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Stroke research: 32 hits

32 independent genomic regions shown to be associated with stroke

Researchers have analyzed genetic data from half a million subjects in a search to identify the underlying causes of stroke, a complex vascular disease. Scientists at Ludwig-Maximilians-Universitaet (LMU) in Munich led the the huge collaborative Project.

Stroke is the second most common cause of both death and disability-adjusted life-years worldwide, but its molecular mechanisms remain poorly understood. A new study now provides extensive novel insight on the biology and pathways leading to stroke. An international research consortium has identified 22 new genetic risk factors for stroke, thus tripling the number of gene regions known to affect stroke risk. The results demonstrate shared genetic influences with multiple related vascular conditions, especially blood pressure, but also coronary artery disease, venous thromboembolism and others. Linking these results with extensive biological databases provides novel clues on stroke mechanisms and illustrates the potential of genetics to identify drug targets for stroke therapy.

The results of the largest genetic study on stroke thus far were now published online in the journal *Nature Genetics*. The study was based on DNA samples of 520,000 European, North- and South American, Asian, African, and Australian participants of whom 67,000 had a stroke. These were derived from 29 large studies. From the millions of genetic variants analyzed, 32 independent genomic regions were shown to be associated with stroke of which two thirds are novel.

The study was conducted by members of MEGASTROKE, a large-scale international collaboration launched by the International Stroke Genetics Consortium, an international multi-disciplinary collaborative of experts in stroke genetics from around the world who have been working together for the past 10 years. MEGASTROKE members include research groups from Germany, France, the UK, Japan, USA, Iceland, Spain, Switzerland, Italy, Belgium, the Netherlands, Denmark, Sweden, Norway, Finland, Estonia, Poland, Singapore, Australia, and Canada.

"Because the extent to which individual variants modify stroke risk is very small, it required a large number of subjects to discover these variants. Our group has leveraged extensive datasets set up by numerous researchers over the past few years," says Martin Dichgans, Professor of Neurology and Director at the Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, and one of the leaders of the current study.

"We can't overstate the importance of international collaboration across different ethnic origins when studying genetics of complex, common diseases like stroke. This large-scale collaboration across continents has been a game changer," says Stephanie Debette, Professor of Epidemiology and Neurologist at University of Bordeaux and Bordeaux University Hospital, leading a research team at INSERM Center U1219, and another leader of the study.

Stroke can originate from alterations in various parts of the vasculature including large arteries, small arteries, the heart, and the venous system and the researchers found genetic risk factors implicated in each of these mechanisms. They showed that some genetic risk factors contribute to specific mechanisms and others to stroke susceptibility at large. They further found shared genetic influences between stroke caused by vessel occlusion (the most common cause of stroke) and stroke caused by rupture of a blood vessel (the most catastrophic cause of stroke), often thought to have opposite mechanisms.

When the researchers took a closer look on the genomic areas pinpointed in the study, they noticed that several of them overlap with genomic areas known to be implicated in related vascular conditions such as atrial fibrillation, coronary artery disease, venous thrombosis, or vascular risk factors, especially elevated blood pressure, and less so hyperlipidemia.

By adding data on gene expression, protein expression, and other characteristics in multiple cell types and tissues compiled by their co-

investigators the researchers obtained first insights into the specific genes, molecular pathways, and cell and tissue types through which the new genetic risk factors cause stroke.

The researchers further found that the genes they identified are enriched in drug targets for antithrombotic therapy, used to re-open occluded blood vessels in patients with acute stroke or to prevent vascular events including stroke. "These findings illustrate the potential of genetics for drug discovery," says Martin Dichgans.

"These genetic findings represent a first step towards developing personalized, evidence-based treatments for this very complex disease. They provide evidence for several novel biological pathways involved in stroke that may lead to the discovery of novel drug targets," said Rainer Malik, a researcher at the ISD, LMU and first author of the study.

"These interesting findings - linking stroke with multiple other disease states and with dysregulation of genes, proteins, and molecular pathways in specific cell types and organs - were generated using novel bioinformatics approaches that utilize and combine information from various international biological databases. Such datasets are invaluable in situations like this when tissue samples from patients are not readily available, underscoring the importance of data sharing, commented Martin Dichgans.

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Scientists find treasure trove of 110 genes linked to breast cancer

Scientists have linked 110 genes to an increased risk of breast cancer in the most comprehensive study ever to unpick the genetics of the disease.

Their study used a pioneering genetic technique to analyse maps of DNA regions linked to an inherited risk of breast cancer and identify the actual genes involved in raising a woman's risk.

Researchers also linked 32 of the new genes to the length of time women survived breast cancer - suggesting these could be important in the development of the disease and potential targets for future treatments.

Scientists at The Institute of Cancer Research, London, looked in detail at 63 areas of the genome that had previously been associated with the risk of breast cancer by mapping studies.

Finding the genes responsible for the increased risk is not straightforward because small sequences of DNA can interact with completely different parts of the genome through a strange phenomenon known as 'DNA looping'.

But the researchers, funded by Breast Cancer Now, used a technique they developed called Capture Hi-C to study interactions between different regions of the genome.

The study - published today (Monday) in *Nature Communications* - uncovered which specific genes were involved and how that might increase a woman's risk of developing breast cancer.

The team at the Breast Cancer Now Toby Robins Research Centre at The Institute of Cancer Research (ICR) found that some of the 63 regions of the genome were physically interacting with genes more than a million letters of DNA code away.

They were able to identify 110 new genes that could potentially be causing an increased risk of breast cancer across 33 of the regions they studied. In the remaining 30 areas, they were unable to find any specific genes.

One third of the target genes for which they had patient data - 32 out of 97 - were also linked to survival in women with oestrogen receptor-positive breast cancer, suggesting they play an important role in the disease. In the future, testing for these genes could help pick out women who are most at risk of developing the disease - or they could be explored as targets for new drugs.

Scientists at the ICR - a research institute and charity - studied DNA loops in cells from four different types of breast cancer and normal, healthy cells to find out which genes were consistently involved in looping interactions.

Most of the 110 genes found in the study had not been linked to breast cancer risk before, and further work will be needed to determine the extent of their role in the disease.

One of these, called FADD, has previously been linked to head and neck cancer and lung cancer and could be a promising target for new cancer therapies.

Previous large-scale genetics studies have implicated 14 of the 110 genes as playing a role in breast cancer risk, such as the oestrogen receptor gene ESR1, showing that Capture Hi-C is an effective tool for picking up risk genes.

Dr Olivia Fletcher, Team Leader in Functional Genetic Epidemiology at The Institute of Cancer Research, London, said: "Our study took the high-level maps of breast cancer risk regions and used them to pull out specific genes that seem to be associated with the disease. "We studied how DNA forms loops to allow physical interactions between a DNA sequence in one part of the genome and a risk gene in another.

"Identifying these new genes will help us to understand in much greater detail the genetics of breast cancer risk. Ultimately, our study could pave the way for new genetic tests to predict a woman's risk, or new types of targeted treatment."

Baroness Delyth Morgan, Chief Executive at Breast Cancer Now, which funded the study, said: "These are really important findings. We urgently need to unravel how the genetic changes in the building blocks of our DNA influence a woman's risk of breast cancer, and this study adds another vital piece to this jigsaw.

"More women are now being diagnosed with breast cancer than ever before, and these crucial findings could ultimately help us more accurately predict who is most at risk and develop new targeted treatments.

"Many of these genes have been relatively undocumented to date and we now hope further research will untangle their exact role in breast cancer risk, and how we could use them to stop more women developing the disease."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said: "Large-scale genomic studies have been instrumental in associating areas of our DNA with an increased risk of breast cancer. This study brings these regions of DNA into sharper focus, uncovering a treasure trove of genes that can now be investigated in more detail.

"The ways in which particular genes influence cancer risk are highly complex. In the future, a better understanding of the genes identified in this study could lead to the discovery of new targeted drugs, or new strategies to improve diagnosis or prevention of the disease."

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Elephant declines imperil Africa's forests

As elephant populations shrink, forest composition and structure will undergo dramatic change

DURHAM, N.C. - Poaching and habitat loss have reduced forest elephant populations in Central Africa by 63 percent since 2001. This widespread killing poses dire consequences not only for the species itself but also for the region's forests, a new Duke University study finds.

Populations of forests elephants, which play key roles in maintaining forest habitat, have declined 63 percent in Central Africa since 2001. Without intervention to prevent further losses, 96 percent of the region's forests could undergo major change. **John Poulsen, Duke University**

"Without intervention to stop poaching, as much as 96 percent of Central Africa's forests will undergo major changes in tree-species composition and structure as local populations of elephants are extirpated and surviving populations are crowded into ever-smaller forest remnants," said John Poulsen, assistant professor of tropical ecology at Duke's Nicholas School of the Environment.

These changes will occur because elephants are ecological engineers that help create and maintain forest habitat by dispersing seeds,

recycling and spreading nutrients, and clearing understories, Poulsen explained.

"Because they are very large animals, they can eat fruits and disperse seeds too big for other animals to digest. And because they are highly mobile, they help disperse these seeds far and wide through their dung," he said.

