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Far from special: Humanity's tiny DNA differences are 'average' in animal kingdom

Paper offers new insights into evolution; as with humans, over 90 percent of animal species today likely originated 100,000-200,000 years ago

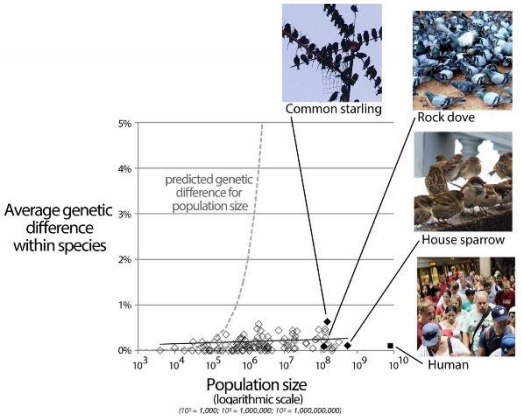
Researchers report important new insights into evolution following a study of mitochondrial DNA from about 5 million specimens covering about 100,000 animal species.

Mining "big data" insights from the world's fast-growing genetic databases and reviewing a large literature in evolutionary theory, researchers at The Rockefeller University in New York City and the Biozentrum at the University of Basel in Switzerland, published several conclusions today in the journal Human Evolution. Among them:

- ***In genetic diversity terms, Earth's 7.6 billion humans are anything but special in the animal kingdom. The tiny average genetic difference in mitochondrial sequences between any two individual people on the planet is about the same as the average genetic difference between a pair of the world's house sparrows, pigeons or robins. The typical difference within a species, including humans, is 0.1% or 1 in 1,000 of the "letters" that make up a DNA sequence.***
- ***Genetic variation - the average difference in mitochondria DNA between two individuals of the same species - does not increase with population size. Because evolution is relentless, however, the lack of genetic variation offers insights into the timing of a species' emergence and its maintenance.***
- ***The mass of evidence supports the hypothesis that most species, be it a bird or a moth or a fish, like modern humans, arose recently and have not had time to develop a lot of genetic diversity. The 0.1% average genetic diversity within humanity today corresponds to the divergence of modern humans as a distinct species about 100,000 - 200,000 years ago - not very long in evolutionary terms. The same is likely true of over 90% of species on Earth today.***
- ***Genetically the world "is not a blurry place." Each species has its own specific mitochondrial sequence and other members of the same species are identical or tightly similar. The research shows that species are "islands in sequence space" with few intermediate "stepping stones" surviving the evolutionary process.***

Among 1st "big data" insights from a growing collection of mitochondrial DNA

"DNA barcoding" is a quick, simple technique to identify species reliably through a short DNA sequence from a particular region of an organism. For animals, the preferred barcode regions are in mitochondria - cellular organelles that power all animal life. (See also http://bit.ly/2HGduvD)



The study results represent a surprise given predictions found in textbooks, and based on mathematical models of evolution, that the bigger the population of a species, the greater the genetic variation one expects to find. In fact, the mitochondrial diversity within 7.6 billion humans or 500 million house sparrows or 100,000 sandpipers from around the world is about the same. The paper notes, however, that evolution is relentless, that species are always changing, and, therefore, the degree of variation within a given species offers a clue into how long ago it emerged distinctly -- in other words, the older the species the greater the average genetic variation between its members. **The Rockefeller University**

The new study, "Why should mitochondria define species?" relies largely on the accumulation of more than 5 million mitochondrial barcodes from more than 100,000 animal species, assembled by scientists worldwide over the past 15 years in the open access

GenBank database maintained by the US National Center for Biotechnology Information.

The researchers have made novel use of the collection to examine the range of genetic differences within animal species ranging from bumblebees to birds and reveal surprisingly minute genetic variation within most animal species, and very clear genetic distinction between a given species and all others.

"If a Martian landed on Earth and met a flock of pigeons and a crowd of humans, one would not seem more diverse than the other according to the basic measure of mitochondrial DNA," says Jesse Ausubel, Director of the Program for the Human Environment at The Rockefeller University, where the research was led by Senior Research Associate Mark Stoeckle and Research Associate David Thaler of the University of Basel, Switzerland.

"At a time when humans place so much emphasis on individual and group differences, maybe we should spend more time on the ways in which we resemble one another and the rest of the animal kingdom."

Says Dr. Stoeckle: "Culture, life experience and other things can make people very different but in terms of basic biology, we're like the birds."

"By determining the genetic variety within species of the animal kingdom, made possible only recently by the burgeoning number of DNA sequences, we've documented the absence of human exceptionalism."

Says. Dr. Thaler: "Our approach combines DNA barcodes, which are broad but not deep, from the entire animal kingdom with more detailed sequence information available for the entire mitochondrial genome of modern humans and a few other species. We analyzed DNA barcode sequences from thousands of modern humans in the same way as those from other animal species."

"One might have thought that, due to their high population numbers and wide geographic distribution, humans might have led to greater genetic diversity than other animal species," he adds. "At least for mitochondrial DNA, humans turn out to be low to average in genetic diversity."

"Experts have interpreted low genetic variation among living humans as a result of our recent expansion from a small population in which a sequence from one mother became the ancestor for all modern human mitochondrial sequences," says Dr. Thaler.

"Our paper strengthens the argument that the low variation in the mitochondrial DNA of modern humans also explains the similar low variation found in over 90% of living animal species - we all likely originated by similar processes and most animal species are likely young."

Genetic variation does not increase with population

The study results represent a surprise given predictions found in textbooks, and based on mathematical models of evolution, that the bigger the population of a species, the greater the genetic variation one expects to find.

"Is genetic diversity related to the size of the population?" asks Dr. Stoeckle. "The answer is no. The mitochondrial diversity within 7.6 billion humans or 500 million house sparrows or 100,000 sandpipers from around the world is about the same."

The paper notes, however, that evolution is relentless, that species are always changing, and, therefore, the degree of variation within a given species offers a clue into how long ago it emerged distinctly -- in other words, the older the species the greater the average genetic variation between its members.

Evolutionary bottlenecks: the fresh new beginning of a species

While asteroids and ice ages have played major roles in evolutionary history, scientists speculate that another great driver may have been the microbial world, notably viruses, which periodically cull populations, leaving behind only those able to survive the deadly challenge.

"Life is fragile, susceptible to reductions in population from ice ages and other forms of environmental change, infections, predation, competition from other species and for limited resources, and interactions among these forces," says Dr. Thaler. Adds Dr. Thaler, "The similar sequence variation in many species suggests that all of animal life experiences pulses of growth and stasis or near extinction on similar time scales."

"Scholars have previously argued that 99% of all animal species that ever lived are now extinct. Our work suggests that most species of animals alive today are like humans, descendants of ancestors who emerged from small populations possibly with near-extinction events within the last few hundred thousand years."

'Islands in sequence space'

Another intriguing insight from the study, says Mr. Ausubel, is that "genetically, the world is not a blurry place. It is hard to find 'intermediates' - the evolutionary stepping stones between species. The intermediates disappear."

Dr. Thaler notes: "Darwin struggled to understand the absence of intermediates and his questions remain fruitful."

"The research is a new way to show that species are 'islands in sequence space.' Each species has its own narrow, very specific consensus sequence, just as our phone system has short, unique numeric codes to tell cities and countries apart."

Adds Dr. Thaler: "If individuals are stars, then species are galaxies. They are compact clusters in the vastness of empty sequence space."

The researchers say that with the bones or teeth of an ancient hominid, like those found in southern France or northern Spain, scientists might shed further light on the rate of evolution of the human species.

"It would be very exciting if over the next few years physical anthropologists and others were able to compare mitochondrial DNA from hominid species over the last 500,000 years," says Dr. Stoeckle.

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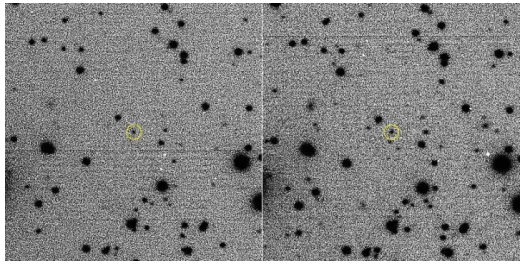
First interstellar immigrant discovered in the solar system

A new study has discovered the first known permanent immigrant to our Solar System.

The asteroid, currently nestling in Jupiter's orbit, is the first known asteroid to have been captured from another star system. The work is published in *Monthly Notices of the Royal Astronomical Society: Letters*.

The object known as 'Oumuamua was the last interstellar interloper to hit the headlines in 2017. However it was just a tourist passing through, whereas this former exo-asteroid - given the catchy name (514107) 2015 BZ509 - is a long-term resident.

All of the planets in our Solar System, and the vast majority of other objects as well, travel around the Sun in the same direction. However 2015 BZ509 is different - it moves in the opposite direction in what is known as a 'retrograde' orbit.



These are images of 2015 BZ509 obtained at the Large Binocular Telescope Observatory (LBTO) that established its retrograde co-orbital nature. The bright stars and the asteroid (circled in yellow) appear black and the sky white in this negative image. **C. Veillet / Large Binocular Telescope Observatory**

"How the asteroid came to move in this way while sharing Jupiter's orbit has until now been a mystery," explains Dr Fathi Namouni, lead author of the study. "If 2015 BZ509 were a native of our system, it should have had the same original direction as all of the other planets and asteroids, inherited from the cloud of gas and dust that formed them."

However the team ran simulations to trace the location of 2015 BZ509 right back to the birth of our Solar System, 4.5 billion years ago when the era of planet formation ended. These show that 2015 BZ509 has always moved in this way, and so could not have been there originally and must have been captured from another system.

"Asteroid immigration from other star systems occurs because the Sun initially formed in a tightly-packed star cluster, where every star had its own system of planets and asteroids," comments Dr Helena Morais, the other member of the team.

"The close proximity of the stars, aided by the gravitational forces of the planets, help these systems attract, remove and capture asteroids from one another."

The discovery of the first permanent asteroid immigrant in the Solar System has important implications for the open problems of planet formation, solar system evolution, and possibly the origin of life itself.

Understanding exactly when and how 2015 BZ509 settled in the Solar System provides clues about the Sun's original star nursery, and about the potential enrichment of our early environment with components necessary for the appearance of life on Earth.

http://bit.ly/2x5ab04

People voyaged to Australia by boat more than 50,000 years ago

Australia was first reached by sizeable groups of people deliberately voyaging between islands

May 21, 2018 by David Stacey, University of Western Australia

Researchers working to solve the mystery of how people first reached Australia have combined sophisticated deep sea mapping, voyage simulation techniques and genetic information to show that arrival was made by sizeable groups of people deliberately voyaging between islands.

Using cutting-edge modelling, similar to techniques used to search for the wreckage of missing Malaysian Airlines plane MH370, the research team, including Professor Peter Veth from The University of Western Australia, researchers from James Cook University, the Australian Centre for Ancient DNA and CSIRO, with the Centre for Excellence for Australian Biodiversity and Heritage (CABAH), simulated hundreds of possible voyaging routes to track likely routes of vessels leaving three sites on the islands of Timor and Roti. They took many factors into account, including winds, ocean currents and paddling.

UWA Archaeology Discipline Chair Dr. Sven Ouzman said the study provided a welcome new insight into the kind of people who first set foot on Australia's shores.

"These would have been skilled maritime navigators who set out on a deliberate voyage to discover new lands," Dr. Ouzman said.

"The coastline of Australia was a very different shape 50,000 years ago but it was not joined to other continents by land. There was a string of islands to the north of Australia and the voyagers would have travelled through them to reach mainland Australia. This was a carefully planned act by a significant number of people – the founding population may have been as high as 100—200.

"The findings provide evidence that the First Australians were skilled in construction of boats, navigation, and planning. This research should help change a perception that the settling of Australia started with a handful of people arriving here by accident, and then losing all ability to use watercraft."

The study, published in the leading journal *Quaternary Science Reviews*, builds on work by UWA, JCU, CABAH and other researchers that revealed a string of more than 100 habitable but now submerged islands strung off the Kimberley coast of northwest Australia were among the first landing points.

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Chimpanzees eat plants that point to new ways of treating diseases

New diseases have led to searches for new solutions, including natural substances, like medicinal plants

Ahoua Constant*

As cancer and other non-infectious diseases continue to rise all over the world it's become harder for scientists to find safe, effective treatments. In addition, bacteria are becoming more and more resistant to drugs and synthetic medicines have become harsher.

These challenges have led to searches for new solutions, including natural substances, like medicinal plants. Plant based medicines are known to have more benefits because they are less poisonous than synthetic versions. They also have compounds that compliment each other that help in disease prevention.

People have been using plants to make medicines for thousands of years. The World Health Organisation estimates that between 75% and 80% of the world's population uses at least some plant based medicines.

Africa has its own store of medicinal plants, such as those used in Côte d'Ivoire, Kenya, Mauritius, South Africa and Zimbabwe.

I have been working with a group of scientists to find new ways to exploit plants for medicinal purposes.

As part of the process we studied the eating habits and behaviour of some wild chimpanzees based at the Taï National Park in the south western region of Côte d'Ivoire. We identified what they ate, which included leaves, fruit and the stems of the plants. We then tested these in a laboratory.

Our idea followed on from a previous study on the park's chimpanzees which focused on the energy and protein balance in their diets. Our study focused on the medicinal properties of what they ate.

Our results suggest that the diets of chimpanzees are made up of plants that are a rich source of compounds that improve their immune systems and protect them from certain diseases.

Our findings have opened the door to exploring the properties of these plants to test their ability to treat disease in humans.

Tolerance to disease

Chimpanzees are the closest animal to humans genetically, sharing 98% of the human DNA. This genetic closeness means that these great apes share certain diseases with humans. These include yeast infections (candidiasis), Ebola and HIV/AIDS. Chimpanzees are also able to get cancer.

Our hypothesis was that some plants in the chimpanzees' diet might be keeping them healthy and that this could be useful in developing medicine for humans too.

