancer Research UK said the next step was to predict who would respond.

Immunotherapy is transforming the treatment of cancer and is now part of routine practice for some skin and lung cancers. It works by taking the brakes off a patients' own immune system so it can attack a tumour. An early stage trial, presented at the world's biggest meeting of cancer doctors and scientists in Chicago, is the first to show that this approach works on prostate cancer too.

In the UK, the disease is the most common cancer in men and it has recently overtaken breast cancer to become the third biggest killer.

Michael English, 72, was one of 258 men who took part in the trial.
He was first diagnosed in 2005, but radiotherapy, chemotherapy and hormone-based therapies did not kill his cancer. Two years ago, he was given the immunotherapy drug pembrolizumab.
He said: "We were astonished when scans showed that the tumour had become undetectable. "Today I'm effectively cancer-free." He says he's now planning out the next 20 years of his life, not the next two.
Researcher Prof Johann de Bono told the BBC: "This is the first evidence that a subset of prostate cancer patients do spectacularly well on immunotherapy. "We have several patients in the Marsden who have had a complete response. "It is a new arrow in the quiver for men with lethal prostate cancer, it's a big deal for these patients."
However, he said that only between 10% and 15% of patients had any response to the therapy at all.
This is an approach that will not help the majority of men.
That is not unusual for immunotherapy. It seems to work incredibly well for a handful of patients, have a temporary effect in others, and do nothing for the rest. The team in London have seen hints that it works best in patients with the most heavily-mutated cancers.
Nell Barrie, from Cancer Research UK, said: "The next step will be to find out how to tell which men will benefit from taking this drug. "This is important as although immunotherapy is exciting, it can have severe side effects."

How immunotherapy drugs work

Your immune system is trained to fight infection, but it also attacks parts of the body if they malfunction - such as in cancers. However, tumours have a few tricks up their sleeve in order to survive.
They can produce a protein called PD-L1 which switches off any part of the immune system that tries to attack them.
Pembrolizumab is one of a suite of drugs called "checkpoint inhibitors" being developed by pharmaceutical companies.
They stop cancers turning off the immune system so the body can keep on attacking the tumour. The findings were presented at the annual meeting of the American Society of Clinical Oncology.

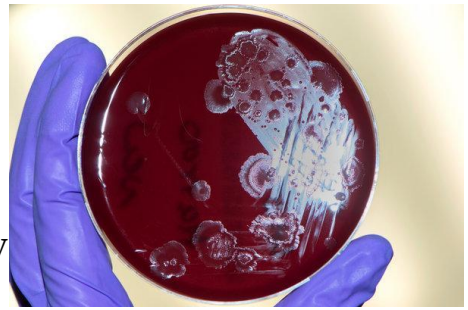
https://nyti.ms/2LnjFpV

Antibiotics Weren't Used to Cure These Patients. Fecal Bacteria Were.

In a small study, doctors used so-called fecal transplants to treat a serious gut infection in patients. The transplants, from healthy donors, were as effective as antibiotics.

By Gina Kolata

The bacteria can take over a person's intestines and be difficult to eradicate. The infection causes fever, vomiting, cramps and diarrhea so severe that it kills 14,000 people a year in the United States alone.
The first line of treatment for the attacking microbes, called Clostridium difficile, is antibiotics. But a group of Norwegian researchers asked if something more unusual — an enema containing a stew of bacteria from feces of healthy people — might work just as well.



C. difficile kills 14,000 people annually in the United States. A new study finds that transplanting healthy bacteria into a person's intestines is just as effective antibiotic treatment. **Louise Murray/Science Source**

The answer, according to a report today in the New England Journal of Medicine, is yes.
Until now, there has never been a clinical trial conducted in more than one medical center that has investigated so-called fecal transplants as a first therapy for C. difficile infections, said Dr. Michael Bretthauer, a gastroenterologist at the University of Oslo and lead author of the new study.

The Food and Drug Administration permits fecal transplants and professional societies endorse them, but only a last resort for treating C. difficile infections after antibiotics have failed, said Dr. Alexander Khoruts, a gastroenterologist at the University of Minnesota.

"The F.D.A. and all the professional societies are in full agreement on this point," he said.

Several small clinical trials and doctors' clinical experience have shown that a fecal transplant can help in that desperate situation.

"It's definitely a paradigm shift to use it earlier rather than later," Dr. Nasia Safdar, an infectious disease specialist at the University of Wisconsin — Madison.