In the elephants' absence, scores of tree species may be left without a means of long-distance seed dispersal, which is essential for forest structure and colonization. Trees whose seeds are dispersed by smaller animals could fill the void, dramatically altering forest composition.

Fewer elephants will also mean a more limited distribution of the nutrients contained in their dung.

"Many of Central Africa's forests are nitrogen limited. Elephants help compensate by moving nutrients, especially nitrogen, across the landscape as they defecate. If populations continue to shrink, this nitrogen will be concentrated in smaller and smaller areas, limiting future tree growth elsewhere," Poulsen said.

Understory density will also be affected.

"Elephants have a large effect on forests by eating or trampling slow-growing plants and opening the understory, allowing more light in and reducing competition for water and nutrients," Poulsen said. "These changes alter the recruitment regimes of tree species -- favoring some and not others."

He and his colleagues published their peer-reviewed study March 1 in the journal Conservation Biology.

To conduct their analysis, they reviewed 158 previous studies on forest elephant behaviors and their cascading ecological impacts. By cross-referencing these impacts with data on local elephant populations, forest tree-species composition and structure, nutrient availability, and understory growth in existing Central African forests -- both protected and unprotected ones alike -- Poulsen and his team determined that up to 96 percent of all forests in the region were susceptible to dramatic changes if elephant populations shrank or disappeared.

"Stopping poaching is an urgently needed first step to mitigating these effects," he said, "but it will not be easy. Long-term conservation will require land-use planning that incorporates elephant habitat into forested landscapes that are being rapidly transformed by industrial agriculture and logging."

Coauthors of the new paper are recent Duke Ph.D. graduate Cooper Rosin; current doctoral students Amelia Meier and Chase Nunez; undergraduate Jennifer Callejas; Master of Environmental Management graduates Emily Mills, Emily Blanchard, Sarah Moore and Mark Sowers; and former postdoc Sally E. Koerner, now on the faculty at the University of North Carolina Greensboro.

Funding came from the Duke University Center for International and Global Studies and the Africa Initiative at Duke.

CITATION: "Ecological Consequences of Forest Elephant Declines for Afrotropical Forests," John R. Poulsen, Cooper Rosin, Amelia Meier, Emily Mills, Chase Nunez, Sally E. Koerner, Emily Blanchard, Jennifer Callejas, Sarah Moore and Mark Sowers. Conservation Biology, *March 1, 2018. DOI: 10.1111/cobi.13035*

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Investigators identify neural circuit, genetic 'switch' that maintain memory precision

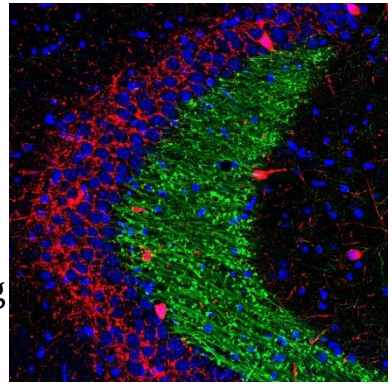
Targeting levels of abLIM3 protein could improve memory in aging, reduce symptoms of PTSD

Investigators from the Massachusetts General Hospital (MGH) Center for Regenerative Medicine and the Harvard Stem Cell Institute (HSCI) have identified a neural circuit mechanism involved in preserving the specificity of memories. They also identified a genetic 'switch' that can slow down memory generalization - the loss of specific details over time that occurs in both age-related memory impairment and in post-traumatic stress disorder, in which emotions originally produced by traumatic experiences are elicited in response to innocuous cues that have little resemblance to the traumatic memory.

"The circuit mechanism we identified in mice allows us to preserve the precision or the details of memories over the passage of time in adult as well as aged animals," says Amar Sahay, PhD, of the MGH Center for Regenerative Medicine and HSCI, corresponding author of a paper appearing in Nature Medicine. "These findings have implications for

the generalization of traumatic memories in PTSD and for memory imprecision in aging."

Memories are generated in the seahorse-shaped brain structure called the hippocampus and stored in the prefrontal cortex at the front of the brain. Memory formation involves cells in a portion of the hippocampus called the dentate gyrus, and memories are thought to be conveyed to the prefrontal cortex via the CA subregions of the hippocampus, specifically subregions CA3 and CA1. The hippocampus also is believed to play a continuing role in the stabilization of memories in the cortex - maintaining the precise details that keep one memory from being confused with another and preventing issues ranging from not being able to remember dinner selections from a week ago to age-related memory issues.



A molecular switch identified by Mass. General Hospital researchers can increase the number of contacts between dentate gyrus cells (green) and CA3 interneurons (red) in the hippocampus, which may improve memory precision in adulthood and aging. **Nannan Guo, PhD, Sahay Lab, Center for Regenerative Medicine, Massachusetts General Hospital**

Hyperactivity of this hippocampal circuitry has been observed in aged animals - rodents, non-human primates and humans - and alterations in hippocampal structure are seen in patients with PTSD. The current study was designed to investigate the hypothesis that inhibitory signals passing from dentate gyrus cells (DGCs) to the CA3 subregion help to constrain hyperactivity and maintain the stability and precision of memories over time.

A key finding by Sahay's team was identification of a protein called abLIM3 - highly expressed in DGCs but absent in the CA field of mouse brains - that acts as a molecular brake on the inhibitory signals DGCs exert onto the CA3 subregion. Experimental manipulation of abLIM3 levels in DGCs in adult mice revealed that decreasing abLIM3 levels increased the delivery of inhibitory signals to CA3 neurons. A series of experiments with mouse models showed that manipulation of abLIM3 levels within DGCs could slow down the process of memory generalization.

Using a classical behavioral conditioning protocol, the investigators first trained the animals to expect an unpleasant sensation, a mild but not painful foot shock, in a particular context, such as being placed into a box with dark walls. Typically, when animals are placed in the same context, they will 'freeze' in expectation of the shock but will do not react to a context not associated with the shock, such as a box with light walls. But after two weeks, the memory will generalize and the animals will 'freeze' when place in any context, even one with little resemblance to that in which they received the foot shock.

In contrast, decreasing abLIM3 levels within DGCs maintained the specificity of the memory over time so that, even two weeks later, the mice would only freeze when placed into the foot-shock associated context. The investigators also found that decreasing abLIM3 levels in aged mice reversed age-related alterations in DGC-CA3 circuitry and improved memory precision. A recent study by another group found significantly increased abLIM3 levels in the circulation of aged humans who are beginning to show signs of memory impairment.

"Our ability to improve memory precision in both adult and aged mice by essentially 'flipping a genetic switch' suggests that targeting abLIM3 expression in DGCs may lead to similar improvement in aged humans, a strategy we are actively pursuing," says Sahay, who is an associate professor of Psychiatry at Harvard Medical School and principal faculty of the Harvard Stem Cell Institute. "Since overgeneralization of traumatic memories is a hallmark of PTSD, we are also keen to assess abLIM3 levels in patients with PTSD and investigate whether reducing abLIM3 expression could prevent the activation of traumatic memories."

Nannan Guo, PhD, of the MGH Center for Regenerative Medicine and Department of Psychiatry is lead author of the Nature Medicine paper. Additional co-authors are Charlotte Herber, Michael TaeWoo Kim, Antoine Besnard, PhD, and Paoyan Lin, MGH Center for Regenerative Medicine; Marta Soden, PhD, and Larry Zweifel, PhD, University of Washington,

Seattle; and Xiang Ma, PhD, and Constance Cepko, PhD, Harvard Medical School. Support for the study includes National Institutes of Health grants R01 MH104175, R01 AG048908, and 1R01 MH111729 and support from the Ellison Family Foundation. A patent application covering the targeting of abLIM3 to improve memory precision in aging and PTSD has been filed.

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More deaths, strokes seen with perioperative beta blocker one year after surgery

One-year follow-up results of POISE trial mirror those seen at 30 days

ORLANDO - During the 12 months after undergoing noncardiac surgery, patients with or at risk for heart disease who were treated with the beta blocker metoprolol for 30 days were less likely than patients who received a placebo to have a heart attack, but more likely to die or have a stroke, according to research presented at the American College of Cardiology's 67th Annual Scientific Session.

These follow-up findings confirm that an increased risk for death or a stroke persists at one year post-surgery in patients treated with metoprolol, said P.J. Devereaux, MD, PhD, director of cardiology at McMaster University in Hamilton, Canada, and lead author of the study. Previously reported results from the same study at 30 days post-surgery showed a similar pattern, with a reduction in heart attacks but increases in deaths and strokes.

"Our results suggest at one year, for every 1,000 patients having noncardiac surgery, treatment with metoprolol would prevent heart attacks in 12 patients but would result in an excess of 13 deaths and six strokes," Devereaux said.

"While there is little doubt that some patients benefit from receiving beta blockers during the period immediately before and after noncardiac surgery, these data show that at least as many patients are seriously harmed," he said. "These data tell us that we need to exercise caution when using beta blockers in this setting until we figure out how to mitigate the substantial risks and enable all patients to obtain the potential benefits of this intervention."