We tested about 132 extracts from 27 plants chosen based on:

- ***how frequently they consumed the plants***
- ***the time of consumption***
- ***the quantity eaten***

The plants were analysed for their ability to prevent the development of cancer and to inhibit cell damage, bacterial and fungal growth. Their nutritional benefits were also analysed.

***The leaves of the* Tristemma coronatum *plant are known to induce sleep.* Author provided.**

The preventive diet

Some of the plants we analysed are already used by people as medicinal plants. But the parts extracted to make medicines are different to those eaten by the chimps.

The plant *Nauclea diderrichii* is a good example. The fruits and leaves are eaten by chimps but the stem bark is used by people to treat fever and jaundice.

Promising plants such as *Tristemma coronatum*, whose leaf extract is known to induce sleep in humans, and *Beilschmiedia mannii*, which is already used to treat lung diseases, were identified.

Other beneficial medicinal plants in their Latin and common names in Côte d'Ivoire dialects respectively include;

- ***Klainedoxa gabonensis* (kroma)**
- ***Nauclea diderrichii* (badi)**
- ***Manniophyton fulvum* (kolomodia, frafrabié, topué, dobuï ,zohé, zoobo)**
- ***Beilschmiedia mannii* (biliè, tienabi, atiokwo, iréklé, biétou, btei, bhoukéssou)**

All are abundant in the Taï National Park.

Our results showed that the tested plants induce an enzyme – quinone reductase – that prevents damage to the body cells. These plants inhibit NF-kB enzyme , which is responsible for causing more than 20% of all reported cases of cancer.

The tested plants showed that 24 extracts (18%) had activity to kill bacteria and six extracts (5%) destroyed yeasts that cause yeast infections. *Tristemma coronatum* killed both bacteria and yeast whereas *Beilschmiedia mannii* was active on bacteria, fungi and cancer. This means that the extracts of these plants have potential for medicinal use in humans.

***Ground with calcium carbonate, fruit from the Klainedoxa Kabonensis plant is used on abscesses and ulcers. Fruit pulp is applied to swellings.* Author provided.**

Developing new medicines

Our study highlighted the high therapeutic and nutritional potential of certain plants which can be considered in developing new medicines.

The next step will be to test these plants on laboratory animals to confirm their benefits. Once the safety and effectiveness is established, we could then start to test them on humans. If these pass the necessary standards, the development of drugs can follow.

**Post-Doctoral Fellow with Afrique One Aspire, Nangui Abrogoua University*

Disclosure statement

Ahoua Constant works for/consults to/owns shares in Centre Suisse de Recherches Scientifiques en Côte d'Ivoire. He receives funding from Swiss Government. He is affiliated with Centre Suisse de Recherches Scientifiques en Côte d'Ivoire.

http://bit.ly/2IzcpKm

Daily egg consumption may reduce cardiovascular disease

Having an egg a day could reduce risk of stroke by 26 percent

People who consume an egg a day could significantly reduce their risk of cardiovascular diseases compared with eating no eggs, suggests a study carried out in China, published in the journal Heart.

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide, including China, mostly due to ischaemic heart disease and stroke (including both haemorrhagic and ischaemic stroke). Unlike ischaemic heart disease, which is the leading cause of premature death in most Western countries, stroke is the most responsible cause in China, followed by heart disease.

Although ischaemic stroke accounted for the majority of strokes, the proportion of haemorrhagic stroke in China is still higher than that in high income countries.

Eggs are a prominent source of dietary cholesterol, but they also contain high-quality protein, many vitamins and bioactive components such as phospholipids and carotenoids.

Previous studies looking at associations between eating eggs and impact on health have been inconsistent, and most of them found insignificant associations between egg consumption and coronary heart disease or stroke.

Therefore, a team of researchers from China and the UK led by Professor Liming Li and Dr Canqing Yu from the School of Public Health, Peking University Health Science Center, set out to examine the associations between egg consumption and cardiovascular disease, ischaemic heart disease, major coronary events, haemorrhagic stroke and ischaemic stroke.

They used data from the China Kadoorie Biobank (CKB) study, an ongoing prospective study of around half a million (512,891) adults aged 30 to 79 from 10 different geographical areas in China.

The participants were recruited between 2004-2008 and were asked about the frequency of their egg consumption. They were followed up to determine their morbidity and mortality.

For the new study, the researchers focused on 416,213 participants who were free of prior cancer, cardiovascular disease (CVD) and diabetes. From that group at a median follow-up of 8.9 years, a total of 83,977 cases of CVD and 9,985 CVD deaths were documented, as well as 5,103 major coronary events.

At the start of the study period, 13.1% of participants reported daily consumption (usual amount 0.76 egg/day) and 9.1% reported never or very rare consumption (usual amount 0.29 egg/day) of eggs.

Analysis of the results showed that compared with people not consuming eggs, daily egg consumption was associated with a lower risk of CVD overall.

In particular, daily egg consumers (up to one egg/day) had a 26% lower risk of haemorrhagic stroke - the type of stroke with a higher prevalence rate in China than in high-income countries - a 28% lower risk of haemorrhagic stroke death and an 18% lower risk of CVD death.

In addition, there was a 12% reduction in risk of ischaemic heart disease observed for people consuming eggs daily (estimated amount 5.32 eggs/week), when compared with the 'never/rarely' consumption category (2.03 eggs/week).

This was an observational study, so no firm conclusions can be drawn about cause and effect, but the authors said their study had a large sample size and took into account established and potential risk factors for CVD.

The authors concluded: "The present study finds that there is an association between moderate level of egg consumption (up to 1 egg/day) and a lower cardiac event rate.

"Our findings contribute scientific evidence to the dietary guidelines with regard to egg consumption for the healthy Chinese adult."

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Link between IBD and Parkinson's might allow doctors to slow down condition

Patients with inflammatory bowel disease (IBD) had 22 percent higher risk of Parkinson's compared with non-IBD individuals, study shows

Doctors may be able to modify or slow down the progress of the neurological condition Parkinson's disease in the future by spotting signs of it in patients with inflammatory bowel disease (IBD), suggest a study published in the journal *Gut*.

Danish researchers found patients with IBD appeared to have a 22% greater risk of developing Parkinson's disease in a study that monitored participants for almost 40 years.

IBD, Crohn's disease and ulcerative colitis are chronic conditions with onset in young adulthood. It has already been suggested in previous studies that inflammation plays a role in the development of Parkinson's disease and multiple system atrophy.

Enteric inflammation - the main symptom of inflammatory bowel disease - can occur in patients with Parkinson's disease and may

reflect the earliest manifestations of the neurological condition's development.

Experts have suspected for some time that there may be a 'gut-brain axis' where the intestinal environment influences the functioning of the central nervous system and intestinal imbalance may precede and cause Parkinson's disease.

Therefore, a team of Danish researchers led by Dr Tomasz Brudek of the Research Laboratory for Stereology and Neuroscience, Bispebjerg and Frederiksberg Hospital, Copenhagen, set out to examine whether IBD was associated with risk of Parkinson's disease and multiple system atrophy.

They carried out a nationwide population-based cohort study involving all individuals diagnosed with IBD in Denmark between 1977 and 2014 - 76,477 people - and more than 7.5 million non-IBD individuals from the general population, who were comparable in terms of gender, age and vital status.

All participants were followed from IBD diagnosis/index date to the occurrence of Parkinson's disease and multiple system atrophy, using data from the Danish National Patient Register.

During the 37-year study period, 335 patients with IBD (0.4%) and 39,784 non-IBD individuals (0.5%) were diagnosed with Parkinson's disease, whereas 13 patients with IBD (0.02%) and 866 non-IBD individuals (0.01%) were diagnosed with multiple system atrophy.

Analysis of the results showed that patients with IBD had a 22% higher risk of Parkinson's disease compared with non-IBD individuals.

This increased risk was present independent of age at IBD diagnosis, gender or length of follow-up.

The overall incidence of multiple system atrophy was low in the study, but analysis suggested a tendency towards higher risk (41% higher) of developing multiple system atrophy in patients with IBD compared with non-IBD individuals. The estimates were similar for women and men.

There was a 35% greater risk of parkinsonism among patients with ulcerative colitis but not a significantly higher risk among patients with Crohn's disease.

This was an observational study, so no firm conclusions can be drawn about cause and effect, but the authors said they believed their work was the first epidemiological study investigating the risk of parkinsonism in an unselected, nationwide cohort of patients with IBD with long-term follow-up - patients were followed for more than 8 million person-years.

The authors concluded: "The study suggests that clinicians should be aware of symptoms of parkinsonism in patients with IBD, and the study demonstrates the need for further investigation into the role of intestinal inflammation and brain gut-microbiome axis in the aetiology of parkinsonism.

"The identification of risk factors associated with prodromal phases of Parkinson's disease may allow for early intervention studies that could modify or slow down disease progress."

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Link between tuberculosis and Parkinson's disease discovered

The mechanism our immune cells use to clear bacterial infections like tuberculosis (TB) might also be implicated in Parkinson's disease

The mechanism our immune cells use to clear bacterial infections like tuberculosis (TB) might also be implicated in Parkinson's disease, according to a new collaborative study led by the Francis Crick Institute, Newcastle University and GSK.

The findings, which will be published in *The EMBO Journal*, provide a possible explanation of the cause of Parkinson's disease and suggest that drugs designed to treat Parkinson's might work for TB too.

Parkinson's protein

The most common genetic mutation in Parkinson's disease patients is in a gene called LRRK2, which makes the LRRK2 protein overactive.

Drugs that block LRRK2 are a promising new treatment for Parkinson's, with many pharmaceutical companies developing drugs to target LRRK2 and clinical trials underway. But how overactive LRRK2 causes Parkinson's and why LRRK2 blockers work was a mystery.

The biological causes of Parkinson's remain largely unknown, making it more difficult to develop and improve treatments. Discovering a mechanism that causes Parkinson's and how drugs affect it could significantly advance efforts to improve treatments.

Insights from TB

By studying what LRRK2 does in immune cells called macrophages that are infected with *Mycobacterium tuberculosis (Mtb)* - the bacterium that causes TB - researchers believe they have uncovered a potential cause of Parkinson's.

Macrophages recognise and engulf Mtb securing it within tight-fitting internal compartments called phagosomes. Another part of the cell called the lysosome then fuses with the phagosome to destroy the bacterium inside.

Using a combination of experimental approaches, Crick and GSK researchers, in collaboration with proteomics specialist Matthias Trost from Newcastle University, found that LRRK2 prevents phagosomes from fusing with lysosomes in both human and mouse macrophages, making them less efficient at clearing bacteria. Deleting the LRRK2 gene or treating the cells with an LRRK2 blocker significantly reduced levels of Mtb.

These findings in cells were supported by experiments in mice. When the researchers deleted the gene for LRRK2 in mice, they found that they exhibited an enhanced early immune response to TB infection, and had significantly lower levels of Mtb in their lungs than control mice up to two weeks after infection.

"We think that this mechanism might also be at play in Parkinson's disease, where abnormal masses of protein called 'Lewy bodies' build up in neurons in the brain and cause damage," said Susanne Herbst, joint first author of the paper and post-doctoral fellow at the Crick.

The team suspect that LRRK2 might be preventing immune cells in the brain from degrading cell debris properly, leading to a build-up of protein in neurons that disrupts their function.

Susanne added: "By studying TB, we have found a possible explanation for why LRRK2 mutations are a genetic risk factor for Parkinson's disease. It's exciting when different fields of research connect up in unexpected ways like this!"

Co-author Patrick Lewis, Associate Professor in Cellular and Molecular Neuroscience at the University of Reading, said: "The dogma in the Parkinson's field has been to focus almost exclusively on what is happening to neurons in the brain to make them degenerate. But over the last few years, there has been a growing appreciation of the integral role of other cells in the brain and particularly the immune system in keeping neurons healthy. This study reinforces why we should think more broadly about the events that cause neurodegeneration, and that some of the answers to Parkinson's disease might come from immunology."

New TB treatments

The findings also suggest that LRRK2 inhibitors could be a powerful new way of combating TB, which kills 1.67 million people every year.

"Drug-resistant TB is a serious emerging problem, and boosting the body's own immune defence against TB is an important step in the battle against antibiotic resistant strains," said Max Gutierrez, Group Leader at the Crick and senior author of the paper.

"LRRK2 inhibiting drugs are already being developed to treat Parkinson's disease and we're trying to see if we can repurpose them as a potential new TB therapy. This should be relatively straightforward because TB infects the lungs, so the LRRK2 inhibitors wouldn't need to cross the blood-brain barrier like they do in Parkinson's disease."

https://wb.md/2IKwH3V

What Did the Autopsy of Mary Jo Kopechne Reveal?

Hello and welcome. I am Dr George Lundberg and this is At Large at Medscape.

George D. Lundberg, MD

What did the autopsy of Mary Jo Kopechne reveal? If you are an American above the age of 65, you will immediately recognize that name. If you are a buff of American political history or even a current moviegoer, the name may also ring a bell.

In July 1969, two days before man took his first steps on the moon on July 20, this 27-year-old white, single, female political worker was found dead, alone, under water, in an overturned Oldsmobile sedan, just off a bridge on Chappaquiddick Island near Cape Cod, Massachusetts, under—still, now 49 years later—mysterious circumstances.

Many questions surrounding the tragic end of her life remain unanswered. A major political dynasty was diverted by the event and its aftermath.

She was last definitively seen alive by friends at a nighttime beach cottage party during a multiday yachting event attended by six single women under 30 and five married men (plus one single older male chauffeur).[1] She is said to have left the party, ostensibly to be driven back to her motel in Edgartown, Massachusetts, by Senator Edward Kennedy.

What happened from their seemingly unobserved departure from the party—sometime between 11:15 PM and 12:45 AM—until the next morning, when fishermen accidentally discovered an overturned, sunken car containing her body in the area of the back seat, remains murky and under dispute. Local witnesses and law enforcement, friends, family, state authorities, an inquest, a grand jury, judges, lawyers, political operatives, numerous investigative reporters, filmmakers, and even Roman Catholic priests have engaged in the still-questioning effort to learn, or to obscure, "truth," depending on their personal motivations.