The study, conducted in Norway, was small — just 20 patients randomly assigned to get the fecal bacteria or antibiotics. That's not enough to determine whether transplants are better than antibiotics.

Instead, the research was intended to show that treatment with fecal bacteria is no worse.

Five out of nine patients who received fecal bacteria were cured immediately of their infections, compared to five of 11 in the group getting antibiotics. Three of the four remaining patients who got fecal bacteria then got antibiotics; two were cured within days.

None of the antibiotic patients whose symptoms persisted after their first round of treatment were cured with a second round of the drugs.

Although the results seem to favor treatment with fecal bacteria, the difference was not large enough to say fecal transplants were actually superior to the drugs. The researchers are planning to start a more definitive study with 200 patients this summer.

The idea behind fecal transplants is to provide a dose of healthy gut bacteria that multiply and crowd out the dangerous germs making patients ill. The bacteria can be extracted from feces and supplied as an enema or in a capsule that patients swallow.

A small company also grows fecal bacteria in a lab and freezes them for transplants. The Norwegian study relied on that company to supply fecal bacteria, but the investigators say the company had no other role in the study.

Researchers are exploring the use of fecal transplants for a variety of conditions, Dr. Bretthauer said, ranging from bowel diseases such as Crohn's disease and ulcerative colitis "to more far-fetched things, such as multiple sclerosis."

So far, he added, the most promising evidence for the fecal transplant's effectiveness is in ulcerative colitis.

One problem with using fecal transplants as a treatment of last resort for C. difficile infections, Dr. Khoruts said, is that it can take a long time for patients to overcome their aversion. On average, he said, these patients struggle through ten months of futile antibiotic treatments before they try a fecal transplant.

Still, some patients newly diagnosed with C. difficile ask Dr. Khoruts why can't they just get a fecal transplant right away. Their reasoning makes sense, he added. Antibiotics that destroy the normal bacteria that protect against C. difficile are the main reason patients developed the infection in the first place.

Transplants, Dr. Khoruts said, "are trying to repair what was broken in the first place, rather than perpetuate the damage."

But when Dr. Bretthauer and his colleagues proposed a study testing fecal transplants compared to antibiotics in newly diagnosed patients, other doctors were not enthusiastic.

"Using feces is a little taboo," Dr. Bretthauer said. "If you are putting someone else's feces into a patient, there has to be a good reason."

And, he said, antibiotics are an approved treatment. Doctors are familiar with the drugs. The ethics board that had to approve the clinical trial suggested a small pilot study instead.

The trial was difficult to set up. The challenge was to get to patients before they were given antibiotics.

"We made friends with the hospital lab which did the C. difficile fecal testing," Dr. Bretthauer said. The laboratory technicians agreed to alert the researchers to new C. difficile cases.

The researchers then rushed to the doctors and asked them to delay giving antibiotics until the patients were asked to enter the study.

The results of the study, Dr. Bretthauer said, "speak for themselves." But not until a larger trial is completed will he have convincing results that could change clinical practice.

Dr. Khoruts said that in he will wait for the large clinical trial before using fecal transplants as a first-line therapy against C. difficile.

But "if you asked me what if my mother had it?" Then, he said, "I wouldn't wait" to offer her a fecal transplant.

https://nyti.ms/2J9IWXX

Good News for Women With Breast Cancer: Many Don't Need Chemo

Many women with early-stage forms of the disease can forego chemo, based on a test that measures the activity of genes involved in breast cancer recurrence.

By DENISE GRADY JUNE 3, 2018

Many women with early-stage breast cancer who would receive chemotherapy under current standards do not actually need it, according to a major international study that is expected to quickly change medical treatment.

"We can spare thousands and thousands of women from getting toxic treatment that really wouldn't benefit them," said Dr. Ingrid A. Mayer, from Vanderbilt University Medical Center, an author of the study. "This is very powerful. It really changes the standard of care."

The study found that gene tests on tumor samples were able to identify women who could safely skip chemotherapy and take only a drug that blocks the hormone estrogen or stops the body from making it. The hormone-blocking drug tamoxifen and related medicines, called endocrine therapy, have become an essential part of treatment for most women because they lower the risks of recurrence, new breast tumors and death from the disease.

"I think this is a very significant advance," said Dr. Larry Norton, of Memorial Sloan Kettering Cancer Center in New York. He is not an author of the study, but his hospital participated. "I'll be able to look people in the eye and say, 'We analyzed your tumor, you have a really good prognosis and you actually don't need chemotherapy.' That's a nice thing to be able to say to somebody."