Beta blockers work by slowing the heart rate and relaxing the blood vessels, which in turn reduces blood pressure. The problem, Devereaux said, is that during the period immediately after major noncardiac surgery (such as a hip or knee replacement, bowel resection or abdominal aortic aneurysm repair), patients are usually treated with opioid medications to relieve pain. The effects of those medications may mask drops in blood pressure or heart rate to dangerously low levels.

"Low blood pressure, or hypotension, is common in this setting and is a main contributor to the adverse effects resulting from perioperative beta blockers," he said.

Patients who become hypotensive for whatever reason after surgery (e.g., sepsis, bleeding, heart failure) find their problem exacerbated when they are receiving a beta blocker, which further lowers blood pressure and makes treating hypotension more challenging.

The PeriOperative Ischemic Evaluation (POISE) trial enrolled 8,351 patients in 23 countries. Eligible patients were 45 years or older and had a history of heart disease, blood-vessel disease, stroke, congestive heart failure or other health problems such as diabetes or impaired kidney function. Patients' median age was 69 and 63 percent were men.

Patients were randomly assigned to receive metoprolol or a placebo, beginning a few hours before surgery and for 30 days afterward. Patients, health care providers and research staff, except those analyzing data, were blinded to which group received metoprolol and which received a placebo. The study's primary endpoint was a composite of the combined rate of death from heart disease, nonfatal heart attack and nonfatal cardiac arrest after 30 days.

At one-year follow-up, fewer patients in the metoprolol group than in the placebo group had heart attacks (5 percent vs. 6.2 percent), but more patients in the metoprolol group had died (9.8 percent vs. 8.5 percent in the placebo group) or had a stroke (2 percent vs. 1.4 percent in the placebo group).

These results followed the same pattern that had previously been seen at the 30-day follow-up: statistically fewer heart attacks in the metoprolol group (4.2 percent vs. 5.7 percent in the placebo group), but statistically more deaths (3.1 percent vs. 2.3 percent in the placebo group) and strokes (1 percent vs. 0.5 percent in the placebo group).

According to Devereaux, some observers have suggested that the metoprolol dose received by patients in the POISE trial (200 mg per day) was too high and that a lower dose would have produced fewer adverse effects. However, a lower dose might also have decreased the drug's effectiveness in reducing heart attacks, he said, noting that the metoprolol dose in POISE only resulted in a seven beats per minute lower heart rate compared with placebo.

"I believe the answer is more continuous patient monitoring during the immediate post-surgical period so that dangerous drops in heart rate or blood pressure are promptly identified and treated," he said.

Devereaux and his colleagues are currently conducting a study to test the effectiveness of remote automated patient monitors in reducing post-surgical cardiac complications.

This study was funded by the Canadian Institutes of Health Research.

http://bit.ly/2FSUyMo

You are not just you—you are a chimera

In Greek mythology, the chimera was a fire-breathing monster—part goat, part snake and part lioness. Guess what? You are a bit like this—a patchwork of genes and foreign cells.

Karl Gruber Freelance Science Writer

You are not just you—you are a chimera

In every part of your body—from the brain cells inside your head and the cells making up all your organs inside your body to the genome within each cell—there are bits and pieces that originally came from someone (or something) else. These foreign cells and genes are found in everyone, and their role is yet to be fully understood.

So, in case you are wondering, here are some ways in which you are a chimera.

A genomic chimera

Let's start with your genome. Rather than being a unique feature of our bodies, our genome is not entirely our own. We share bits and pieces with other species. Back in the day, it seems like our ancestors really liked to mix things up.

For instance, people with non-African ancestry share as much as 2% of their genome with Neanderthals—ancient human cousins who lived some 30,000 years ago.

Some tribes in Oceania share up to 5% of their genome with Denisovans—a mysterious group of ancient humans who lived 80,000 years ago in Siberia, Russia. But it doesn't stop there.

Viruses are also an integral part of our genome. For example, pieces of one type of viruses, called retroviruses, are present in more than 8% of our genome. This is quite a number, especially if you realise there are about 19,000 protein-coding genes, or just a bit over 1% of our genome.

Scientists think some of these viruses have been in our genome for quite a while, even dating back to 30 million years ago, way before we were considered officially human. It seems that some of these ancient viruses were acquired by our chimp ancestors before our own species formed and stuck around until our times. Our patchwork make-up doesn't stop with our genome. Our cells, too, have a mixed up story tell.

A chimera of cells

Did you know that some of your cells still live in your mum's body and that some of your mum's cells are still found in you? Yeah, it is a bit mind boggling.

The condition is called microchimerism, and it has been known for about 100 years. It has been studied more meticulously in the past decades, but there is still no consensus regarding what these microchimeric cells do in the body. But it seems to happen during all pregnancies in both directions.

"Maternal microchimerism is very common, likely to occur in every individual and occurs in every known mammalian species that has been studied (mice, non-human primates and so on). Same with fetal

microchimerism—these cells have been found for decades in mothers after pregnancy, so these cells likely persist in individuals for life," says Dr Sing Sing Way, an infectious disease paediatrician at Cincinnati Children's Hospital.

The piece of you in mum

It all starts when you are a tiny baby inside your mum, connected via the umbilical cord. While pregnant, your mum's blood carries not only food and oxygen, but also cells from both of you get exchanged.

The idea is that the presence of these baby cells helps your mum's immune system realise that her baby is not a dangerous bug that needs zapping but a friendly bug. But there is more.

After you were born, some of these cells stay around in your mum's body, settling in different organs, and some studies have shown that these chimeric cells may actually be helping your mum with future pregnancies. In some cases, it has been shown that women carrying microchimeric cells lived for longer than their counterparts lacking cells.

One intriguing link involves cancer. Several studies have found these microchimeric cells in tissues affected by different types of cancer, like breast, skin and cervical cancer. The idea is that these cells are there to help fight the tumour. But it could go both ways, as scientists don't know yet whether these cells are friend or foe.

"In general, your cells participate in repair tasks of your mum's body … although this can sound helpful, we're not sure it always is," says Associate Professor Kiarash Khosrotehrani at the University of Queensland.

The observation that these microchimeric cells are less common in women with different types of cancers seems to support the idea of a protective role for these cells. But it is all speculative, as there is no mechanism on the table yet.

The piece of mum in you

The same applies the other way around. While you were in your mum's belly, a small number of cells from your mum made it all the way into your body. And, even while you were breastfeeding from mum, you likely received a few cells from her along with the tasty milk.

All these 'mum cells' stayed with you, settling in different places. Now studies suggest that these cells may be playing important roles. One study in mice, for example, found that carrying these microchimeric cells resulted in reproductive benefits for the female offspring.

Other benefits reported for these cells include improved tolerance of transplanted organs. Microchimeric cells have also been linked to type 1 diabetes and scleroderma, a condition characterised by hardening of the skin, but further research is needed to clarify their role.

So, in a way, you are not just you. You are a crazy mix of different persons and species, which all together make up who you are.

http://bit.ly/2peDSWd

Skulls show women moved across medieval Europe, not just men

The newcomers who arrived in the little farming villages of medieval Germany would have stood out: They had dark hair and tawny skin, spoke a different language and had remarkably tall heads.

by Frank Jordans

Now scientists who investigated the unusually shaped skulls say they provide evidence that women also migrated long distances across medieval Europe, not just men. A genetic analysis showed the women traveled from what is now Romania, Bulgaria and northern Greece at a time when the continent was being reshaped by the collapse of the Roman Empire.

In a study published Monday by the *Proceedings of the National Academy of Sciences*, researchers say the women's elongated heads—a result of binding done after birth—suggest they might have been high-class individuals.

"These women looked extremely different to the local women, very exotic if you will," said one of the researchers, Joachim Burger, a population geneticist at the University of Mainz, Germany.

With colleagues from Europe and the United States, Burger compared the genetic profile of almost 40 human remains unearthed from 5th and 6th century burial sites in Bavaria, along the Isar and Danube rivers.

They expected to find the telltale signs of centuries of Roman presence in the area—soldiers from the Mediterranean leaving their genetic mark on the location population. Instead, it looked "very central or northern European—blond and fair-skinned, like modern-day Scandinavians," Burger said.

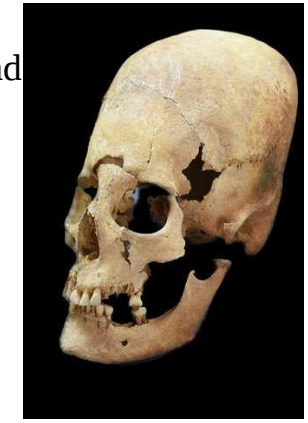
Undated photo provided by the State collection for Anthropology and Palaeoanatomy Munich shows strong, intermediate and non-deformed skulls, from left, from the Early Medieval sites Altenerding and Straubing in Bavaria, Germany. Scientists investigating unusual skulls found at dozens of 5th and 6th century burial sites say they appear to provide evidence of long-distance female migration at a time when the continent was being reshaped by the collapse of the Roman empire. **(State collection for Anthropology and Palaeoanatomy Munich via AP)**

The exception was a group with deformed skulls. Known from various cultures across the world, artificially elongated skulls may have been considered a form of beauty or denoted high status because of the time and effort required to bandage a child's head, said Burger.