So, what did the autopsy reveal? Nothing. There was no autopsy. Donald Mills, MD, the local associate medical examiner (not a pathologist) called it accidental drowning.[2] The body was quickly shipped to another state for burial. Later efforts to exhume her remains for postmortem examination were denied.

What could have been the value of a properly performed autopsy in preventing some of the subsequent confusion? These pertinent questions probably could have been answered:

- ***Was she dead of foul play before the car went into the water?***
- ***Did she suffer brain damage from the collision of car with water?***
- ***Was her neck broken when the car landed upside down on the pond bottom? The top was dented and the windshield shattered.***
- ***Did she die of suffocation in a diminishing air bubble before her head became immersed in water, and how long did she survive in the overturned car?***
- ***Did she drown?***
- ***What was the source of the blood described by witnesses on her clothing?***
- ***Had she recently had sexual intercourse? And if so, with whom?***
- ***Was she pregnant?***
- ***What was the alcohol level of her blood, urine, gastric contents, and vitreous?***

My pathology colleagues and I discussed this actively at that time, and Harry Nelson wrote an article published in the *Los Angeles Times* on July 31, 1969, about why autopsy should (still) be done.[3] Without

autopsy, these questions, and perhaps many others, are left unanswered and add to the intrigue and the suspicion of a long-term cover-up. Who was really trying to hide what, and why?

Eleven Reasons Why Autopsies Are Performed

In 2015, after Justice Scalia's sudden unexplained death, I described the 11 reasons for autopsy:

1. To establish cause of death
2. To assist in determining the manner of death (homicide, suicide, accident, misadventure, natural, or undetermined)
3. To compare premortem and postmortem findings
4. To produce accurate vital statistics
5. To monitor the public health
6. To assess the quality of medical practice
7. To instruct medical students and physicians
8. To identify new and changing diseases
9. To evaluate the effectiveness of therapies such as drugs, surgical techniques, and prostheses
10. To reassure family members
11. To protect against false liability claims and settle valid claims quickly and fairly

Was the decision not to perform an autopsy on the body of Mary Jo Kopechne a result of ignorance on the part of an authority, primarily Dr Donald Mills? Or was it due to influence by a very powerful political family concerned about what [the details] might disclose? Remember these lessons the next time you are confronted with a death, especially if it's sudden, unexpected, and unwitnessed.

That's my opinion. I am Dr George Lundberg, at large at Medscape.

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http://bit.ly/2J8iY6f

Humans are giving many other species cancer

Meta-analysis finds enough to classify Homo sapiens as an "oncogenic species".

Fiona McMillan reports.

Because we modify the environment in a way that can cause cancer in wildlife, humans can be defined as an "oncogenic species", say the authors of a new paper in the journal *Nature Ecology and Evolution*.

Cancer incidence in humans is currently on the rise, and much of this increase has been linked with changes in diet and lifestyle, as well as exposure to pollutants.

Human activity is causing many wildlife species to also experience changes in diet and habitat, but how this affects cancer rates has not been as well explored.

Now, an international team of researchers led by Frédéric Thomas at Centre de Researches Écologiques & Évolutives sur le Cancer (CREEC), in France, has analysed multiple studies that collectively show a clear association between human activity and cancer risk in wild animals.

The scientists provide a summary of the mechanisms by which humans are inducing cancer in other animals.

First and foremost is pollution. Environmental contaminants disrupt cell growth through a variety of mechanisms, including DNA damage, interference with immune function, and disruption of hormonal balance.

One study showed that 27% of beluga whales in the highly polluted Saint Lawrence Estuary in Canada had cancer. In another study, chlorine-based pesticides were associated with increased cancer rates in California sea lions. Meanwhile, radionucleotide contamination from the Chernobyl disaster in 1986 has been linked to increased tumours in local birds.

The authors also caution that the global accumulation of micro-plastics represents a potentially serious cancer threat to wildlife, as does exposure to agricultural pesticides.

Human-sourced food is also a problem. We provide food to animals intentionally via feeding, and unintentionally through waste. This material can contain hazards, such as mycotoxins from fungus that grows on discarded food, or toxins derived from certain antibiotics that become carcinogenic in sunlight. Moreover, the food itself can be low quality, leading to nutrient deficiency and decreased immune health, and can also alter gut microbiota, all of which are linked with increased cancer risk.

Beyond contaminants and diet, humans may be increasing cancer prevalence in wildlife through light pollution. The authors propose that Artificial Light at Night (ALAN), could be considered “an environmental endocrine disruptor for wildlife.”

ALAN is linked with elevated cancer risk in humans, most likely through disruption of key hormones vital to sleep regulation and cancer suppression. Artificial lighting could have a similar effect on wildlife, making it easier for cancers to form.

Human-caused habitat change can also reduce genetic diversity within animal populations, which can increase cancer susceptibility, say the authors. Reduced genetic diversity in snow leopards and western barred bandicoots has been shown to reduce their capacity to fight off cancer-causing pathogens. Moreover, loss of variation in a single gene in California sea lions has been linked with a rise in urogenital carcinoma, while decreased genetic diversity in certain fox and zebra species has been followed by a rise in cancer prevalence.

Thomas and colleagues believe that human-activity driven cancer in wild animals is currently underestimated and more research is needed to better understand how human behaviour, cancer and ecology are intertwined.

https://bbc.in/2INAXvp

Missing microbes 'cause' childhood cancer

Our modern germ-free life is the cause of the most common type of cancer in children, according to one of Britain's most eminent scientists.

By James Gallagher Health and science correspondent, BBC News

Acute lymphoblastic leukaemia affects one in 2,000 children.

Prof Mel Greaves, from the Institute of Cancer Research, has amassed 30 years of evidence to show the immune system can become cancerous if it does not "see" enough bugs early in life.

It means it may be possible to prevent the disease.

Combined events

The type of blood cancer is more common in advanced, affluent societies, suggesting something about our modern lives might be causing the disease.

There have been wild claims linking power cables, electromagnetic waves and chemicals to the cancer. That has been dismissed in this work published in Nature Reviews Cancer.

Instead, Prof Greaves - who has collaborated with researchers around the world - says there are three stages to the disease.

- ***The first is a seemingly unstoppable genetic mutation that happens inside the womb***
- ***Then a lack of exposure to microbes in the first year of life fails to teach the immune system to deal with threats correctly***
- ***This sets the stage for an infection to come along in childhood, cause an immune malfunction and leukaemia***

This "unified theory" of leukaemia was not the result of a single study, rather a jigsaw puzzle of evidence that established the cause of the disease.

Prof Greaves said: "The research strongly suggests that acute lymphoblastic leukaemia has a clear biological cause and is triggered

by a variety of infections in predisposed children whose immune systems have not been properly primed."

Evidence that helped build the case included:

- ***An outbreak of swine flu in Milan that led to seven children getting leukaemia***
- ***Studies showing children who went to nursery or had older siblings, which expose them to bacteria, had lower rates of leukaemia***
- ***Breastfeeding - which promotes good bacteria in the gut - protects against leukaemia***
- ***Lower rates in children born vaginally than by caesarean section, which transfers fewer microbes***
- ***Animals bred completely free of microbes developed leukaemia when exposed to an infection***

This study is absolutely not about blaming parents for being too hygienic. Rather it shows there is a price being paid for the progress we are making in society and medicine. Coming into contact with beneficial bacteria is complicated, it's not just about embracing dirt.

But Prof Greaves adds: "The most important implication is that most cases of childhood leukaemia are likely to be preventable." His vision is giving children a safe cocktail of bacteria - such as in a yoghurt drink - that will help train their immune system. This idea will still take further research.

In the meantime, Prof Greaves said parents could "be less fussy about common or trivial infections and encourage social contact with other and older children".

Dr Alasdair Rankin, the director of research at the blood cancer charity Bloodwise, said: "We urge parents not to be alarmed by this study.

"While developing a strong immune system early in life may slightly further reduce risk, there is nothing that can be currently done to definitively prevent childhood leukaemia."

Good germs

This study is part of a massive shift taking place in medicine.

To date we have treated microbes as the bad guys. Yet recognising their important role for our health and wellbeing is revolutionising the understanding of diseases from allergies to Parkinson's and depression and now leukaemia.

Prof Charles Swanton, Cancer Research UK's chief clinician, said: "Childhood leukaemia is rare and it's currently not known what or if there is anything that can be done to prevent it by either medical professionals or parents.

"We want to assure any parents of a child who has or has had leukaemia, that there's nothing that we know of that could have been done to prevent their illness."

http://bit.ly/2J63EXG

Blue dye tablet helps identify polyps during colonoscopy

Oral-delayed release methylene blue aids in finding cancerous and pre-cancerous lesions

Washington, D.C.- Ingestion of a blue dye tablet during bowel prep for colonoscopy could be a significant advance in the early detection of colorectal cancer (CRC). When used in conjunction with colonoscopy, the blue dye increased adenoma detection rate (ADR) by nearly 9 percent, according to a study scheduled for presentation at Digestive Disease Week® (DDW) 2018.

Study implications

Every year, nearly 137,000 people are diagnosed with CRC, and more than 50,000 people die from the disease. Yet, the disease is largely preventable with regular screening and is treatable with early detection. The challenge is that polyps are not always detected during screening -- many polyps are flat or subtle, making them difficult to identify and remove.

"Identification of cancerous and pre-cancerous lesions is of utmost importance to prevent CRC," said Alessandro Repici, MD, professor of gastroenterology and director of endoscopy at Humanitas University Medical School in Milan, Italy, and a primary investigator of the study. "Our study, which used the highest standard of care, allowed gastroenterologists to better detect and remove difficult-to-see polyps, which has great implications for further preventing this disease."

Study design

Researchers studied 1,205 patients scheduled for colonoscopy at 20 centers worldwide, with each patient randomly assigned to one of three groups: patients who received a full dose of the blue dye, oral delayed-release methylene blue, during the normal colonoscopy preparation process; patients who received a placebo during preparation; and a group of patients who received a half dose of the study drug. The third group was not part of the analysis but was included for masking purposes to make it harder for participating physicians to know which patients were in the active group.

Study results

In patients whose preparation included the full 200 mg dose of the oral delayed-release methylene blue, adenomas, or polyps, and carcinomas were found in 56.3 percent of patients. In the placebo group, which utilized the standard of care, adenomas and carcinomas were identified in 47.8 percent. Both groups were screened with the most up-to-date technology available with monitored withdrawal time and blinded second review to avoid execution bias. More flat and small lesions (less than 5 millimeters) were found in patients who used the full dose of the oral delayed-release methylene blue. Additionally, research showed that with the exception of blue feces and urine discoloration, which were expected effects, less than 6 percent of patients experienced mild adverse effects when taking the tablet.

"While utilizing blue dye to increase ADR is not a new concept, the fact that this technology now comes in tablet form is a major advance," Michael B. Wallace, MD, MPH, professor of medicine and director of the Digestive Disease Research Program at Mayo Clinic in Jacksonville, Florida, and a primary investigator on the Phase III trial. "Our research shows the oral delayed-release methylene blue provides gastroenterologists with a new means to improve their ADR with no additional inconvenience or safety risks to the patient and no supplemental time required to the endoscopist."

Previously, the blue dye had to be mixed by the providers on site, and then sprayed during the colonoscopy, which could be an imprecise, time-consuming and generally localized process. With the development of the tablet form, the majority of the dye releases in the colon in time for highlighting and detecting mucosal lesions during the colonoscopy.

Study investigators added that the use of Methylene Blue MMX or other technologies should never be considered a substitute for good colonoscopy technique.

Colorectal cancer screening saves lives. Colonoscopy is the only screening method that can screen for and prevent colorectal cancer. According to a study published in the New England Journal of Medicine, every 1 percent increase in the ADR corresponds to a 3 percent decline in the incidence of CRC and a 5 percent decline in CRC fatalities.

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Why You Say 'Um' Before Certain Words

What's that … um … word?

By Mindy Weisberger, Senior Writer

If you pay closer attention to those moments when an "um" an "uh" or an awkward pause inserts itself into your conversation, you may notice that the flub usually comes just before a noun, according to a new study.

Researchers found that when people are midsentence and a word is pronounced more slowly, or seems just beyond their grasp, that word is more likely to be a noun than a verb. This might happen because visualizing nouns before we say them temporarily slows our speech, while action words like verbs require less time to "see" in our minds before they leave our mouths, the study authors said.

The complex interaction of various factors shapes the speed of a person's speech, and these factors include the frequency and familiarity of the words used, the researchers wrote in the study.

In fact, scientists have previously observed that pauses preceding unfamiliar or complicated words reflect the comparative difficulty of planning those words, lead study author Frank Seifart, a researcher with the Department of Literary Studies and Linguistics at the University of Amsterdam in the Netherlands, told Live Science in an email.

For the new study, the researchers analyzed thousands of speech recordings, listening for the rhythms of 288,848 words in total, from phrases in nine diverse languages spoken in Europe, North America, Mexico, Siberia, the Himalayas, the Amazon rainforest and the Kalahari Desert.

In all nine languages, the scientists found that pauses — whether silent or "filled" with a placeholder sound — were 60 percent more likely to occur before nouns than before verbs. The researchers further found that people were twice as likely to hem and haw before saying a noun than they were before uttering a verb, even if the verb was complex or unfamiliar.

In common speech, nouns are typically used only when they add information that is new or unexpected; otherwise they are frequently omitted or replaced with pronouns, the researchers said. Therefore, people need more "planning time" to say nouns than verbs, even when the nouns in question aren't particularly complicated, the researchers noted in the study.

Their findings suggested that even though the languages demonstrated significant diversity in grammatical structure and cultural context, certain speech rhythms persistently followed strong universal patterns — and those patterns can be linked to the use of nouns or verbs, Seifart said in the email.