The findings apply to about 60,000 women a year in the United States, according to Dr. Joseph A. Sparano of Montefiore Medical Center in New York, the leader of the study.

"The results indicate that now we can spare chemotherapy in about 70 percent of patients who would be potential candidates for it based on clinical features," Dr. Sparano said.

But Dr. Sparano and Dr. Mayer added a note of caution: The data indicated that some women 50 and younger might benefit from chemo even if gene-test results suggested otherwise. It is not clear why. But those women require especially careful consultation, they said. (Most cases of breast cancer occur in older women: The median age at diagnosis in the United States is 62.)

The study, called TAILORx, is being published by The New England Journal of Medicine and was to be presented on Sunday at a meeting of the American Society of Clinical Oncology in Chicago. The study began in 2006 and was paid for by the United States and Canadian governments and philanthropic groups. Genomic Health, the company that makes the gene test, helped pay after 2016.

This year, about 260,000 new cases of breast cancer are expected in women in the United States, and 41,000 deaths. Globally, the most recent figures are from 2012, when there were 1.7 million new cases and more than half-a-million deaths.

Chemotherapy can save lives, but has serious risks that make it important to avoid treatment if it is not needed. In addition to the hair

loss and nausea that patients dread, chemo can cause heart and nerve damage, leave patients vulnerable to infection and increase the risk of leukemia later in life. TAILORx is part of a wider effort to fine-tune treatments and spare patients from harsh side effects whenever possible.

Endocrine therapy also has side effects, which can include hot flashes and other symptoms of menopause, weight gain and pain in joints and muscles. Tamoxifen can increase the risk of cancer of the uterus.

Patients affected by the new findings include women who, like most in the study, have early-stage breast tumors measuring one to five centimeters that have not spread to lymph nodes; are sensitive to estrogen; test negative for a protein called HER2; and have a score of 11 to 25 on a widely used test that gauges the activity of a panel of genes involved in cancer recurrence.

The gene test, called Oncotype DX Breast Cancer Assay, is the focus of the study. Other gene assays exist, but this one is the most widely used in the United States. It is performed on tumor samples after surgery, to help determine whether chemo would help. The test is generally done for early-stage disease, not more advanced tumors that clearly need chemo because they have spread to lymph nodes or beyond.

The test, available since 2004, gives scores from 0 to 100. It costs about $3,000, and insurance usually covers it. Previous research has shown that scores 10 and under do not call for chemotherapy, and scores over 25 do. But most women who are eligible for the test have scores from 11 to 25, which are considered intermediate.

“This has been one of the large unanswered questions in breast cancer management in recent times, what to do with patients with intermediate scores,” Dr. Norton said. “What to do has been totally unknown.” He added, “A lot of patients in that range are getting chemo.”

Dr. Sparano said many patients have been receiving chemo because in 2000 the National Cancer Institute recommended it for most women, even those whose disease had not spread to lymph nodes, based on studies showing it could prevent the cancer from recurring elsewhere in the body and becoming incurable.

“Recurrences were being prevented, and lives prolonged,” Dr. Sparano said. “But we were probably overtreating a lot of these women. For every 100 women we were treating, we were probably preventing about 4 distant recurrences.” Dr. Mayer said, “We couldn’t figure out who we really needed to treat.”

The availability of the gene test in 2004 helped researchers sort out women with very high or very low risk.

“But we really didn’t know what to do with women in the middle,” Dr. Mayer said. “Some seemed to benefit and some didn’t. We were back to square zero, safe rather than sorry, giving chemo to a lot who didn’t need it.”

Data began to emerge suggesting that women in the middle were not being helped by chemo, and many doctors began recommending it less often. But a definitive study was needed, which is how TAILORx came about.

The study began in 2006 and eventually included 10,253 women ages 18 to 75. Of the 9,719 patients with complete follow-up information, 70 percent had scores of 11 to 25 on the gene test. They had surgery and radiation, and then were assigned at random to receive either endocrine therapy alone, or endocrine therapy plus chemo. The median follow-up was more than seven years.

Over time, the two groups fared equally well. Chemo had no advantage. After nine years, 93.9 percent were still alive in the endocrine-only group, versus 93.8 percent in those who also got chemo. In the endocrine group, 83.3 percent were free of invasive disease, compared with 84.3 percent who got both treatments. There were no significant differences.