While the practice is often associated with the Huns who swept into Europe from the East during the 5th century, the genetic makeup of the women found in Bavaria showed little Asian ancestry, suggesting that either head binding had been adopted by people living in southeastern Europe or emerged there independently.

"This is a sound study with quite interesting results," said Jean-Jacques Hublin of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. He had no role in the research.

"Usually large-distance movements involve more males—explorers, soldiers, political elite, etc.—and short range movements are more common for females (spouses moving to their husband's family)," Hublin said via email.



While it's unclear why the women—apparently without men—traveled such a long distance, the study's authors speculate that they may have represented strategic alliances between distant populations across Europe.

Photo provided by the State collection for Anthropology and Palaeoanatomy Munich shows an artificially deformed female skull from Altenerding, an Earyl Medieaval site in Bavaria., Germany. Scientists investigating unusual skulls found at dozens of 5th and 6th century burial sites say they appear to provide evidence of long-distance female migration at a time when the continent was being reshaped by the collapse of the Roman empire. **(State collection for Anthropology and Palaeoanatomy Munich via AP)**

"They must have come on purpose," said Burger. "It's not a single case, there are quite a few of them."

Despite their foreign origins, the women integrated into Bavarian society, according to the researchers. They wore the same clothes as the locals and were buried with the same artifacts. Burger said further research is needed to see whether the women intermarried with the local population.

More information: *Krishna R. Veeramah el al., "Population genomic analysis of elongated skulls reveals extensive female-biased immigration in Early Medieval Bavaria," PNAS (2018). www.pnas.org/cgi/doi/10.1073/pnas.1719880115*

http://bit.ly/2tUO5fe

Like Ancient Snowball Earth, Frozen Planets May Still Be Habitable

A new model suggests ice-locked worlds might contain oases of temperate land that could support life

By Shannon Hall on March 13, 2018

Roughly 650 million years ago vast sheets of glaciers stretched from the poles to the tropics, entombing Earth within a frozen skin that

lingered for millions of years. And this had happened before: Our "pale blue dot" has transformed into a pearly-white "snowball Earth" at least three times in our planet's history. But these deep freezes present a conundrum: They should have been deadly and yet life clearly survived. There is both geologic evidence our earliest microscopic ancestors did not freeze to death and genetic indications the lineages of a range of single-celled organisms extend beyond snowball Earth. The question is how.

A new study published to the preprint server arXiv and submitted to *Earth and Planetary Science Letters* might provide a resolution. Adiv Paradise, an astronomy graduate student at the University of Toronto (U.T.), and his colleagues modeled a variety of possible snowball worlds—varying the numbers of volcanoes they host and the amount of stellar light they receive—only to find many of these worlds would never escape snowball status. Those that had little volcanic activity would never emit enough carbon dioxide to spark the runaway global warming needed to wake them from their cryogenic slumber (as likely happened on Earth). Yet surprisingly, many of these worlds could also support large unfrozen pockets of land. Some of those areas remain dry, like the McMurdo Dry Valleys in Antarctica, but others develop local hydrological cycles, allowing liquid water to pool and flow across their surfaces.

Such oases are one explanation for how snowball worlds might remain habitable—a result that could describe not just Earth but many of the planets astronomers are discovering across the galaxy. "Before we might have brushed a snowball off as not being habitable, and we would have missed that there could be pockets of life," says co-author Diana Valencia, an astrophysicist at U.T.

Indeed, the study aligns with previous work on the most recent freezing episode in Earth's history. In 2015 Douglas Benn, a glaciologist at the University of Saint Andrews in Scotland, published a study that shows Earth's climate was sensitive to variations in our planet's orbit around the sun, resulting in cycles of ice sheet advance and retreat. The latter allowed lakes to pool, rivers to flow and simple microbial life to flourish—even during a snowball event. Benn and his colleagues saw such cycles in computer models they created of Earth's climate and they also found sedimentary deposits in the Arctic Ocean islands of Svalbard that preserve evidence for the advance and retreat of the ice sheets. The findings imply the last snowball Earth would not have been a total "deep freeze"—that ice-free pockets of land existed where water could flow—thus sustaining a crucial refuge where life could persist until more favorable conditions returned.

But ice-free zones are not the only mechanism proposed to explain how life survived on snowball Earth. Since 1992 researchers have hypothesized an array of ideas, and every scientist appears to favor a different one, says James Kasting, a geologist at The Pennsylvania State University. He has argued life might endure below a thin layer of ice. In Antarctica lakes freeze so slowly that they do not include air bubbles and thus remain transparent to sunlight—allowing photosynthetic life to thrive beneath several meters of ice. And Paul Hoffman, a retired geologist from Harvard University, argues dust might provide the most likely reprieve for life. As snow collects dust it can more readily absorb sunlight, causing ponds of meltwater to form on the ice. Such ponds are well known in polar environments today to host thriving ecosystems of algae and cyanobacteria (although Benn notes scientists have no direct geologic evidence of these ponds at the time of snowball Earth). Finally, no geologist argues against hydrothermal vents, where volcanically active areas spew water at superhot temperatures. Hot springs in Antarctica and Iceland, after all, create warm oases that ooze with life today.

Ultimately, the jury is still out on which mechanism helped life pull through snowball Earth. Although Kasting notes that the ice-free zones hypothesized by both Paradise and Benn provide one potential solution, there are several caveats to the latest model. Both he and Hoffman would like to see Paradise's team include sea glacier flow, for example, because it is possible that ice could flow from the poles to the equator,

covering the nonglaciated areas they propose. And Paradise himself lists an array of caveats for his model: it is low in resolution, took a few computing shortcuts and does not include certain processes like the effects of atmospheric dust.

At the end of the day, there might be yet another survival mechanism that no one has thought of yet, Kasting says. Or it could also be several mechanisms worked together to help life endure here on Earth. Benn argues life likely did not survive in one major environment, but multiple environments. As such, snowballs might remain habitable with the help of ice-free zones, thin ice sheets, ponds of meltwater and hydrothermal vents. Indeed, Joseph Kirschvink, a geobiologist at the California Institute of Technology who coined the phrase “snowball Earth,” has always been surprised that so many people expected life to vanish within the deep freeze. “Life is hard to extinguish—even on a snowball,” he says.

http://bit.ly/2Dub9B7

Rice U. lab surprised to find its drug-delivery system can help even without drugs

Sometimes when you're invested in a project you fail to notice things that turn out to be significant.

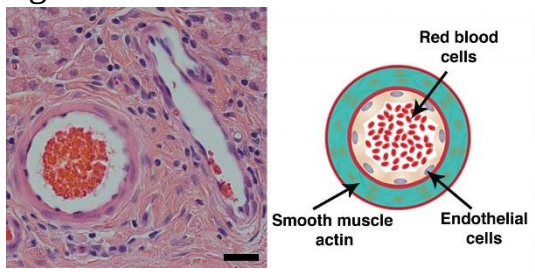
Researchers in the Rice lab of chemist and bioengineer Jeffrey Hartgerink had just such an experience with the hydrogels they developed as a synthetic scaffold to deliver drugs and encourage the growth of cells and blood vessels for new tissue.

To do so, they often tested the gels by infusing them before injection with bioactive small molecules, cells or proteins. What they didn't realize until recently was that the hydrogel itself has significant therapeutic qualities.

The lab reported in the Elsevier journal Biomaterials that a particular hydrogel, a self-assembling multidomain peptide (MDP) with the amino acid sequence K2(SL)6K2, is indeed bioactive.

Once Hartgerink and his team started to investigate the phenomenon, they found that even without additives their MDP is rapidly infiltrated by host cells, provokes a temporary inflammatory response, does not develop a fibrous capsule, supports the infiltration of a mature vascular network and recruits nerve fibers.

"We were surprised to find this strong effect in what we had previously considered to be a control peptide," Hartgerink said. "As it turned out, the inherent structure and chemistry of this peptide, despite being quite simple, results in a strong biological response."



Tests showed that subcutaneous implants, left, of a hydrogel developed at Rice University encouraged blood vessel and cell growth as new tissue replaced the degrading gel. **Hartgerink Research Group/Rice University**

The hydrogel, which can be delivered through a syringe, is designed to degrade over six weeks and leave behind healthy tissue. Because the peptides are designed from the bottom up to mimic their natural counterparts, the lab found they create an optimal environment for the body's own systems to encourage healing.

The researchers reported the natural inflammatory response when a foreign substance like a hydrogel is introduced into a system and draws cells that secrete proteins involved in cellular infiltration, scaffold degradation, vascularization and innervation. Tests on injected hydrogel showed a "statistically significant" increase in the presence of cytokines known to provoke an inflammatory response, as well as an increase in anti-inflammatory agents, both of which remained steady after day three and through two weeks.

That, Hartgerink said, indicates the hydrogel appears to harness the body's innate capacity to heal as it transitions from a pro-inflammatory to a pro-healing environment.