The findings were published online May 14 in the journal Proceedings of the National Academy of Sciences.

http://bit.ly/2sdv5Es

'Serendipitous' use of antimalarial drug may have improved outcome for cancer patient

The case report discusses whether the patient's autoimmune disease and its treatment could have contributed to achieving such a 'striking' response to treatment

A cancer patient with advanced ovarian cancer had a "remarkable" journey to recovery that may be partially attributed to a treatment she received for a completely different disease, according to a case report published in *ecancermedicalscience*. The case report discusses whether the patient's autoimmune disease and its treatment could have contributed to achieving such a "striking" response to treatment.

Researchers led by Dr Franco Muggia, Professor of Medicine at NYU Langone's Perlmutter Cancer Center, New York, USA, describe a case of a patient who received treatment for dermatomyositis, an autoimmune condition that causes muscle weakness and skin rashes. For this condition, she received treatment that included hydroxychloroquine and quinacrine, which are more commonly known as antimalarial drugs.

But the patient later presented with an advanced and aggressive form of ovarian cancer. Although effective treatments exist, this type of cancer is usually expected to recur within a median of 18 months to 2 years.

Dr Muggia's patient surprised her doctors with her immediate and lasting response to the cancer treatment.

Three years on, the patient continues to be disease-free - both from ovarian cancer and dermatomyositis. Follow-up has shown no signs of cancer, and the patient is reportedly symptom-free.

Previously published evidence in ecancermedicalscience has shown that antimalarial drugs hydroxychloroquine and quinacrine may play a role in cancer treatment, as they appear to work together with cancer drugs, making treatments more effective.

The medical community is becoming increasingly interested in "repurposed" drugs, or drugs that were originally developed for one condition, then found to be useful for other conditions.

"This is an interesting example of serendipity - an incidental finding of a cancer patient responding strongly to a non-cancer drug used for the treatment of a co-morbid condition," says Dr Pan Pantziarka of The Anticancer Fund, Belgium, and one of the leaders of the Repurposing Drugs in Oncology (ReDO) Project. "It's important to publish such cases as they may provide early data for later preclinical and clinical investigation."

Dr Muggia stresses that conclusions cannot be drawn from the example of one patient. "However, the depth of the response of an aggressive high-grade serous ovarian cancer to the initial platinum-taxane doublet, after months of dermatomyositis and treatment with anti-malarial drugs, should encourage further inquiries into the role of autophagy, its subsequent inhibition, and immunity in enhancing responses to [platinum-based] chemotherapy."

Dr Pantziarka says, "There is already strong evidence that anti-malarials such as hydroxychloroquine and chloroquine possess anticancer activity, as was summarised by the ReDO Project last year. If replicated, it would show yet again the therapeutic value still to be realised in so many of our existing non-cancer medicines."

Dr Muggia adds, "Much remains to be learned about ovarian cancer biology and autophagy. We hope the current report catalyzes additional work in this area."

At the time of publication, Dr Muggia's patient remained disease-free.

Editor's Notes

This paper was authored by Isabella Cadena, Annie Yang, Pascale Levine, Andrea Downey, Victoria P. Werth, John Curtin, and Franco Muggia.

http://bit.ly/2GMkplD

Why We Need to Take Pet Loss Seriously

How to handle grief after a pet's death—and why we all need to change our attitudes about it

By Guy Winch on May 22, 2018

Getty Images

Doug's amateur soccer team had just lost their playoff game and he needed a pick-me-up. So he decided to stop by the local animal shelter on his way home.

He was by no means looking to adopt an animal but puppies always put a smile on his face. "Rookie mistake," he told me in our psychotherapy session. "You set foot in one of these places and no way you're not leaving with a puppy." Delia, the puppy in question, was a five-month-old mutt. "I had her for seventeen years," Doug said, wiping tears from his eyes, "Almost my entire adult life. I knew it would be rough when she died but I had no idea…I was a total wreck. I cried for days. I couldn't get any work done. And worst of all, I was too embarrassed about it to tell anyone, even my old soccer teammates who loved Delia. I spent days at work crying in private and muttering "allergies" whenever someone glanced at my puffy eyes."

Losing a beloved pet is often an emotionally devastating experience. Yet, as a society, we do not recognize how painful pet loss can be and how much it can impair our emotional and physical health. Symptoms of acute grief after the loss of a pet can last from one to two months with symptoms of grief persisting up to a full year (on average). *The New England Journal of Medicine* recently reported

that a woman whose dog died experienced Broken Heart Syndrome—a condition in which a person's response to grief and heartbreak is so severe, they exhibits symptoms that mimic a heart attack, including elevated hormone levels that can be thirty times greater than normal.

While grief over the loss of a cherished pet may be as intense and even as lengthy as when a significant person in our life dies, our process of mourning is quite different. Because pet loss is disenfranchised, many of the societal mechanisms of social and community support are absent when a cherished pet dies. Few of us ask our employers for time off to grieve a beloved cat or dog as we fear doing so would paint us as overly sentimental, lacking in maturity or emotionally weak. And few employers would grant such requests were we to make them. Studies have found that social support is a crucial ingredient in recovering from grief of all kinds. Thus, we are not only robbed of crucial support systems when our pet dies, but our own perceptions of our emotional responses are likely to add an additional layer of emotional distress. We may feel embarrassed and even ashamed about the severity of the heartbreak we feel and consequently, hesitate to disclose our distress to our loved ones. We might even wonder what is wrong with us and question why we are responding in such 'disproportional' ways to the loss.

Feeling intense grief that is then layered with shame about these feelings not only makes pet loss a bigger threat to our emotional health than it would be otherwise, it complicates the process of recovery by making it more lengthy and complex than it should be.

Further, given our societal attitude that invokes responses such as "It's just an animal" and "You can just get another one" we are likely to overlook the variety of ways our lives are impacted by pet loss (both real, practical, and psychological) which can blind us to steps we need to take in order to recover. Losing a pet can leave significant voids in our life that we need to fill: It can change our daily routines, causing ripple effects that go far beyond the loss of the actual animal. For example, whether they are trained to or not, all pets function as therapy animals to some extent. Cats, dogs, horses, and other cherished pets provide companionship, they reduce loneliness and depression and they can ease anxiety. Thus when we lose them we actually lose a significant and even vital source of support and comfort.

Caring for our pet also lets us develop routines and responsibilities around which we often craft our days. We get exercise by walking our dog and we socialize with other dog owners at the dog runs/parks/beaches. When our dog dies we might experience a significant drop in casual social interaction and feel left out of the unofficial community of dog owners to which we belonged. We awake early every day to feed our cat (or we are woken by them if we forget) but we get a lot more done because of it. Without our cat we might experience a real drop in productivity. Or we spend hours over the weekend out of the city so we can ride our horse, and find ourselves going stir crazy when our horse is no longer around. Losing a pet thus disrupts established routines that provide us with structure, support our emotional well-being and give our actions meaning. This is why, in addition to emotional pain, we feel aimless and lost in the days and weeks after our pet dies.

Lastly, we often consider ourselves parents to our pets and are even known as such in our communities. Everyone who owns a dog knows that neighbors on the street are far more likely to know our dogs name than they are to know ours. When our dog dies we can become invisible and lose a meaningful aspect of our identity. We post images and videos of our animals on social media and are followed for that reason. Losing a pet can impact many aspects of our own identities.

Recovering from pet loss, as in all forms of grief, requires us to recognize these changes and find ways to address them. We need to seek social support from people we know will understand and sympathize with our emotional pain and not judge us for it. Our best bet is to reach out to people we know who have also lost pets as they are likely to understand our anguish and offer the best support. Many animal clinics offer bereavement groups for pet owners.

We also need to fill the voids the loss has created in our lives, and there are more of them than we might realize. We might need to reorganize our routines and daily activities so we don't lose the secondary benefits we derived from having our pet.

For example, if our exercise came from walking our dog we need to find alternative ways to reach our daily 'step goals'. If our social media reach was built on our cat's starring Instagram popularity we need to find other ways to remain relevant social-media-wise. If we spent most Saturday mornings with our Vizsla meetup group, we need to find other outlets through which we can socialize and enjoy the outdoors.

If we were known in our neighborhood as "Delia's dad" as Doug was, we need to find other ways of feeling connected and involved in our community.

Doug suffered far more than he should have because of the shame and isolation he experienced. It's time we gave grieving pet owners the recognition, support and consideration they need. Yes, it is up to us to identify and address our emotional wounds when our pet dies, but the more validation we received from those around us, the quicker and the more complete our psychological recovery would be.

http://bit.ly/2saV2EK

To have or not to have...your left atrial appendage closed

Surgery to close the left atrial appendage is likely the right choice for certain patients but not all.

ROCHESTER, Minn. -- Each year in the U.S., more than 300,000 people have heart surgery.

To reduce risk of stroke for their patients, surgeons often will close the left atrial appendage, which is a small sac in the left side of the heart where many blood clots form, during these surgeries. Mayo Clinic researchers report today in JAMA that adding this procedure is likely the right choice for certain patients but not all.

"Our study showed that this intervention is associated with reduced risks of stroke and mortality," says Xiaoxi Yao, Ph.D., a health services researcher at Mayo Clinic and the study's first author. "This is especially true for patients with pre-existing atrial fibrillation, who are at a particularly high risk of stroke."

Exploring the data

To reach these conclusions, Dr. Yao and her research colleagues used the OptumLabs Data Warehouse. The OptumLabs Data Warehouse contains de-identified administrative claims data, including medical claims and eligibility information from a large national U.S. health insurance plan, as well as electronic health record data from a nationwide network of provider groups.

They examined the records of nearly 76,000 adult patients who had a coronary artery bypass or heart valve surgery between Jan. 1, 2009, and March 30, 2017. Of these patients, 5.8 percent (4,374 patients) also had the left atrial appendage closed during the surgery.

The research team compared these patients to propensity score-matched patients who did not undergo the surgical closure, evaluating outcomes for 4,295 patients in each group.

They found that patients who received the additional procedure were less likely to have a stroke. They were also less likely to die from any cause.

If the patient had atrial fibrillation before surgery, the numbers were even more positive: lower risks of stroke or death.

However, if a patient did not have atrial fibrillation before surgery, those undergoing the surgical closure became somewhat more likely to develop atrial fibrillation within 30 days after the surgery (27.7 versus 20.2 percent).

Furthermore, in patients with and without pre-existing atrial fibrillation, the surgical closure of the left atrial appendage was associated with a higher rate of health care utilization related to atrial fibrillation, measured over an average of two years of follow-up.

What patients need to know

"Atrial fibrillation itself is a risk factor for stroke," says Peter Noseworthy, M.D., a Mayo Clinic cardiologist and senior author of the study. "So for patients who do not have atrial fibrillation to begin with, the potential benefit of closing the left atrial appendage now could be attenuated by later development of atrial fibrillation."

"We saw that the benefit for patients with pre-existing atrial fibrillation was relatively large," says Dr. Yao.

"We believe that may make it particularly attractive for patients who are not able or willing to take long-term anticoagulation medication, but we should stress that we have not formally tested whether these patients can safely stop their anticoagulation."

The research team has collaborated on a number of projects centered on the safety and effectiveness of different treatments intended to reduce the stroke risk for patients with atrial fibrillation.

"Our findings provide an important piece of information for decision-making," says Dr. Noseworthy. "Armed with this new evidence, physicians and surgeons can now discuss the pros and cons of left atrial appendage closure with their patients."

This study was funded by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery. Center research is focused on transforming clinical practice. Researchers seek to discover new ways to improve health; translate those discoveries into evidence-based, actionable treatments, processes and procedures; and apply this new knowledge to improve patient care.

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

Publish translations of the best Chinese papers

The best research papers published in Chinese or other languages should be routinely translated and republished

Juan Tao, Chengzhi Ding & Yuh-Shan Ho

Language is still a barrier to scientific development (see, for example, V. S. Lazarev and S. A. Nazarovets *Nature* **556**, 174; 2018). We suggest that the best research papers published in Chinese or other languages (for instance, highly cited articles) should be routinely translated and republished to render them more visible to the English-language-dominated research community.

Since 1979, around 79 million papers have been published in Chinese — including in China's highest-quality journals, according to the China National Knowledge Infrastructure databases (http://oversea.cnki.net; see also *Nature* **553**, 390; 2018). Many important advances are therefore going unseen by Western researchers.

An example is a landmark study by Youyou Tu, who shared a Nobel prize in 2015 for the discovery of artemisinin and the treatment of malaria (Y. Tu *et al. Acta Pharm. Sin.* **16**, 366–370; 1981), which was cited only once outside China. And as of 2 May, all but 3 of 347 citations of the most-cited Chinese-language paper in the Web of Science Core Collection came from Chinese authors. (The paper discusses a radioisotope technique that is used to date rocks; see F. Y. Wu *et al. Acta Petrol. Sin.* **23**, 185–220; 2007.)

Breakthroughs such as Microsoft's algorithm for Chinese–English machine translation could speed up international sharing of Chinese publications (see go.nature.com/2jhxuwo). Efforts need to focus on which papers should be selected for translation by engaging with publishers, authors and other experts, and on resolving copyright-ownership issues.

Nature **557**, 492 (2018) doi: 10.1038/d41586-018-05235-5

https://go.nature.com/2KWM0Df

Thank you' has little currency worldwide

Surprisingly few people express gratitude for small favours.

Scientists who eavesdropped on nearly 1,000 conversations around the world report that people who receive favours rarely say 'thank you'.

To test that idea, Simeon Floyd at San Francisco University of Quito in Ecuador and his colleagues obtained informed consent to install cameras equipped with microphones in homes and public spaces on five continents, allowing the researchers to record conversations in eight languages.

The team recorded almost 1,000 examples of people asking for a favour — such as a request for a cigarette — and receiving it. In only 5.5% of those cases did the recipient express appreciation with either words or a gesture. Speakers of Cha'palaa, an unwritten language spoken in Ecuador, did not once express thanks in 97 exchanges that included a favour being requested and granted.

The results indicate that explicit gratitude is not a universal social currency. Instead, people help each other on the assumption that others will help them. *R. Soc. Open Sci.* (2018)

http://bit.ly/2saXDhY

Study finds that obesity surgery is associated with a massive fall in risk of melanoma skin cancer

Bariatric surgery is associated with a sharp fall in the risk of developing malignant melanoma skin cancer

New research presented at the European Congress on Obesity in Vienna, Austria (23-26 May), shows that obesity (bariatric) surgery is associated with a 61% fall in the risk of developing malignant melanoma skin cancer, and a 42% drop in the risk of skin cancer in general. The study is by Magdalena Taube and colleagues from University of Gothenburg, Sweden.