But the researchers wrote that the chemotherapy benefit varied with the combination of recurrence score and age, “with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.”

Bari Brooks, 58, a patient of Dr. Mayer’s from White House, Tenn., learned from a mammogram that she had breast cancer in 2009 when she was 49. Dr. Mayer told her she was a candidate for chemo, and also for the study — in which she might or might not get chemo.

Could she handle the risk of missing out on a treatment that might save her life? Or the risk of side effects that might be needless? “It wasn’t even a decision I had to think about,” said Ms. Brooks, who works in human relations for Vanderbilt University. “It was yes, I want to do it.”

She added: “You realize how insignificant everything is. Money, it doesn’t matter how much you have. Work, what projects you have, it doesn’t matter. What have I contributed in my life and what do I want to contribute? This was a situation where I could also contribute. I was honored and grateful to be part of it.”

She decided that if she was assigned to chemo, “I would approach it that I was being cleansed rather than poisoned.” She did land in the group that got both chemo and endocrine therapy. Did the chemo help?

Maybe, maybe not. She has no regrets. And no evidence of cancer.

Dr. Mayer said that Ms. Brooks’ philosophical attitude was not unusual, and that women who signed up for studies understood they were taking a leap of faith and might wind up getting the ‘wrong’ or less desirable treatment.

“They’re grateful that they helped to advance knowledge for other women,” Dr. Mayer said. “I never underestimate how nice and how altruistic people can be. Women look out for each other.”

http://bit.ly/2JcJDe

Study shows taking aspirin before or after coronary

Artery bypass graft is associated with a lower risk of death

New research presented at this year's Euroanaesthesia congress in Copenhagen, Denmark shows that in patients undergoing a coronary artery bypass graft (CABG) surgery, taking aspirin before and after surgery is associated with an 18% to 34% reduced mortality risk after 4 years. The study is by Professor Jianzhong Sun, Director of Clinical Outcomes Research at the Department of Anesthesiology, Thomas Jefferson University and Hospitals, Philadelphia, USA, and colleagues.

CABG surgery is used to restore normal blood flow to an obstructed artery in the heart. Cardiac surgery frequently provokes a state of extreme and complex stress with a greatly elevated risk of blood clots and an increased predisposition to long-term vascular disease and mortality. It is hoped that perioperative aspirin (taken before and after the operation) may reduce these adverse effects.

Preoperative and postoperative uses of aspirin are defined as within 5 days preceding surgery and continuously on discharge respectively. The discharge prescription of aspirin often is indicated for patients with CABG and it should be continued indefinitely, except for patients with contraindications. The reported rates of patient aspirin adherence for cardiovascular protection are high, range from 72% to 92% in the literature.

Most previous studies on aspirin's effects in cardiac surgery were limited by the length of follow-up. And little is known about perioperative aspirin's effect on the long-term survival in patients undergoing CABG surgery. This study from institutions in the US and China studied the effects of perioperative aspirin on long-term mortality in patients undergoing coronary artery bypass graft (CABG).

The team looked at the medical records of 9,584 patients who received cardiac surgery in three hospitals, selecting the 4,132 individuals who underwent CABG. This selection was then further divided into four groups; in which patients had one of preoperative or postoperative aspirin, both, or neither.

Among the studied patients, 76.5% received preoperative aspirin, 23.5% did not, 92.3% received postoperative aspirin, and just 7.7% did not. Patients taking preoperative aspirin were significantly more likely to have other risk factors including smoking, diabetes, peripheral vascular disease, angina, high blood pressure, and previous heart attacks.

For patients taking preoperative aspirin, 4-year mortality was 14.8% versus 18.1% for those not taking preoperative aspirin, a statistically significant mortality reduction of 18%. For postoperative aspirin, there was a larger mortality reduction: those taking aspirin had a 4-year mortality rate of 10.7%, compared with 16.2% in the non-aspirin patients -- a statistically significant mortality reduction of 34%.

Professor Sun says: "Our study showed that aspirin was associated with similar effectiveness to other proven medical treatments in patients with cardiovascular disease, such as statins and ACE inhibitors."

He concludes: "Among patients undergoing CABG, perioperative uses of aspirin were associated with significant reduction in 30-day mortality and improvement in long-term survival, without significant increased postoperative bleeding complications. We believe that all patients undergoing CABG should take aspirin before and after the procedure, except those for whom aspirin is contraindicated."