"As we eventually discovered, this exceptional peptide allows the body to carry out healing on its own, but with a significant boost," he said. "We believe the key step is the initial, and very rapid, cell infiltration. Once these cells are on location, they produce everything they need for

an impressive regenerative response, including angiogenesis and neurogenesis."

Hartgerink said the lab is pursuing application of the peptide for wound-healing in diabetic ulcers.

Rice graduate student Amanda Moore is lead author of the study. Co-authors are Rice graduate students Tania Lopez Silva, Nicole Carrejo, Carlos Origel Marmolejo and I-Che Li. Hartgerink is a professor of chemistry and of bioengineering.

The National Institutes of Health, the Welch Foundation, the National Science Foundation, the Mexican National Council for Science and Technology and a Stauffer-Rothrock Fellowship supported the research.

http://bit.ly/2pqe4bs

Biophysicists discover how small populations of bacteria survive treatment

Finding could lead to better antibiotic drug protocols

Small populations of pathogenic bacteria may be harder to kill off than larger populations because they respond differently to antibiotics, a new study by Emory University finds.

The journal eLife published the research, showing that a population of bacteria containing 100 cells or less responds to antibiotics randomly -- not homogeneously like a larger population.

"We've shown that there may be nothing special about bacterial cells that aren't killed by drug therapy -- they survive by random chance," says lead author Minsu Kim, an assistant professor in the Department of Physics and a member of Emory's Antibiotic Resistance Center.

"This randomness is a double-edged sword," Kim adds. "On the surface, it makes it more difficult to predict a treatment outcome. But we found a way to manipulate this inherent randomness in a way that clears a small population of bacteria with 100 percent probability. By tuning the growth and death rate of bacteria cells, you can clear small populations of even antibiotic-resistant bacteria using low antibiotic concentrations."

The researchers developed a treatment model using a cocktail of two different classes of antibiotic drugs. They first demonstrated the effectiveness of the model in laboratory experiments on a small population of E. coli bacteria without antibiotic-drug resistance. In later experiments, they found that the model also worked on a small population of clinically-isolated antibiotic-resistant E. coli.

"We hope that our model can help in the development of more sophisticated antibiotic drug protocols -- making them more effective at lower doses for some infections," Kim says. "It's important because if you treat a bacterial infection and fail to kill it entirely, that can contribute to antibiotic resistance."

Antibiotic resistance is projected to lead to 300 million premature deaths annually and a global healthcare burden of $100 trillion by 2050, according to the 2014 Review on Antimicrobial Resistance. The epidemic is partly driven by the inability to reliably eradicate infections of antibiotic-susceptible bacteria.

For decades, it was thought that simply reducing the population size of the bacteria to a few hundred cells would be sufficient because the immune system of an infected person can clear out the remaining bacteria.

"More recently, it became clear that small populations of bacteria really matter in the course of an infection," Kim says. "The infectious dose -- the number of bacterial cells needed to initiate an infection -- turned out to be a few or tens of cells for some species of bacteria and, for others, as low as one cell."

It was not well understood, however, why treatment of bacteria with antibiotics sometimes worked and sometimes failed. Contributing factors may include variations in the immune responses of infected people and possible mutations of bacterial cells to become more virulent.

Kim suspected that something more fundamental was a factor. Research has shown unexpected treatment failure for antibiotic-susceptible infections even in a simple organism like the C. elegans worm, a common model for the study of bacterial virulence.

By focusing on small bacteria populations, the Emory team discovered how the dynamics were different from large ones. Antibiotics induce

the concentrations of bacterial cells to fluctuate. When the growth rate topped the death rate by random chance, clearance of the bacteria failed. The researchers used this knowledge to develop a low-dose cocktail drug therapy of two different kinds of antibiotics. They combined a bactericide (which kills bacteria) and a bacteriostat (which slows the growth of bacteria) to manipulate the random fluctuation in the number of cells and boost the probability of the cell death rate topping the growth rate.

Not all antibiotics fit the model and more research is needed to refine the method for applications in a clinical setting.

"We showed that the successful treatment of a bacterial infection with antibiotics is even more complicated than we thought," Kim says. "We hope this knowledge leads to new strategies to fight against infections caused by antibiotic-resistant bacteria."

http://bit.ly/2Gxj5ok

Study debunks fears of increased teen suicide risk from popular flu drug

Other side effects remain a concern

A new study published by researchers from the University of Illinois at Chicago suggests that the drug oseltamivir -- commonly known as Tamiflu -- does not cause an increased risk of suicide in pediatric patients.

The U.S. Food and Drug Administration originally approved the drug in 1999, but subsequent case reports of abnormal behavior in adolescents who used the medication led the agency in 2006 to require that all packaging of the drug include a warning label about potential neuropsychiatric side effects, such as hallucinations, delirium, self-harm and even suicide.

However, clinical studies examining the association between the use of Tamiflu and neuropsychiatric side effects in children, including suicide, have so far been inconclusive and limited by methodology and potential confounding factors.

"When the FDA puts a warning out about a drug, doctors and the public take notice," said corresponding author Dr. James Antoon, assistant professor of clinical pediatrics in the UIC College of Medicine. "While the warnings are necessary, they are often not based on conclusive clinical data, which can make it difficult for physicians to truly know the potential side effects of a drug as they evaluate its possible benefits for individual patients."

To fill this gap, Antoon and his colleagues in the UIC College of Pharmacy retrospectively studied the association between the use of Tamiflu -- the only commercially available medication approved by the FDA to treat the flu -- and the most consequential of those reported side effects: suicide.

"The potential link between a drug and suicide is a particularly difficult topic to study," Antoon said. "Many events, which can happen simultaneously or over time, can influence a person to attempt suicide, as can an illness itself -- so it can be difficult to study scientifically.

"That's why we used a novel method called a case-crossover design," Antoon said. "This analysis is different because it allowed us to use each individual subject as his or her own comparison -- we retrospectively studied how patients behaved when on Tamiflu and compared it to their behavior when they were not taking the drug."

The researchers identified 21,047 children between the ages of 1 and 18 who attempted suicide during five recent flu seasons (2009-2013) from a national administrative claims database. Of this group, 251 of those children were exposed to Tamiflu, which was determined based on outpatient pharmacy dispensing data. The mean age of this group was 15 years, 61 percent were female, and 65 percent had an underlying mental health diagnosis.

"For each of the 251 patients, we assigned the 10-day period immediately before the suicide attempt as the case period and we identified up to four earlier control periods of the same length, in the same flu season," Antoon said. "This helped us to account for within-

person confounders, like depression, mental health, trauma and abuse, and other factors, like race or ethnicity."

The researchers repeated the analysis with flu diagnosis alone, without the use of Tamiflu, to see if the infection itself could have been a confounding factor associated with suicide risk.

"We did not find any association between exposure to Tamiflu and suicide in pediatric patients," Antoon said.

While Antoon believes the findings, which are published in the *Annals of Family Medicine*, will help to alleviate some fears health care providers may have about prescribing the medication in healthy children, he says doctors will likely continue to prescribe Tamiflu with caution.

"I think physicians will welcome a large, rigorous study on this topic and factor this information into their decision-making process," he said. "While this study addresses suicide, there are still many other questions about other possible neuropsychiatric side effects of the drug, which we plan to study in the future. There are also other reasons to use caution when prescribing the drug, including resistance and efficacy in children."

Co-authors on the paper are Rachel Harrington, Sruthi Adimadhyam, Todd Lee and Glen Schumock from the UIC College of Pharmacy.

The study was partially funded by an NCI training grant (5R25-CA057699) to Harrington.

http://bit.ly/2GuIKhe

Astronomers discover galaxies spin like clockwork

Astronomers have discovered that all galaxies rotate once every billion years, no matter how big they are.

The Earth spinning around on its axis once gives us the length of a day, and a complete orbit of the Earth around the Sun gives us a year.

"It's not Swiss watch precision," said Professor Gerhardt Meurer from the UWA node of the International Centre for Radio Astronomy Research (ICRAR).

"But regardless of whether a galaxy is very big or very small, if you could sit on the extreme edge of its disk as it spins, it would take you about a billion years to go all the way round."

Professor Meurer said that by using simple maths, you can show all galaxies of the same size have the same average interior density.

"Discovering such regularity in galaxies really helps us to better understand the mechanics that make them tick-you won't find a dense galaxy rotating quickly, while another with the same size but lower density is rotating more slowly," he said.

Professor Meurer and his team also found evidence of older stars existing out to the edge of galaxies.

"Based on existing models, we expected to find a thin population of young stars at the very edge of the galactic disks we studied," he said.

"But instead of finding just gas and newly formed stars at the edges of their disks, we also found a significant population of older stars along with the thin smattering of young stars and interstellar gas."

"This is an important result because knowing where a galaxy ends means we astronomers can limit our observations and not waste time, effort and computer processing power on studying data from beyond that point," said Professor Meurer.

"So because of this work, we now know that galaxies rotate once every billion years, with a sharp edge that's populated with a mixture of interstellar gas, with both old and young stars."

Professor Meurer said that the next generation of radio telescopes, like the soon-to-be-built Square Kilometre Array (SKA), will generate enormous amounts of data, and knowing where the edge of a galaxy lies will reduce the processing power needed to search through the data.