Melanoma is a deadly skin cancer, the incidence of which has increased steadily in many countries of the world, especially high-income countries. For example, in the UK, cases have more than doubled since the 1990s, and it is the fifth most common cancer in men and women, with over 15,000 cases each year and more than 2,000 deaths.*

Obesity is an established risk factor for cancer and some studies indicate that intentional weight loss sometimes reduces the risk. However, evidence for a link between obesity, weight loss, and malignant melanoma is limited. In this study, the authors used data from the matched Swedish Obese Subjects (SOS) study - a prospective controlled intervention trial examining bariatric surgery outcomes - to analyse the impact of weight loss on melanoma incidence.

The surgery group consists of 2007 subjects who chose surgical treatment, and the control group consists of 2040 individuals matched for 18 variables (including sex, age, anthropometric measurements, cardiovascular risk factors, psychosocial variables, and personality traits). To analyse malignant melanoma incidence, statistical tests were used to compare time to first melanoma cancer diagnosis between the surgery and control groups. In additional analyses, risk ratios between the surgery and control groups were compared.

The authors found that bariatric surgery markedly reduced the risk of melanoma. Over a median follow-up time of 18 years, they observed a 61% reduced risk of malignant melanoma and a 42% reduced risk of skin cancer in general compared to controls given usual obesity care.

The authors conclude: "In this long-term study, bariatric surgery reduced the risk of malignant melanoma. This finding supports the idea that obesity is a melanoma risk factor, and indicates that weight loss in individuals with obesity can reduce the risk of a deadly form

of cancer that has increased steadily in many countries over several decades."

http://bit.ly/2s8l0cO

AVATS surgery shown to be option for patients deemed 'inoperable'

Video-assisted thoracoscopic surgery (VATS) is a well established procedure,

"Video-assisted thoracoscopic surgery (VATS) is a well established procedure, but patients with poor pulmonary function often cannot have it because it is risky for them to go under general anesthesia," said study author, Ara Klijian, MD, of Sharp Grossmont Hospital, La Mesa, California and Scripps Mercy Hospital, San Diego. "I extended the VATS procedure so that it is done under local anesthesia with sedation. This enabled me to do a variety of procedures including lobectomies, esophageal surgeries, decortications and other types of thoracic surgery, with better outcomes."

Over the last 5 years, Dr. Klijian has performed more than 500 AVATS procedures without significant mortality or morbidity. In the current study, 246 patients with lung cancer had the AVATS procedure. Dr. Klijian demonstrated that patient safety was not compromised, that patients had a lower length of stay (1.6 days for patients who had a lobectomy, or removal of a lung) and better patient satisfaction.

Patients receiving the AVATS procedure typically have multiple chronic health conditions, as described in the abstract below, and poor lung function, which would typically increase the risk of surgical complications. "By eliminating the need for endotracheal intubation and the comorbidity associated with general anesthesia, the AVATS procedure brings new, previously considered inoperable patients into the surgical arena," Dr. Klijian said. "My long-term data have shown that this approach has better outcomes than traditional lung surgery with this select group of patients. It also reduces risks of hospital-acquired infection, as outpatient postoperative care minimizes the use of catheters."

In the AVATS and VATS procedures, a tiny camera (thoracoscope) and surgical instruments are inserted into the chest through small incisions in the chest wall. The thoracoscope transmits images of the inside of the chest onto a video monitor, guiding the surgeon in performing the procedure. The availability of the AVATS procedure is expected to increase, as Dr. Klijian has presented the technique and trained a number of other surgeons.

Abstract Number: 6958

Title: Awake Video-Assisted Thoracic Surgery for Patients with Poor Pulmonary Function

Author: A Klijian, Cardiothoracic Surgery, Sharp & Scripps Hospitals, San Diego, United States

Patients with poor pulmonary function are often precluded from surgical therapy. Awake video-assisted thoracic surgery (AVATS) done under local anesthesia and sedation allows for surgical resection of lung cancer previously deemed inoperable. Wedge resection, segmentectomy and even lobectomy are feasible and have been performed with outcomes comparable or better than those done under general anesthesia. Over 500 AVATS cases have been performed without significant morbidity or mortality. Lung resections for cancers done via AVATS have a length of stay for lobectomy of 1.6 days, even in patients with FEV1 under 0.6. These patients have multiple comorbidities including diabetes, COPD, atrial fibrillation, hypertension and hepatic and/or renal dysfunction. Of the patients undergoing resection, 203 of the 246 patients had FEV1 less than 0.8. Postoperative care of these patients has also been streamlined to minimize use of central lines, arterial, urinal and epidural catheters to minimize nosocomial infections. AVATS is a safe option in select lung cancer patients, who previously would be classified inoperable, resulting in lower length of stay, better patient satisfaction and presumably lower costs.

http://bit.ly/2LBYWzc

Why birds don't have teeth

New research suggests that birds gave up teeth to speed up egg hatching

Why did birds lose their teeth? Was it so they would be lighter in the air? Or are pointy beaks better for worm-eating than the jagged jaws of dinosaur ancestors?

Actually, birds gave up teeth to speed up egg hatching, a research paper published Wednesday suggests, challenging long-held scientific views on the evolution of the toothless beak. Compared to an incubation period of several months for dinosaur eggs, modern birds hatch after just a few days or weeks.

This is because there is no need to wait for the embryo to develop teeth—a process that can consume 60 percent of egg incubation time, said researchers Tzu-Ruei Yang and Martin Sander from the University of Bonn. While in the egg, the embryo is vulnerable to predators and natural disasters, and faster hatching boosts survival odds. This would be a concern for dinos and birds—all egg layers. In mammals, embryos are protected inside the mother.

"We suggest that (evolutionary) selection for tooth loss (in birds) was a side effect of selection for fast embryo growth and thus shorter incubation," Yang and Sander wrote in the journal Biology Letters.

Previous studies had concluded that birds—living descendants of avian dinosaurs—lost their teeth to improve flight.

Brooding over it

But this did not explain why some non-avian dinosaurs in the Mesozoic era had independently evolved similar toothless beaks, said the duo. Other studies had concluded that beaks were better for eating bird food. But some dinosaurs with a very different, meat-eating diet had also discarded teeth in favour of pointed beaks.

Yang and Sander said their breakthrough came from a study published last year, which found that the eggs of non-flying dinosaurs took longer to hatch than previously thought—about three to six months. This was because of slow dental formation, which researchers analysed by examining growth lines—almost like tree rings—in the fossilised teeth of two dinosaur embryos.

Faster incubation would have been aided by early birds and some dinos taking to brooding their eggs in open nests rather than burying them as of old, said the research team.

They conceded their hypothesis was not consistent with toothlessness in turtles, which still have a long incubation period.

More information: The origin of the bird's beak: New insights from dinosaur incubation periods, Biology Letters, rsbl.royalsocietypublishing.or … .1098/rsbl.2018.0090

http://bit.ly/2kwhB3k

Skin responsible for greater exposure to carcinogens in barbecue smoke than lungs

Skin is a more important pathway for uptake of cancer-causing compounds produced during barbecuing than inhalation

With summer coming, it's only a matter of time before the smells and tastes of barbecued foods dominate the neighborhood. But there's a downside to grilling that can literally get under your skin. In a study appearing in Environmental Science & Technology, scientists report that skin is a more important pathway for uptake of cancer-causing compounds produced during barbecuing than inhalation. They also found that clothing cannot fully protect individuals from this exposure.

In the U.S., 70 percent of adults own a grill or a smoker, and more than half of them grill at least four times a month, according to the Barbecue Industry Association. But barbecuing produces large amounts of polycyclic aromatic hydrocarbons, or PAHs. These carcinogenic compounds can cause respiratory diseases and DNA mutations. Eating grilled foods is the most common source of PAHs arising from barbecuing. However, according to a previous study by Eddy Y. Zeng and colleagues, bystanders near barbecues were likely

exposed to considerable amount of PAHs through skin exposure and inhalation, even if they didn't eat the grilled foods. Building on that study, the team sought to more precisely quantify skin uptake of PAHs from barbecue fumes and particles.

The researchers divided volunteers into groups at an outdoor barbecue to provide them with varying degrees of exposure to the food and the smoke. After analyzing urine samples from the volunteers, the researchers concluded that, as expected, diet accounted for the largest amount of PAH exposure. However, the skin was the second-highest exposure route, followed by inhalation. They say oils in barbecue fumes likely enhance skin uptake of PAHs. The team also found that while clothes may reduce skin exposure to PAHs over the short term, once clothing is saturated with barbecue smoke, the skin can take in considerable amounts of PAHs from them. They suggest washing clothes soon after leaving a grilling area to reduce exposure.

The authors acknowledge funding from the National Natural Science Foundation of China. The paper's abstract will be available on May 23 at 8 a.m. Eastern time here: http://pubs.acs.org.doi/abs/10.1021/acs.est.8b01689

http://bit.ly/2GVaZnR

Disadvantaged students with lower grades do just as well on medical degrees

Students with lower A Levels from poorly performing schools do just as well on medical degrees

University of York

Students from some of England's worst performing secondary schools who enroll on medical degrees with lower A Level grades, on average, do at least as well as their peers from top performing schools, a new study has revealed.

The research also found that students from poorly performing schools who match the top A Level grades achieved by pupils from the best performing schools, go on to do better during a medical degree. The authors of the research are now calling for medical school entry criteria to be relaxed for all pupils applying from low-performing schools.

The study, led by academics from the University of York alongside partners at the Universities of Dundee and Durham, analysed data from UK medical degree courses and linked it to information on secondary schools from the Department for Education.

Some universities, such as Birmingham, Southampton and Kings College London, have already trialled A Level 'grade discounting' for medical school place offers for some disadvantaged applicants.

Lead author of the paper, Lazaro Mwandigha, from the Department of Health Sciences at the University of York said: "This study suggests that relaxing A Level grade entry requirements for students from the worst performing secondary schools is beneficial. Although there are important further questions about how to fairly classify schools, the study demonstrates that these students are, on average, just as able to keep up with the pace of a medical degree".

There is fierce competition to study medicine in the UK with normally around 11-12 applications made for each place on offer. Partly as a result of this, entry grade requirements have crept up to AAA or A* AA at A Level. Despite only 5.3% of children in the UK going to private school, around half of medical degree places are currently filled by students who attended selective schools.

Supervising author Dr Paul Tiffin said: "This study is the first robust evidence that grade discounting for pupils from underperforming schools is justified. At the moment around 20% of UK schools are providing 80% of our medical students so A Level achievement should be viewed in terms of the context in which a pupil learns in order to help increase fairness and widen participation in medicine."

While they acknowledge it is not a "cure all" solution, the researchers argue that lowering entry grades for certain pupils could work as part of a package of measures.

Dr Lewis Paton, another member of the research team at the University of York, said: "Bright pupils from less well performing schools sometimes don't apply to medical school because they or their teachers don't think they'll make the grades required to get in. If medical schools started to contextualise A Level results, it could make access to studying medicine appear more achievable."

The researchers argue that widening access to medical degrees is not just a matter of social fairness; it is also something that would benefit the UK's health services.

Dr Tiffin added, "The NHS needs more doctors from under-represented minority groups. Having doctors from a wider range of backgrounds would enable health professionals to better understand and meet the UK's diverse healthcare needs."

Clare Owen, Assistant Director of the Medical Schools Council, said "This research adds important data to our understanding of how entry requirements relate to subsequent performance. The Medical Schools Council recognises the benefits of admissions which take applicants' backgrounds into account and this year published a guide which collects together the best practice of medical schools as they implement contextual admissions. Each medical school must decide on the best approach for its circumstances and this research will help them by making a significant contribution to the evidence base"

The study looked at data on medical students who had taken the UK Clinical Aptitude Test (UKCAT) - the admissions test used by most UK universities for admissions to their medical degree programmes. The dataset included information on schools attended by applicants, A level results, admissions to medical degrees and performance on the course.

*What is the effect of secondary (high) schooling on subsequent medical school performance? A national, UK based, cohort study is published in **BMJ Open**. The study was partly funded by The National Institute for Health Research (NIHR).*

http://bit.ly/2ku6rMz

Rehabilitating lactate: From poison to cure

Once thought to cause muscle fatigue, it's now being investigated as a treatment for disease

George Brooks has been trying to reshape thinking about lactate - in the lab, the clinic and on the training field - for more than 40 years, and finally, it seems, people are listening. Lactate, it's becoming clear, is not a poison, it's the antidote.

In a recent article in the journal *Cell Metabolism*, Brooks, a professor of integrative biology at the University of California, Berkeley, reviews the history of the misunderstanding of lactate - often called lactic acid - a small molecule that plays a big role in metabolism. Typically labeled a "waste" product produced by muscles because lactate rises to high levels in the blood during extreme exercise, athletic trainers and competitive athletes think of lactate as the cause of muscle fatigue, reduced performance and pain.

Starting in the 1970s, however, Brooks, his students, postdoctoral fellows and staff were the first to show that lactate wasn't waste. It was a fuel produced by muscle cells all the time and often the preferred source of energy in the body: The brain and heart both run more efficiently and more strongly when fueled by lactate than by glucose, another fuel that circulates through the blood.

"It's a historic mistake," Brooks said. "It was thought that lactate is made in muscles when there is not enough oxygen. It has been thought to be a fatigue agent, a metabolic waste product, a metabolic poison. But the classic mistake was to note that when a cell was under stress, there was a lot of lactate, then blame it on lactate. The proper interpretation is that lactate production is a strain response, it's there to compensate for metabolic stress. It is the way cells push back on deficits in metabolism."

Gradually, physiologists, nutritionists, clinicians and sports medicine practitioners are beginning to realize that high lactate levels seen in

the blood during illness or after injury, such as severe head trauma, are not a problem to get rid of, but, in contrast, a key part of the body's repair process that needs to be bolstered.