"When the SKA comes online in the next decade, we'll need as much help as we can get to characterise the billions of galaxies these telescopes will soon make available to us."

Original Publication:
'Cosmic clocks: A Tight Radius - Velocity Relationship for HI-Selected Galaxies`, published in the Monthly Notices of the Royal Astronomical Society on March 14th, 2018. Available at http://www.icrar.org/cosmic-clocks

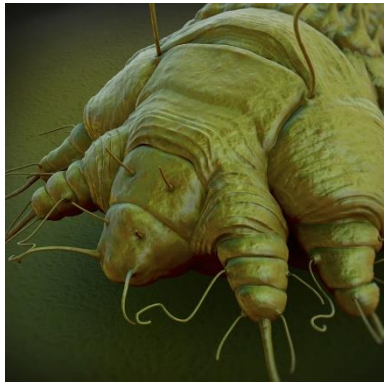
http://bit.ly/2Isrmdz

Homeopathy cancer paper withdrawn after arrest of lead authors

Investigation finds multiple problems – and no evidence – in a paper that claimed scabies could reduce tumour growth.

Andrew Masterson reports.

A journal paper claiming to show the success of a homeopathic treatment for cancer has been withdrawn by the publishers following a series of awkward discoveries – including the arrest of its two lead authors. The paper, published in the journal *Evidence-Based Complementary and Alternative Medicine*, was retracted in late February after readers voiced concerns and a formal investigation flagged multiple ethical problems.



A scabies mite. Not a cure for cancer, it turns out. **Science Picture Co/Getty Images**

The subject of the paper was "psorinum therapy" and its use in treating stomach, gall bladder, pancreatic and liver cancers. Psorinum is a peculiar favourite of homeopaths, described as a substance "prepared from the fluid of blisters from scabies infested skin".

The website *Homeopathy Plus* says that people who need psorinum "usually lack vitality and are prone to mental disturbances". The site recommends its use in treating a range of skin conditions, along with a few outliers such as ulcers and insomnia – but notably not cancer.

The lead authors of the retracted paper, father and son team Aradeep and Ashim Chatterjee, clearly thought differently. In 2001, the pair set up a trial of cancer patients, administering the scabies-fluid, along with other homeopathic substances, and a complete absence of conventional cancer meds.

This situation alone prompted readers to raise ethical questions, as did the fact that the trial did not include control or placebo inclusions. According to the science monitoring site *RetractionWatch*, however, matters became considerably more complicated when journal publishers Hindawi launched a formal investigation.

First up, the authors claimed ethics clearance for their study was granted by a review board overseeing the Critical Cancer Management Research Centre and Clinic in Kolkata, India. This raised two problems. First, the Chatterjees turned out to own the clinic in question. Second, the ethics approval was granted in 2001 – which is weird, because the clinic didn't open its doors until 2008.

Attempting to resolve these apparent inconsistencies, Hindawi sought to contact the lead authors. They were told Aradeep Chatterjee had been arrested for practicing medicine without the proper qualifications in June 2017. His father was reported to have also been arrested, two months later. Three of four additional authors said they did not agree with the paper's conclusions, and the fourth did not respond.

After Hindawi retracted the paper, RetractionWatch contacted the publishers of the *Journal of Clinical Oncology*, in which the Chatterjees have also been published. The editors are investigating.

Sadly, despite an investigation finding that the Chatterjees' "research" contained no credible evidence, several homeopathy outlets continue to encourage cancer patients to use psorinum to treat the disease.

http://bit.ly/2IskTza

A Surprising Use for Old iPhones: Brain Surgery!

In most cases, you'd probably want the doctor who's about to perform your brain surgery to set her smartphone aside before poking into your cranium.

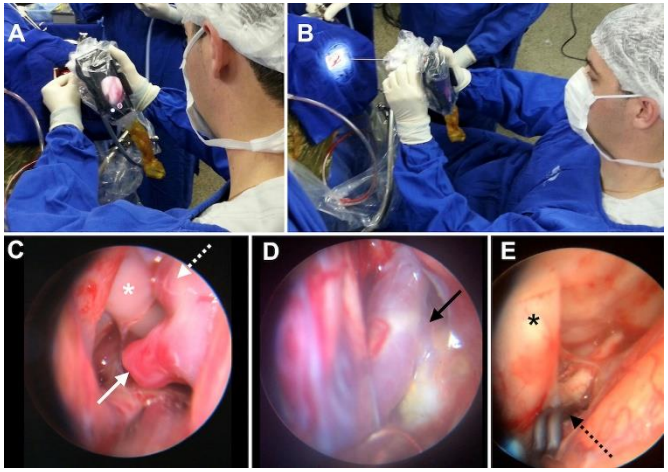
By Brandon Specktor, Senior Writer

And, in most cases, you'd be right. But what if the doctor's smartphone was a crucial part of the surgical tool kit?

According to a new paper published today (March 13) in the Journal of Neurosurgery, brain surgeons in Brazil have begun attaching old iPhones to their surgical equipment to replace the bulky, expensive

video cameras and monitors they typically use — and the doctors like it.

In fact, swapping in a smartphone made certain "minimally invasive" surgeries cheaper, more efficient, and easier to teach to rookie surgeons, the authors wrote. This phone-friendly method could even become a valuable workaround in countries whose infrastructure cannot support expensive medical equipment.



Brain surgeons in Brazil have begun attaching old iPhones to their endoscopes (panels A and B) to get a clearer view into patients' brains (panels C, D and E)
Courtesy of the American Association of Neurological Surgeons

"Our initial goal was to reduce the cost of the neuroendoscopic video set," study co-author Mauricio Mandel, a doctor at the University of São Paulo Medical School, said in a statement."In the end, we came across a new, more intuitive and fluid method of performing these procedures."

Mandel and his colleagues tested their smartphone camera on a series of neuroendoscopy surgeries — essentially, procedures that involve cutting a small hole in the patient's nose, mouth or head and using an endoscope (a long, flexible tube) to feed a camera and other surgical tools through the incision.

Typically, these procedures require a long, thin video camera to slip through the endoscope and capture the view inside the patient's head. This video feed gets transmitted to a monitor standing by the side of the operating table, which the surgeons look up at (rather than looking down at their patient).

In the new study, the authors mounted iPhones (models 4, 5 and 6) onto their endoscopes using a special adapter. Using this apparatus, they performed brain surgeries on 42 patients. This setup allowed the surgeons to keep their focus down on the patient, looking at the phone screen rather than up at a monitor, for the duration of the surgery. Using the phone's built-in Wi-Fi, the surgeons streamed the live footage to a video monitor elsewhere in the room so other members of the team could watch.

According to the authors, all 42 surgeries were successful and no complications involving the smartphones occurred. What's more, once surgeons started using a smartphone-endoscope, they chose not to switch back to the conventional method.

Funny as it may sound, there are lots of advantages to integrating smartphones into surgeries, the authors said. According to the paper, the phone's high-definition display provided an "excellent view" of the surgical site, and could be manipulated or enhanced in real time via the touch screen. Smartphones are cheaper and more portable than standard endoscopic video equipment, the authors added, and they don't require an external power source. If a surgery runs long, a surgeon can simply recharge the phone's battery without interrupting the procedure.

So, if your surgeon can't put down her iPhone, don't fret — it may be for the sake of a more streamlined surgery. If she's just using it to watch "Grey's Anatomy," however, you might have a problem.

http://bit.ly/2FOnySq

High numbers of elderly Japanese women will soon live in poverty, predicts new model

Behavior changes in the Japanese population and an unfavorable pension system are creating a system that will disproportionately impoverish elderly Japanese women

Around one in four elderly Japanese women will live below the poverty level in the near future -- with the figure rising to 50% for never-married and divorced women. In contrast, only about 10% of Japanese men will become impoverished. This is the prediction of a new model of current Japanese pension system, published today in *Frontiers in Physics*, that

investigates how and why elderly women in the country will enter poverty.

"The advent of a super-aged society is forecast for Japan in the near future, and impoverishment of people is our main concern," says Seiichi Inagaki, author of the study and a researcher at the International University of Health and Welfare in Japan.

"It is considered that many elderly women will face a poverty problem, however, there is no future estimate on poverty rates that shows how and why elderly women will enter poverty. This study provides the future estimates that answer these questions."

The current pension system in Japan was designed more than half a century ago for post-war families. In those times, women typically quit their jobs to have children and become housewives, and the pension system was relatively generous for women in these circumstances.

Since then, however, women have increasingly chosen not to marry, or else are divorced. Under the current pension system such women receive only a fraction of the pension calculated for married women -- and these payments will not be sufficient to keep these women above poverty levels.

Inagaki provides detailed predictions on these worrying trends using a dynamic microsimulation pension model called the Integrated Analytical Model for Household Simulation (INAHSIM). Such models are a commonly used tool to predict the future financial outcomes of pension systems for individual groups of people within a system, although the simulation is limited to public benefits and does not incorporate other financial assets.

"This study illustrates how the poverty rate will increase in the future," says Inagaki. "In the end, many never-married or divorced women will be living in poverty in their old age due to the unfavorable public pension system and their higher risk of living in a single-person household. This will raise the overall poverty rate."

These simulations indicate that roughly 50% of never-married or divorced women will become impoverished in the next 50 years, compared to only 10 to 20% of widows or married women. Overall, the study forecasts that nearly 25% of elderly Japanese women will be impoverished, in contrast with only about 10% of Japanese men.

"These results imply that the current social security system will not work well for these women," says Inagaki. "I hope that the government will consider reform of the social security system and take appropriate measures for these women."

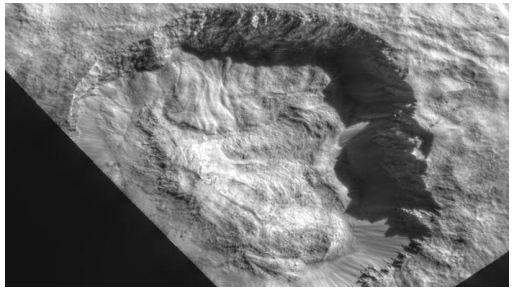
The article is part of a special research collection on Coordination and Cooperation in Complex Adaptive Systems: Theory and Application

http://go.nature.com/2pldQj7

Dwarf planet boasts icy winters and spring thaws

The seasons drive aquatic activity on Ceres.

The dwarf planet Ceres seems to have an active seasonal water cycle, data from NASA's Dawn spacecraft suggest.



Dawn has orbited the dwarf planet, which circles the Sun between the orbits of Mars and Jupiter, since 2015. Researchers enlisted the craft to observe a shadowed, icy cliff in Ceres' Juling crater.

In winter, ice spreads across a wall of the Juling crater on Ceres. **IAPS/INAF**

Over the course of six months, as winter deepened at the crater, one of the spacecraft's instruments measured changes in the light reflected off the cliff. Analysis suggests that the area of the cliff covered by ice increased from 3.6 square kilometres to 5.5 square kilometres during the period, says a team led by Andrea Raponi at the Institute for Space Astrophysics and Planetology in Rome.

Scientists have previously seen water vapour spurting from Ceres during the spring season. That observation, combined with the latest findings, suggests that water might freeze on Ceres during winter and sublimate when temperatures rise.

Sci. Adv. (2018)

http://bit.ly/2HDoPvZ

Unraveling how mesenchymal stem cells from gum tissue accelerate wound healing

Ever notice how a cut inside the mouth heals much faster than a cut to the skin? Gum tissue repairs itself roughly twice as fast as skin and with reduced scar formation

One reason might be because of the characteristics of gingival mesenchymal stem cells, or GMSCs, which can give rise to a variety of cell types.

"This study represents the convergence of a few different paths we've been exploring," says Songtao Shi, chair and professor of Penn Dental Medicine's Department of Anatomy and Cell Biology and the senior author on the study. "First, we know as dentists that the healing process is different in the mouth; it's much faster than in the skin. Second, we discovered in 2009 that the gingiva contains mesenchymal stem cells and that they can do a lot of good therapeutically. And, third, we know that mesenchymal stem cells release a lot of proteins. So here we asked, How are the gingival mesenchymal stem cells releasing all of these materials, and are they accelerating wound healing in the mucosal tissues?"

The work appears in the journal Science Translational Medicine.

Xiaoxing Kou, a visiting scholar at Penn Dental Medicine, was the first author on the work. Shi and Kou collaborated with colleagues Chider Chen and Anh Le from Penn Dental Medicine as well as Yanheng Zhou from Peking University, Xingtian Xu from the University of Southern California, Los Angeles, Claudio Giraudo and Maria L. Sanmillan from the Children's Hospital of Philadelphia, and Tao Cai from the National Institute of Dental and Craniofacial Research.

From earlier work by Shi's group and others, it was clear that mesenchymal stem cells perform many of their functions by releasing signaling molecules in extracellular vesicles. So to understand what distinguishes mesenchymal stem cells in the gingiva from those in the skin, the Penn-led team began by comparing these extracellular vesicles between the two types. They found that the GMSCs contained more proteins overall, including the inflammation-dampening IL-1RA, which blocks a proinflammatory cytokine. IL-1RA also happens to be used as a therapy to treat rheumatoid arthrisits, an inflammatory condition.

Next the team zoomed in to look at what might be controlling the release of IL-1RA and other cytokines. They had a suspect in the protein Fas, which they had earlier connected to immune regulation. They found that in gingival MSCs had more Fas than skin MSCs, and that mice deficient in Fas had reduced IL-1RA as well as reduced secretion of IL-1RA.

Further molecular probing revealed that Fas formed a protein complex with Fap-1 and Cav-1 to trigger the release of small extracellular vesicles. To identify the connection with wound healing, they examined wound tissue and found that IL-1RA was increased in GMSCs around the margins of wounds. Mice lacking IL-1RA or in which the protein was inhibited took longer to heal gingival wounds.

In contrast, when the researchers isolated IL-1RA that had been secreted from GMSCs and injected it into wounds, it significantly accelerated wound healing.

"We found that mesenchymal stem cells, and especially gingival mesenchymal stem cells, release large amount of cytokines through an extracellular vesicle," says Kou.

These findings may have special significance for people with diabetes, a major complication of which is delayed wound healing. In the study, the researchers found that GMSCs in mice with diabetes were less able to secrete extracellular vesicles compared to GMSCs in healthy mice, and their GMSCs also had less IL-1RA secretion. Introducing extracellular vesicles secreted from the GMSCs of healthy mice reduced wound healing time in diabetic mice.

"Our paper is just part of the mechanism of how these stem cells affect wound healing," Kou says, "but I think we can build on this and use these cells or the extracellular vesicles to target a lot of different

diseases, including the delayed wound healing seen in diabetic patients." Moving forward, Shi, Kou and colleagues want to move their work into the clinic.

"We are targeting translational therapies," says Shi. "These cells are easy to harvest from the gingiva, and that makes them a beautiful cell for clinical use. We have a lot of work ahead of us, but I can see using these cells to reduce scar formation, improve wound healing, and even treat many inflammatory and autoimmune diseases."

The study was supported by the National Institutes of Health (grants DE017449, DE019932, DE025915, AI123538, and GM123020), Penn Dental, the Pew Biomedical Scholars Award, and the American Association of Immunologists.

http://bit.ly/2FQHCDm

Chemists use abundant, low-cost and non-toxic elements to synthesize semiconductors

Solution-Grown Sodium Bismuth Dichalcogenides: Toward Earth-Abundant, Biocompatible Semiconductors

AMES, Iowa - One of the problems for Javier Vela and the chemists in his Iowa State University research group was that a toxic material worked so well in solar cells.

And so any substitute for the lead-containing perovskites used in some solar cells would have to really perform. But what could they find to replace the perovskite semiconductors that have been so promising and so efficient at converting sunlight into electricity?

What materials could produce semiconductors that worked just as well, but were safe and abundant and inexpensive to manufacture?

"Semiconductors are everywhere, right?" Vela said. "They're in our computers and our cell phones. They're usually in high-end, high-value products. While semiconductors may not contain rare materials, many are toxic or very expensive."

Vela, an Iowa State associate professor of chemistry and an associate of the U.S. Department of Energy's Ames Laboratory, directs a lab that specializes in developing new, nanostructured materials. While thinking about the problem of lead in solar cells, he found a conference presentation by Massachusetts Institute of Technology researchers that suggested possible substitutes for perovskites in semiconductors.

Vela and Iowa State graduate students Bryan Rosales and Miles White decided to focus on sodium-based alternatives and started an 18-month search for a new kind of semiconductor. The work was supported by Vela's five-year, $786,017 CAREER grant from the National Science Foundation. CAREER grants are the foundation's most prestigious awards for early career faculty.

They came up with a compound that features sodium, which is cheap and abundant; bismuth, which is relatively scarce but is overproduced during the mining of other metals and is cheap; and sulfur, the fifth most common element on Earth. The researchers report their discovery in a paper recently published online by the *Journal of the American Chemical Society*. The paper's subtitle is a good summary of their work: "Toward Earth-Abundant, Biocompatible Semiconductors."

"Our synthesis unlocks a new class of low-cost and environmentally friendly ternary (three-part) semiconductors that show properties of interest for applications in energy conversion," the chemists wrote in their paper. In fact, Rosales is working to create solar cells that use the new semiconducting material.

Vela said variations in synthesis - changing reaction temperature and time, choice of metal ion precursors, adding certain ligands - allows the chemists to control the material's structure and the size of its nanocrystals. And that allows researchers to change and fine tune the material's properties.

Several of the material's properties are already ideal for solar cells: The material's band gap - the amount of energy required for a light particle to knock an electron loose - is ideal for solar cells. The material, unlike other materials used in solar cells, is also stable when exposed to air and water. So, the chemists think they have a material that will work well in solar cells, but without the toxicity, scarcity or costs.