"After injury, adrenaline will activate the sympathetic nervous system and that will give rise to lactate production," Brooks said. "It is like gassing up the car before a race."

Without this added fuel, the body wouldn't have enough energy to repair itself, and Brooks says that studies suggest that lactate supplementation during illness or after injury could speed recovery.

Over the course of decades of research, Brooks has discovered that there are at least three main uses of lactate in the body: It's a major fuel source, it's the major material to support blood sugar level and it's a powerful signal for metabolic adaptation to stress.

"The reason I wrote the review is that people in all these different disciplines are seeing different effects of lactate, and I am pulling it all together," said Brooks. "Lactate formulations have been used for decades to fuel athletes during prolonged exertions; it's been used widely for resuscitation after injury and to treat acidosis. Now, in clinical experiments and trials, lactate is being used to help control blood sugar after injury, to fuel the brain after brain injury, to treat inflammation and swelling, for resuscitation in pancreatitis, hepatitis and dengue infection, to fuel the heart after myocardial infarction and to manage sepsis."

Brooks's research has already benefitted endurance athletes. In 1989, he worked with a sports firm to create an energy drink called Cytomax that includes a lactate polymer that can gives athletes an energy boost before and during competition. A combination of lactate, glucose and fructose, it takes advantage of the different ways the body uses fuel: lactate can get into the blood twice as fast as glucose - peaking in just 15 compared to 30 minutes after drinking. Most sports drinks contain only glucose and fructose.

Lactate shuttle

Brooks is a physiologist who has focused on exercise and nutrition since joining the UC Berkeley faculty in 1971. He discovered that normal muscle cells produce lactate all the time, and coined the term "lactate shuttle" to describe the feedback loops by which lactate is an intermediary supporting the body's cells in many tissues and organs.

We all store energy in several forms: as glycogen, made from carbohydrates in the diet and stored in the muscles; and as fatty acids, in the form of triglycerides, stored in adipose tissue. When energy is needed, the body breaks down glycogen into lactate and glucose and adipose fat into fatty acids, all of which are distributed throughout the body through the bloodstream as general fuel. However, Brooks said, he and his lab colleagues have shown that lactate is the major fuel source.

Glucose and glycogen are metabolized through a complex series of steps that culminate in lactate. For almost a century, scientists and clinicians believed that lactate is only made when cells lack oxygen. However, using isotope tracers, first in lab animals and then in people, Brooks found that we make and use lactate all the time.

This is what he calls the lactate shuttle, where "producer" cells make lactate and the lactate is used by "consumer" cells. In muscle tissue, for example, the white, or "fast twitch," muscle cells convert glycogen and glucose into lactate and excrete it as fuel for neighboring red, or "slow twitch," muscle cells, where lactate is burned in the mitochondrial reticulum to produce the energy molecule ATP that powers muscle fibers. Brooks was the first to show that the mitochondria are an interconnected network of tubes -- a reticulum - like a plumbing system that reaches throughout the cell cytoplasm.

The lactate shuttle is also at work as working muscles release lactate that then fuels the beating heart and improves executive function in the brain.

In discovering the lactate shuttle and mitochondrial reticulum, Brooks and his UC Berkeley colleagues have revolutionized thinking about metabolic regulation in the body; not just in the body under stress, but all the time.

For decades scientists and clinicians believed that in cells, glycogen and glucose are degraded to the lactate precursor substance called pyruvate. That turned out to be wrong, since pyruvate is always converted to lactate, and in most cells lactate rapidly enters the mitochondrial reticulum and is burned. Working with lactate tracers, isolated mitochondria, cells, tissues and intact organisms, including humans, Brooks and UC colleagues discovered what had been missed and, consequently, misinterpreted. More recently, others have used magnetic resonance spectroscopy (MRS) to confirm that lactate is continuously formed in muscles and other tissues under fully aerobic (oxygenated) conditions.

Brooks notes that lactate can be a problem if not used. Conditioning in sports is all about getting the body to produce a larger mitochondrial reticulum in cells to use the lactate and thus perform better.

Tellingly, when lactate is around, as during intense activity, the muscle mitochondria burn it preferentially, and even shut out glucose and fatty acid fuels. Brooks used tracers to show that both the heart muscle and the brain prefer lactate to glucose as fuel, and run more strongly on lactate. Lactate also signals fat tissue to stop breaking down fat for fuel.

"One of the important things about lactate is that it gets into the circulation and participates in inter-organ communication," said Jen-Chywan "Wally" Wang, a UC Berkeley professor of nutritional sciences and toxicology. "Which is why it's very important in normal metabolism and an integral part of whole-body homeostasis."

Lactate is the body's VISA

In his review, Brooks emphasizes three major roles for lactate in the body: It's a major source of energy; a precursor for making more glucose in the liver, which helps support blood sugar; and a signaling molecule, circulating in the body and blood and communicating with different tissues, such as adipose tissue, and affecting the expression of genes responsible for managing stress.

For example, studies have shown that lactate increases the production of Brain-Derived Neurotropic Factor (BDNF), which in turn, supports neuron production in the brain. And, as a fuel source, lactate immediately improves the brain's executive function, whether lactate is infused or comes from exercise.

"It's like the VISA of energetics; lactate is accepted by consumer cells everywhere it goes," he said.

The fact that lactate is an all-purpose fuel makes it a problem in cancer, however, and some scientists are looking for ways to block the lactate shuttles in cancer cells to cut off their energy supplies.

"Recognition that lactate shuttles among producer and consumer cells in tumors offers the exciting possibility of reducing carcinogenesis and tumor size by blocking producer and recipient arms of lactate shuttles within and among tumor cells," he wrote in his review.

All this presages a turnaround in the appreciation of lactate, though Brooks admits that textbooks - except for his own, Exercise Physiology: Human Bioenergetics and Its Applications, now in its fourth edition - still portray lactate as a bad actor.

"Lactate is the key to what is happening with metabolism," Brooks said. "That is the revolution."

http://bit.ly/2si1TfO

The obesity paradox:

Large study finds people hospitalized for infections are twice as likely to survive if they are overweight or obese

A study of more than 18,000 patients in Denmark, presented at this year's European Congress on Obesity in Vienna, Austria (23-26), shows that patients admitted to hospital for treatment for any infectious disease are around twice as likely to survive if they are overweight or obese. This research on the so called 'obesity paradox' is by Sigrid Gribsholt, Aarhus University Hospital Department of Clinical Epidemiology, Denmark, and colleagues.

The association between body mass index (BMI) and mortality remains controversial. From an evolutionary perspective, obesity and associated proinflammatory defences may protect against death from infections. In this new study, the authors examined the impact of body-mass index on outcome after any acute incident hospital admission for infection in a population based study.

The study team identified 35,406* persons with an incident acute medical or surgical inpatient admission for an infectious disease during 2011?2015 in the Central Denmark Region. They examined risk of death within 90 days after discharge date in association with underweight, overweight and obesity, versus normal weight as reference. They adjusted for potential confounding factors, and examined the influence of recent weight change, comorbidities, cancer, and tobacco smoking on the association between BMI and mortality.

Compared with patients of normal weight, the adjusted risk of death following infection was 2.2 times higher in patients with underweight. However, no mortality increase was observed among patients with stable underweight, i.e., no recent weight loss which could indicate other health problems. In contrast, patients with overweight were 40% less likely to die and those who were obese 50% less likely to die than those of normal weight.

Among patients with obesity, presence or absence of recent weight changes, comorbidities, cancer, or smoking had little effect on the association with decreased mortality.

The authors conclude: "Overweight and obesity were associated with substantially reduced 90 day mortality following incident hospital admission for infection. An association between underweight and increased mortality was confined to patients with recent weight loss, suggesting confounding by other hidden disease."

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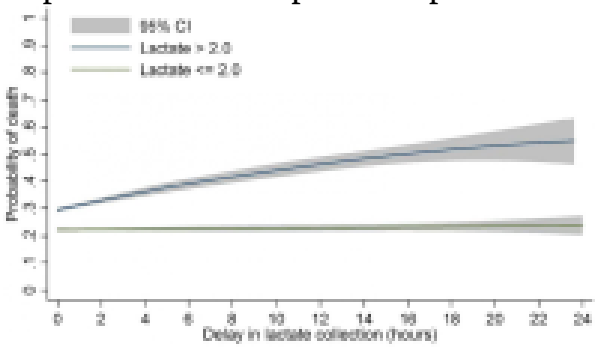
Each hour of delay in detecting abnormal lactates in patients with sepsis increases the odds of in-hospital death

Earlier lactate measurements correlate with quicker treatment with antibiotics and better outcomes, according to a new study in the journal CHEST®

Glenview, IL - The rising incidence of sepsis, a leading cause of in-hospital death, has prompted the Centers for Medicare and Medicaid Services (CMS) to issue protocols known as care bundles to standardize and improve sepsis care. Because of a known association between elevated lactate levels and increased mortality, the guidelines mandate that lactate levels should be tested soon after the onset of sepsis. A new study in the journal CHEST® found that a significant proportion of patients with suspected sepsis do not have their lactates measured within the recommended timeframe. These patients experienced delayed antibiotic therapy and IV fluid administration, as well as increased risk of in-hospital death.



This is the relationship between delay in initial lactate measurement and the probability of in-hospital mortality for patients meeting SEP-1 criteria, stratified by level of initial lactate value (mmol/L) and adjusted for patient location, eCART score, and lactate value. **CHEST**

According to first author Xuan (Susan) Han, MD, Department of Medicine, University of Chicago, Chicago, IL, USA, "Sepsis continues to be a major public health problem in the US, one with persistently high mortality despite continued efforts to improve care. Our goal with this study was to better understand, on a more granular level, how sepsis bundles affect the patients we apply them to."

The guidelines, issued in 2015 by the CMS, are SEP-1 (Severe Sepsis and Septic Shock Early Management Bundle). One of the recommendations is the measurement of serum lactate between six hours before and three hours after severe sepsis presentation, followed by a repeat within six hours of presentation if the initial lactate is elevated.

"Systematic early lactate measurements in patients presenting with sepsis would result in a significant increase in the number of lactates measured on patients but may be of benefit in identifying patients with elevated initial lactates who are at risk for poorer outcomes. Patients with early lactate measurements received earlier interventions such as antibiotic administration, which is known to improve mortality in sepsis," explained Matthew M. Churpek, MD, MPH, PhD, of the Department of Medicine and Center for Healthcare Delivery, Science and Innovation at the University of Chicago, Chicago, IL, USA.

To see what was being done in actual clinical practice, researchers at the University of Chicago reviewed the records of close to 150,000 patients admitted to a single tertiary care academic hospital from November 2008 to January 2016. Information regarding each patient's characteristics, vital signs, laboratory measurements, and medical therapy was analyzed. There was a particular focus on lactate measurements and levels.

They identified 5,762 admissions that met the three SEP-1 criteria for severe sepsis within a six-hour period. Of these, only 60 percent had an initial lactate drawn within the SEP-1 specified timeframe. Fourteen percent had their levels measured between three and 24 hours after the time of first suspicion of sepsis ("delayed lactates"), and more than one quarter had no lactate measurements at all.

Whether lactates were measured promptly varied with where the patient was being treated. Seventy-nine percent of patients treated in the emergency department had levels measured within the specified time period compared with 55 percent in the intensive care unit (ICU) but only 32 percent in hospital wards. "Our study demonstrates that a large number of patients become newly septic on the wards. This is an important population of patients in which to effectively and quickly identify and treat sepsis," commented Dr. Churpek.

Mortality increased with higher initial lactate levels. For example, in the ICU, the mortality rate was 35 percent for patients with a normal initial lactate level compared with 62 percent for those with elevated lactate levels. Most troubling, in patients with elevated lactate levels at the first draw, each hour of delay was associated with a 2 percent increase in the odds of in-hospital death. Importantly, it took approximately twice as long for patients with delayed lactate measurements to receive antibiotics and more than three times as long for them to receive fluids when compared with patients who had lactates drawn within the SEP-1 window.

"The SEP-1 bundle is the most recent national effort at standardizing and improving sepsis care, but the evidence supporting its various measures is mixed or lacking. In addition, SEP-1 has been highly controversial. This study better characterized the patients affected by SEP-1, as well as the impact of one component of SEP-1, lactate measurement, on hospitalized patients. Systematic early lactate measurements when a patient presents with sepsis may thus be useful in prompting earlier, potentially life-saving interventions," added Dr. Churpek.

http://bit.ly/2sjfH9w

The three muses of scientific discovery

Inspiration, experimentation and happy accidents are all pathways to a breakthrough

By Derek Lowe

How much of a great new idea is supposed to come from sheer inspiration? The related questions are how much should be coming from brute-force experimentation (these days generally machine-aided) and how much from sheer accident and coincidence? Those are, I would submit, three of the main sources for what looks, from a distance, like a single spring of knowledge. So when we triumphantly dip a cup into it, what's the blend we're drinking?

We can bring in some distinguished expert witnesses to speak to each point. For lone inspiration, we have Isaac Newton's answer to a question about how he was able to come up with so many discoveries in mathematics and physics: 'By thinking on them continually'. (Note: this is necessary, but not sufficient, to become the next Isaac Newton.)

For trial-by-error experimentation, there's Thomas Edison's remark about the perspiration-to-inspiration ratio of genius (99 to one was his estimate). And for being in the right place at the right time, I would cite Francis Crick on the discovery of the DNA structure: 'It's true that by blundering about we stumbled on gold, but the fact remains that we were looking for gold.'

The ability to pick the right area to look is not to be underestimated; it's actually a high-level scientific function

Crick had a point there, as he often did. To quote one more distinguished witness, Louis Pasteur: 'Fortune favours the prepared mind.' Prize-winning discoveries have been wadded up and thrown into the trash or poured into the waste jar by people who didn't realise what they were looking at. And that may be the most important ingredient of all: the ability to recognise something worthwhile when it does arrive. None of these methods (grabbing your head with both hands and staring at the ceiling, setting up hundreds of repetitive trials or blundering about) will prove efficacious otherwise. The ability to pick the right area to look is not to be underestimated; it's actually a high-level scientific function.

This is more important than ever before thanks to our increasing dependence on machines. This dependence has been increasing from at least the 17th century, but it's been accelerated by advances in both the physical and intellectual sides of industry. Physically, automation and miniaturisation have made brute-force experimentation feasible in ways that would have made Edison completely lose consciousness. And intellectually, various data-mining and machine-learning approaches have allowed us to work with far more information than the human mind is capable of dealing with.

I believe we should celebrate this, but it's not a view that's shared universally. To pick one example, finding new chemical reactions by random experimentation, which is now feasible through automated reaction screening, is looked at by some as inelegant at best and somehow 'cheating' at worst. New reactions and new discoveries, they argue, should come through brainpower and inspiration and not through blundering about more rapidly than ever. But anyone in drug discovery who feels this way, frankly, should consider the intersection of that worldview with the realities of high-throughput screening. There is no greater display of experimental brute force. (As an aside, when I was first starting out in the drug industry a new room had been prepared for the hot new field of computer-aided drug design, with a 'CADD' sign on the door. The chemists across the hall responded with a sign of their own: BADD, for brain-aided drug design.)

Am I saying that flashes of insight and inspiration aren't needed? Certainly not – they're vital. But they are not sufficient, either. We have to be ready for happy accidents when they happen, and we have

to be ready to let low-level experimentation show us the way when that's appropriate, too. A romantic view of human capabilities is of little use against problems that we have no guarantee are even capable of being solved by humans. The Elizabethan scientist Francis Bacon called on science to achieve 'the effecting of all things possible', and we'll need every tool in the chest to realise it. We should put down our pride and our preconceptions and get to work.

http://bit.ly/2siU1eT

Clothes Treated with 'Hot Feet' Coating Could Keep Ticks Away

Scientists at the Centers for Disease Control and Prevention (CDC) think they can fight the scourge of tick-borne diseases by encouraging people to douse their clothes in a chemical called permethrin.

By Rafi Letzter, Staff Writer

In a new study, published today (May 24) in the Journal of Medical Entomology, researchers showed that permethrin-treated clothes can seriously mess up a tick's stride. Stick some adult ticks on a pair of regular pants tilted at a 45-degree angle, and 100 percent of them will still be clinging on 5 minutes later.

The blacklegged tick (Ixodes scapularis), lone star tick (Amblyomma americanum), and American dog tick (Dermacentor variabilis) all found themselves damaged by permethrin in clothes. **CDC Public Health Image Library**

Stick adult ticks on a pair of tilted pants treated with permethrin, though, and 42.5 percent will tumble off entirely. Even those that remain get seriously messed up. The researchers found that only 25 percent of the ticks were moving normally even 24 hours after exposure.

"All tested tick species and life stages experienced irritation, the 'hot-foot' effect, after coming into contact with permethrin-treated clothing," Lars Eisen, a CDC entomologist who worked on the study, said in a statement.

Permethrin isn't a new chemical. You can already buy clothes coated in the stuff, which one manufacturer markets as repelling "mosquitoes, ticks, ants, flies, chiggers and midges" and persisting on the clothes through at least 70 rounds in the washing machine. Drugs.com recommends it as a treatment for lice and scabies, and states that it's not known to be toxic to humans — though it can cause some mild irritation in some people.

Researchers said in the paper that it's still not known how long permethrin remains effective in clothing, because all the clothes they tested were "pristine" and freshly treated. But these results do suggest real benefits to permethrin-treated socks, pants and other clothes, they said.

Ticks are responsible for a number of serious diseases, as Live Science has previously reported, including Lyme disease. And their range appears to be spreading, likely due to climate change . That means that, for scientists at the CDC, the project of stopping them is ever more urgent.

http://bit.ly/2Jq8oKi

Congress Passes "Right to Try" Bill

Medical groups have criticized the legislation, which will give terminal patients access to experimental treatments, as dangerous and unnecessary.

By Jim Daley | May 23, 2018

On Tuesday (May 22), the US House of Representatives passed controversial legislation that will allow patients with life-threatening illnesses to use experimental medications without the approval of the Food and Drug Administration. The Senate already passed the bill in August 2017. After some wrangling with the language, the House

passed the Senate's version at the prodding of the White House, most recently expressed in a statement released Monday (May 21). President Donald Trump is expected to sign the bill quickly, according to *The Washington Post*.

"Far too many patients in our country are faced with terminal illnesses for which there are no treatments approved by the Food and Drug Administration (FDA)," the White House statement reads. "The Administration believes that these patients and their families should be able to seek access to potentially life-saving therapies while those treatments are still under review by the FDA."

Critics of the legislation argue that it may make patients vulnerable to con artists. Removing FDA supervision of new drugs would "provide fly-by-night physicians and clinics the opportunity to peddle false hope and ineffective drugs to desperate patients," Frank Pallone (D-NJ) argued during the House floor debate, *The Post* reports. If the bill will benefit patients, Pallone said, "why does every major patient group overwhelmingly oppose it?"

In February, Michael Becker, a former biotech executive who has terminal cancer, told *NPR* why he opposes the bill. "The problem becomes that you have a lot of false hope as a terminal cancer patient. You want to cling to anything that's going to sound like it's an opportunity to live longer or have a better quality of life," said Becker. "That hope can sometimes cover up the realities of some of the more sinister aspects of getting a drug, which are things go wrong. So I could take a drug that was purported to help me, and it may actually make my condition worse."

Over the past year, FDA commissioner Scott Gottlieb has been ambivalent so-called right-to-try proposals. Last fall, *STAT News* reported that Gottlieb voiced concerns over the bill's potential to undermine the FDA's authority. But in a May 17 tweet, Gottlieb says he is "comfortable" with what lawmakers have developed.

https://theatln.tc/2ktkXE8

The Asteroid That Smote the Dinosaurs Burned the Birds Out of Trees

Forest fires killed off tree-dwelling species and left the ground-dwelling ones to restart the avian dynasty.

An artist's impression of a bird walking through a burning forest after the dinosaur-killing asteroid struck Earth. **Philip Krzeminski**

Around 66 million years ago, at the end of the Cretaceous period, an asteroid the size of Mount Everest smote the Earth. It landed in Mexico's Yucatan peninsula, punching a 20-mile deep crater into the ground. That impact, and the climatic upheaval that happened afterwards, ended the long reign of the dinosaurs. Of this dynasty of ruling reptiles, only the birds—a specialized group of feathered dinosaurs—survived. But the birds didn't escape unscathed.

Birds first appeared around 150 million years ago, during the late Jurassic period. They evolved from small predatory dinosaurs that were similar to *Velociraptor*. By the end of the Cretaceous, they were flourishing. But the same catastrophe that finished off their dinosaur cousins also killed most of them off. Even incredibly diverse and widespread groups, like the enantiornithines (eh-NAN-tee-OR-nih-theens), died out. The surviving birds were forced to re-evolve much of the diversity that once existed, and most groups of modern birds arose from those survivors, in the aftermath of the asteroid strike.

But which lineages survived, and why?

"A lot of people have focused quite intensively on trying to understand what went extinct [at the end of the Cretaceous]," says Daniel Field, from the University of Bath. "But we know very little about how or why birds managed to sneak across." In a new study,

Field and his colleagues have shown that the species that made it through the extinction event mostly lived on the ground, as modern chickens do today. They walked and strutted into the future, while their relatives that perched in branches and flew through trees largely died out—because many of those branches and trees were on fire.

Field's team looked at the habits of modern birds, and worked backward in time to reconstruct the likely lifestyles of their shared ancestors. The ancestral species that gave rise to all living ones "was almost certainly a ground-dwelling bird," Field says. That's not to say it was flightless; it was probably something like today's tinamous, small-bodied birds from Central and South America that *can* fly but mostly choose not to. It was only after a short period that many groups independently took to the trees once again, replacing the tree-dwelling species that had disappeared.

Pollen grains provide a clue as to why this was the case. They fossilize incredibly well, and scientists can easily recover them in the hundreds of thousands. By looking at these ancient grains at a site in North Dakota, the team showed that all over the world, tree pollen almost completely disappears in the immediate aftermath of the asteroid strike. During that time window, the pollen is replaced by the spores of ferns—pioneer plants that are usually the first to regrow in landscapes denuded by fires and other catastrophes.

This so-called fern spike also exists in almost every other continent. "This seems to be a really global signature," says Field. "Within 1,500 kilometers of the impact site, forests would have been flattened." But the heat that radiated from the impact also ignited wildfires on a global scale, scorching trees worldwide. Any trees that escaped the flames then had to deal with a curtain of acid rain, and a blanket of atmospheric soot and ash that blocked out much of the sun's energy.

As the trees burned and withered, any birds that foraged, perched, nested, and courted among them would likely have died. Field's team estimates that it took a thousand years for forests to recover, and for birds to start readapting to life within them.

There's one possible problem with this interpretation, says Zhonghe Zhou from the Institute of Vertebrate Paleontology and Paleoanthropology, or IVPP, in Beijing. It certainly *seems* from the fossil record that tree-dwelling birds died out after the asteroid strike. Then again, those species are less likely to fossilize well than ground-dwelling birds. "We need more fossil evidence to support [Field's] hypothesis," Zhou says.

"It's a great idea," adds Jingmai O'Connor, also from the IVPP. "But we need to get over this one-answer-for-everything way of thinking. No one factor caused the end-Cretaceous extinction and similarly no one factor caused the extinctions within [the birds]."

Field actually agrees. Massive fires may well have kicked the tree-dwelling species out of their perches, but other factors were at work, too. His own team had previously shown that smaller species stood a better chance of survival, maybe because only they could find enough food in charred, sun-starved landscapes. O'Connor has suggested that the evolution of a more efficient digestive system allowed some groups to better thrive than others. And other researchers have suggested that reproductive traits, like laying bigger eggs, were important.

Living away from trees wasn't a universal lifeline, either. Luis Chiappe, from the Natural History Museum of Los Angeles County, notes that not all enantiornithines lived in trees, and the ground-dwelling lineages also went extinct. Field's hypothesis doesn't explain why. Nor does it clarify why marine species, such as the cormorant-like *Hesperornis* and the tern-like *Ichthyornis*, also died out.

"Forest loss was only one of several factors working in combination that determined which bird lineages survived," O'Connor adds.

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Calling Out the FDA's 'We Don't Regulate Medicine' Mantra

Opinion: The FDA Can Do a Better Job of Regulating Drug Approvals

Vinay Prasad, MD, MPH

The US Food and Drug Administration (FDA) likes to say, "We don't regulate the practice of medicine." As an example, in a recent journal article, authors from the FDA wrote: "[T]he practice of medicine is outside the FDA's purview."[1] And regarding the FDA's decision to rescind the approval for Avastin in breast cancer, an FDA spokeswoman said, "The drug will still be available and the FDA doesn't regulate the practice of medicine."[2]

"We don't regulate medicine" is something of an FDA catch phrase, and while it is technically true, it is also naive. It's like a cop who sees a car swerving and shrugs it off with, "I don't tell people how to drive."

Of course, the FDA does not tell you how to practice medicine (and no one wants them to), and the cop does not tell you how fast to accelerate and where to turn. But they are each responsible for enforcing standards—in the cop's case, for how we drive; and in the FDA's case, the standard for drug approval.

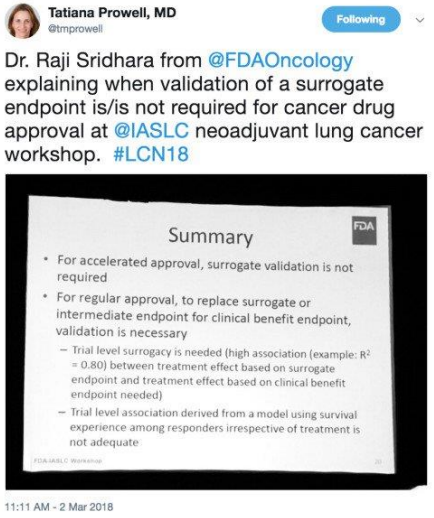
The problem with the FDA is that they have set the bar too low.

The problem with the FDA is that they have set the bar too low and, at times, failed to meet even their own stated threshold for drug approval. Consider this: Nearly two thirds of cancer drugs are being approved solely on the basis of surrogate markers of benefit—like tumors shrinking on scans—as opposed to improvements in quantity or quality of life.[3] This would be okay as long as the FDA later asked drug makers to show that these drugs improve survival or quality of life. But research by Chul Kim, of Georgetown University, and I has found that only 14% (5/36) of drugs approved on the basis of a surrogate later showed a survival benefit with a follow-up of 4.4 years on the US market.[3]

Some approvals that are based on a surrogate endpoint are through the FDA's accelerated approval program, meaning there is a postmarketing study to verify efficacy, and having this program makes sense and is a good idea.

However, other approvals that are based on a surrogate are regular approvals, meaning the FDA doesn't require a postmarketing study of efficacy. Here you have to be cautious. You really need to know that the surrogate has a proven track record of predicting survival because you may not get more information later.

The FDA agrees and says regular approvals must be based on "established" surrogates.[4] Here is a tweet of a slide from an employee of the FDA:



The FDA says clearly, "For regular approval...validation is necessary." But the FDA is not demanding that validated surrogates be used. Kim and I found that for 11 of 30 (37%) regular approvals, there is no validation study in the entire medical literature, period.[4] They just don't exist. In only 3 of 30 (10%) approvals is there a strong, proven correlation between the surrogate and survival.[4]

The cop who says, "I don't tell people how to drive" is right. But when someone blows past at 92 miles an hour and the cop doesn't act, you might respond, "But you enforce the speed limit, right?" Similarly, the FDA doesn't tell you how to practice medicine. But they do say that regular approval requires validated surrogate endpoints, and they don't enforce that rule.

Growing Concern

Approving many new drugs give the impression of advancement and innovation, but it is only advancement and innovation if patients are better off. There is a growing cadre of experts who are concerned that this may not always be the case.

Ajay Aggarwal in *Nature* recently wrote, "[A] drug that shrinks tumors might not help to extend people's lives." He added, "Approvals that let drugs stay in the marketplace on the basis only of quick, easy surrogate end-points are unlikely to produce highly effective treatments; we will simply get more drugs providing marginal value."[5]

This is precisely my concern.

When the FDA Forgets Their 'We Don't Regulate Medicine' Mantra

But in some cases, the FDA is doing the opposite—giving approvals where they are not necessary, where doctors can already use those drugs for that purpose as part of the practice of medicine.

For example, the FDA seems to forget their "we don't regulate medicine" slogan when it comes to certain approvals—specifically, if a cancer drug is already on the US market and the FDA approves it for a second or third purpose on the basis of bad data.

Doctors already have access to these drugs; they can already use them for the alternative purpose. It's called off-label prescribing, and it is ubiquitous in cancer medicine. It will even be reimbursed, if recommended by one of several compendia or guidelines. If the FDA doesn't regulate medicine, and the data behind these expanded indications are bad, there is no need for the FDA to weigh in. They don't have to approve it.

Just look at sunitinib for adjuvant kidney cancer, an approval that came out this year. We've used sunitinib for metastatic kidney cancer for over a decade, but this year, the FDA said it is authorized for use in the adjuvant setting, for high-risk patients after the tumor is resected.[6]

Make no mistake—this was a bad approval.

Make no mistake—this was a bad approval. The drug didn't improve survival in two adjuvant studies.[7] It didn't even delay recurrence in one.[7] And it lowers quality of life.[8,9] The doctors who discussed it at the drug advisory meeting had a misunderstanding of what had been shown.[10] They didn't seem to know that overall survival results were in the supplement of the paper. Researchers have gone as far as calling this approval "regulatory capture," meaning it was so bad that it is as if the FDA is working for the drug companies, not the people.[11]

To the FDA: If you don't regulate the practice of medicine, you don't need to give second or third approvals based on unproven surrogates, like sunitinib in the adjuvant setting for kidney cancer, or pertuzumab for neoadjuvant breast cancer.[12]

After all, doctors could still use it if they wanted. If they felt strongly, they could even put it in the guidelines. Instead, you can say, "We don't regulate the practice of medicine. Do what you want, but you will only have our blessing when you show that the drug truly benefits patients."

Constructive Criticism

Unquestionably, the world is a better place with the FDA than without them. The FDA does an okay job, but they can be better. Here is my constructive criticism:

- ***Only use regular approval when it meets your own standard—the surrogate endpoint used in the clinical trial has been validated.***
- ***As long as you continue to say, "We don't regulate the practice of medicine," let that cut both ways. You don't have to bend over backwards to give second or third approvals based on bad data. You can say no.***

Cops don't tell us how to drive, but we want them to pull over reckless drivers. The FDA is no different. No one wants them in the exam room, but they have a mandate to approve cancer drugs that are safe and effective. "Effective" means that they make people live longer or better, and not merely change the results of CT scans. It is time that the FDA remembered that.

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http://bit.ly/2Ly4H16

New link found between alcohol, genes and heart failure

Scientists have revealed a new link between alcohol, heart health and our genes

The researchers investigated faulty versions of a gene called titin which are carried by one in 100 people or 600,000 people in the UK. Titin is crucial for maintaining the elasticity of the heart muscle, and faulty versions are linked to a type of heart failure called dilated cardiomyopathy.

Now new research suggests the faulty gene may interact with alcohol to accelerate heart failure in some patients with the gene, even if they only drink moderate amounts of alcohol.

The research was carried out by scientists from Imperial College London, Royal Brompton Hospital, and MRC London Institute of Medical Sciences, and published this week in the latest edition of the Journal of the American College of Cardiology. The study was supported by the Department of Health and Social Care and the Wellcome Trust through the Health Innovation Challenge Fund.

In the first part of the study, the team analysed 141 patients with a type of heart failure called alcoholic cardiomyopathy (ACM). This condition is triggered by drinking more than 70 units a week (roughly seven bottles of wine) for five years or more. In severe cases the condition can be fatal, or leave patients requiring a heart transplant.

The team found that the faulty titin gene may also play a role in the condition. In the study 13.5 per cent of patients were found to carry the mutation - much higher than the proportion of people who carry them in the general population.

These results suggest this condition is not simply the result of alcohol poisoning, but arises from a genetic predisposition - and that other family members may be at risk too, explained Dr James Ware, study author from the National Heart and Lung Institute at Imperial.

"Our research strongly suggests alcohol and genetics are interacting - and genetic predisposition and alcohol consumption can act together to lead to heart failure. At the moment this condition is assumed to be simply due to too much alcohol. But this research suggests these patients should also be checked for a genetic cause - by asking about a family history and considering testing for a faulty titin gene, as well as other genes linked to heart failure," he said.

He added that relatives of patients with ACM should receive assessment and heart scans - and in some cases have genetic tests - to see if they unknowingly carry the faulty gene.

In a second part of the study, the researchers investigated whether alcohol may play a role in another type of heart failure called dilated cardiomyopathy (DCM). This condition causes the heart muscle to become stretched and thin, and has a number of causes including viral infections and certain medications. The condition can also be genetic, and around 12 per cent of cases of DCM are thought to be linked to a faulty titin gene.

In the study the team asked 716 patients with dilated cardiomyopathy how much alcohol they consumed.

None of the patients consumed the high-levels of alcohol needed to cause ACM. But the team found that in patients whose DCM was caused by the faulty titin gene, even moderately increased alcohol intake (defined as drinking above the weekly recommended limit of 14 units), affected the heart's pumping power.

Compared to DCM patients who didn't consume excess alcohol (and whose condition wasn't caused by the faulty titin gene), excess alcohol was linked to reduction in heart output of 30 per cent.

More research is now needed to investigate how alcohol may affect people who carry the faulty titin gene, but do not have heart problems, added Dr Paul Barton, study co-author from the National Heart and Lung Institute at Imperial:

"Alcohol and the heart have a complicated relationship. While moderate levels may have benefits for heart health, too much can cause serious cardiac problems. This research suggests that in people with titin-related heart failure, alcohol may worsen the condition.

"An important wider question is also raised by the study: do mutations in titin predispose people to heart failure when exposed to other things that stress the heart, such as cancer drugs or certain viral infections? This is something we are actively seeking to address."

The research was supported by the Department of Health and Social Care and Wellcome Trust through the Health Innovation Challenge Fund, the Medical Research Council, the NIHR Cardiovascular Biomedical Research Unit at Royal Brompton & Harefield NHS Foundation Trust and the British Heart Foundation.

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Study finds that chewing gum while walking affects both physical and physiological functions, especially in middle-aged and elderly men

Chewing gum while walking increases heart rate and energy expenditure

New research presented at this year's European Congress on Obesity (ECO) in Vienna, Austria (23-26) May shows chewing gum while walking increases heart rate and energy expenditure. The study was conducted by Dr Yuka Hamada and colleagues at Waseda University, Graduate School of Sport Sciences, Saitama, Tokyo, Japan.

Although there have been a number of studies which have examined the effect of chewing gum on physiological functions while at rest, none have focused specifically on how it impacts the body while walking, which is the basis for this study.

The authors recruited 46 male and female participants aged 21-69 to participate in two trials in random order. In one trial, individuals were given 2 pellets of gum (1.5g and 3 kilocalories per pellet) to chew while walking at their natural pace for 15 minutes after a 1-hour rest period. The control trial involved the same 1-hour rest and 15 minute

walk, however participants were given a powder to ingest which contained the same ingredients as gum, but did not require them to chew.

In each trial resting heart rate, mean heart rate during walking, distance covered, and cadence (rate at which they took steps) were measured. Mean walking speed was calculated from the distance travelled during the 15 minutes, and stride length was estimated from the mean walking speed and mean step count. Total energy expenditure during the walk was estimated based on the mean walking speed and the body mass of each participant.

The study found that in all participants, the mean heart rate while walking as well as the change in heart rate from being at rest was significantly higher in the gum trial than in the control trial.

The team then performed stratified analyses by sex and age, separating the group into male and female, as well as young (39 and under), middle-aged and elderly (40 and older). Both male and female participants in the gum trial had a significantly higher mean heart rate while walking and change in heart rate, however in males there was also a significant increase in the distance walked and mean walking speed when compared to the control trial. (see p627, full paper, link below).

While all ages experienced a significantly larger change in heart rate in the gum trial, middle-aged and elderly participants also had a significantly higher mean heart rate while walking compared to the control.

Combining these analyses to incorporate both sex and age showed that chewing gum had the greatest effect in middle-aged and elderly men who experienced a significant positive effect on distance walked, mean walking speed, mean step counts, mean heart rate while walking, change in heart rate, and total energy expenditure compared to the control trial.

The authors conclude: "Chewing gum while walking affects a number of physical and physiological functions in men and women of all ages. Our study also indicates that gum chewing while walking increased the walking distance and energy expenditure of middle-aged and elderly male participants in particular."

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World's Largest Pterosaur Jawbone Discovered in Transylvania

The largest pterosaur jawbone on record has just been analyzed

By Laura Geggel, Senior Writer | May 25, 2018 07:00am ET

The largest pterosaur jawbone on record has just been analyzed, and it's so big that it likely helped the prehistoric beast gulp down freshwater turtles and large dinosaur eggs for dinner more than 66 million years ago, a new study finds.

The reconstructed skull of Dracula, another pterosaur found in the same region of Romania as the newly analyzed specimen. **Axel Schmidt/Dinosaurier Museum**

The fossil of the pterosaur's robust lower jaw is a mere 7.4 inches (18.8 centimeters) long, but the jawbone likely measured longer than a yardstick — or between 37 and 43 inches (94 and 110 cm) — when the reptile was alive, the researchers wrote in the study.

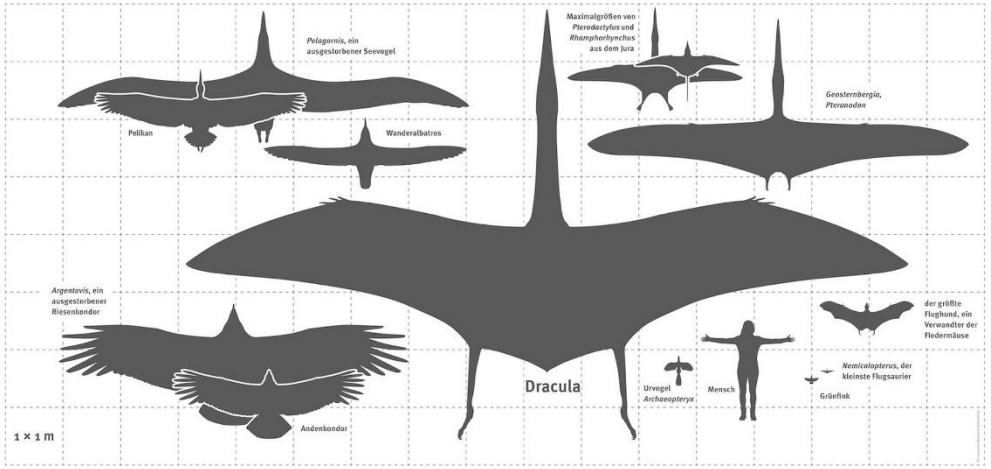
This absurdly long jaw is "more than three times the size of the complete, 290-millimeter-long [11.4 inches] holotype mandible of *Bakonydraco*," a pterosaur that appears to be closely related to the newly analyzed creature, the researchers wrote in the study.

Study co-researcher Dan Grigorescu, a geologist at the University of Bucharest in Romania, collected the fossilized jawbone at the junction of two creeks in the Haţeg Basin, near the village of Vălioara, which is in Transylvania, Romania, in 1984. But the fossil

wasn't recognized as belonging to a pterosaur until 2011, when lead study researcher Mátyás Vremir, a geologist at the Transylvanian Museum Society, and study co-researcher Gareth Dyke, a paleontologist at the University of Debrecen in Hungary, realized its importance, according to National Geographic.

During the Cretaceous period, when this pterosaur was alive, Haţeg Basin was an island inhabited by dwarf dinosaurs, which were smaller than their counterparts on the mainland. Vremir unearthed the fossilized remains of one of these weird, stocky dinosaurs — a predator known as *Balaur bondoc* — in 2009, Live Science previously reported.

But Haţeg is also known for large pterosaurs, including *Hatzegopteryx*, which likely stood as tall as a giraffe, with a wingspan of up to 36 feet (10.9 meters). Another pterosaur from Haţeg, nicknamed Dracula, had an even larger wingspan of up to 39 feet (12 m).



The newly studied specimen is slightly smaller than Dracula, shown here.
Dinosaurier Museum

"Islands are notorious for throwing up oddities. We have a bunch of weird dinosaurs from Haţeg and a lack of really big carnivores, so the pterosaurs were basically tyrannosaur surrogates," Dave Hone, a paleontologist at Queen Mary University of London in England, told National Geographic.

But just because the newly studied pterosaur — which has yet to be scientifically named — has the largest jawbone ever found, it doesn't necessarily mean it was the biggest pterosaur on record, the researchers said. Rather, it probably had a wingspan of over 26 feet (8 m) and likely belonged to a family of pterosaurs known as the Azhdarchids, the researchers wrote in the study.

"It's always exciting to see new Azhdarchid material in the literature, especially fossils of giant pterosaurs," Kierstin Rosenbach, a doctoral student in the Department of Earth and Environmental Sciences at the University of Michigan who wasn't involved in the study, told Live Science.

The researchers discussed the different sizes and shapes of Azhdarchid pterosaurs — characteristics that are much appreciated by paleontologists who study pterosaurs, she said. That's because there appears to be a division within Azhdarchidae that the researchers elaborated on: "The authors state that Azhdarchids could have either long necks with thin skulls or short necks with robust skulls," Rosenbach said.

So, which camp does the newly analyzed pterosaur fall into? It's likely "a robust, short-skulled azhdarchid," the researchers said in the study. The study was published online April 17 in the journal Lethaia.