"We believe the experimental and computational results reported here," they wrote in their paper, "will help advance the fundamental study and

exploration of these and similar materials for energy conversion devices."

http://bit.ly/2pjk3Nu

Saving lives with platypus milk

A breakthrough by Australian scientists has brought the introduction of an unlikely hero in the global fight against antibiotic resistance a step closer; the humble platypus.

The platypus belongs to the monotreme family, a small group of mammals that lay eggs and produce milk to feed their young. **Laura Romin and Larry Dalton.**

Due to its unique features - duck-billed, egg-laying, beaver-tailed and venomous- the platypus has long exerted a powerful appeal to scientists, making it an important subject in the study of evolutionary biology.

In 2010 scientists discovered that platypus milk contained unique antibacterial properties that could be used to fight superbugs.

Now a team of researchers at Australia's national research agency, the Commonwealth Scientific and Industrial Research Oganisation (CSIRO), and Deakin University have solved a puzzle that helps explain why platypus milk is so potent - bringing it one step closer to being used to save lives.

The discovery was made by replicating a special protein contained in platypus milk in a laboratory setting. "Platypus are such weird animals that it would make sense for them to have weird biochemistry," CSIRO scientist and lead author on the research published in *Structural Biology Communications*, Dr Janet Newman said.

"The platypus belongs to the monotreme family, a small group of mammals that lay eggs and produce milk to feed their young. By taking a closer look at their milk, we've characterised a new protein that has unique antibacterial properties with the potential to save lives."

As platypus don't have teats, they express milk onto their belly for the young to suckle, exposing the mother's highly nutritious milk to the environment, leaving babies susceptible to the perils of bacteria.

Deakin University's Dr Julie Sharp said researchers believed this was why the platypus milk contained a protein with rather unusual and protective antibacterial characteristics. "We were interested to examine the protein's structure and characteristics to find out exactly what part of the protein was doing what," she said.

Employing the marvels of molecular biology, the Synchrotron, and CSIRO's state of the art Collaborative Crystallisation Centre (C3), the team successfully made the protein, then deciphered its structure to get a better look at it. What they found was a unique, never-before-seen 3D fold. Due to its ringlet-like formation, the researchers have dubbed the newly discovered protein fold the 'Shirley Temple', in tribute to the former child-actor's distinctive curly hair.

Dr Newman said finding the new protein fold was pretty special.

"Although we've identified this highly unusual protein as only existing in monotremes, this discovery increases our knowledge of protein structures in general, and will go on to inform other drug discovery work done at the Centre," she said.

In 2014 the World Health Organisation released a report highlighting the scale of the global threat posed by antibiotic resistance, pleading for urgent action to avoid a "post-antibiotic era", where common infections and minor injuries which have been treatable for decades can once again kill. The scientists are seeking collaborators to take the potentially life-saving platypus research to the next stage.

http://bit.ly/2tWnTAW

The coffee cannabis connection

Coffee affects cannabis and steroid systems

CHICAGO --- It's well known that a morning cup of joe jolts you awake. But scientists have discovered coffee affects your metabolism in dozens of other ways, including your metabolism of steroids and the

neurotransmitters typically linked to cannabis, reports a new study from Northwestern Medicine.

In a study of coffee consumption, Northwestern scientists were surprised to discover coffee changed many more metabolites in the blood than previously known. Metabolites are chemicals in the blood that change after we eat and drink or for a variety of other reasons.

The neurotransmitters related to the endocannabinoid system -- the same ones affected by cannabis -- decreased after drinking four to eight cups of coffee in a day. That's the opposite of what occurs after someone uses cannabis. Neurotransmitters are the chemicals that deliver messages between nerve cells.

Cannabinoids are the chemicals that give the cannabis plant its medical and recreational properties. The body also naturally produces endocannabinoids, which mimic cannabinoid activity.

In addition, certain metabolites related to the androsteroid system increased after drinking four to eight cups of coffee in a day, which suggests coffee might facilitate the excretion or elimination of steroids. Because the steroid pathway is a focus for certain diseases including cancers, coffee may have an effect on these diseases as well.

"These are entirely new pathways by which coffee might affect health," said lead author Marilyn Cornelis, assistant professor of preventive medicine at Northwestern University Feinberg School of Medicine. "Now we want to delve deeper and study how these changes affect the body."

Little is known about how coffee directly impacts health. In the new study, Northwestern scientists applied advanced technology that enabled them to measure hundreds of metabolites in human blood samples from a coffee trial for the first time. The study generates new hypotheses about coffee's link to health and new directions for coffee research. The paper will be published March 15 in the *Journal of Internal Medicine*.

Drinking lots of coffee for science

In the three-month trial based in Finland, 47 people abstained from coffee for one month, consumed four cups a day for the second month and eight cups a day for the third month. Cornelis and colleagues used advanced profiling techniques to examine more than 800 metabolites in the blood collected after each stage of the study.

Blood metabolites of the endocannabinoid system decreased with coffee consumption, particularly with eight cups per day, the study found. The endocannabinoid metabolic pathway is an important regulator of our stress response, Cornelis said, and some endocannabinoids decrease in the presence of chronic stress.

"The increased coffee consumption over the two-month span of the trial may have created enough stress to trigger a decrease in metabolites in this system," she said. "It could be our bodies' adaptation to try to get stress levels back to equilibrium."

The endocannabinoid system also regulates a wide range of functions: cognition, blood pressure, immunity, addiction, sleep, appetite, energy and glucose metabolism. "The endocannabinoid pathways might impact eating behaviors," suggested Cornelis, "the classic case being the link between cannabis use and the munchies."

Coffee also has been linked to aiding weight management and reducing risk of type 2 diabetes.

"This is often thought to be due to caffeine's ability to boost fat metabolism or the glucose-regulating effects of polyphenols (plant-derived chemicals)," Cornelis said. "Our new findings linking coffee to endocannabinoids offer alternative explanations worthy of further study." It's not known if caffeine or other substances in coffee trigger the change in metabolites.

Although Cornelis studies the effects of coffee, she didn't drink it growing up in Toronto or later living in Boston. "I didn't like the taste of it," Cornelis said. But when she moved to join Northwestern in 2014, she began to enjoy several cups a day. "Maybe it's the Chicago water," she mused, "but I do have to add cream and sweetener."

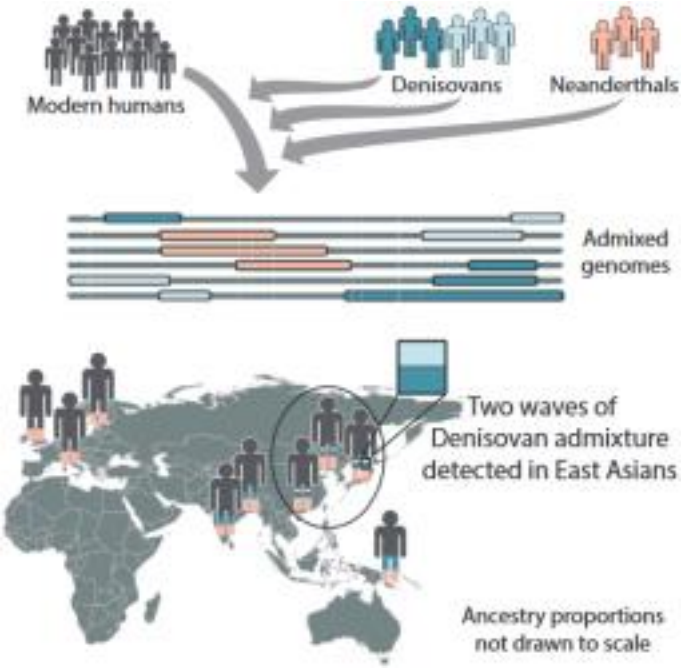
The study was supported by the American Diabetes Association, the German Federal Ministry of Health and other sources.

http://bit.ly/2pjuaSs

Modern humans interbred with Denisovans twice in history

Modern humans co-existed and interbred not only with Neanderthals, but also with the mysterious Denisovans

Modern humans co-existed and interbred not only with Neanderthals, but also with another species of archaic humans, the mysterious Denisovans. While developing a new genome-analysis method for comparing whole genomes between modern human and Denisovan populations, researchers unexpectedly discovered two distinct episodes of Denisovan genetic intermixing, or admixing, between the two. This suggests a more diverse genetic history than previously thought between the Denisovans and modern humans.



This graphical abstract shows two waves of Denisovan ancestry have shaped present-day humans **Browning et al./Cell**

In a paper published in Cell on March 15, scientists at the University of Washington in Seattle determined that the genomes of two groups of modern humans with Denisovan ancestry--individuals from Oceania and individuals from East Asia--are uniquely different, indicating that there were two separate episodes of Denisovan admixture.

"What was known already was that Oceanian individuals, notably Papuan individuals, have significant amounts of Denisovan ancestry," says senior author Sharon Browning, a research professor of biostatistics, University of Washington School of Public Health. The genomes of modern Papuan individuals contain approximately 5% Denisovan ancestry."

Researchers also knew Denisovan ancestry is present to a lesser degree throughout Asia. The assumption was that the ancestry in Asia was achieved through migration, coming from Oceanian populations. "But in this new work with East Asians, we find a second set of Denisovan ancestry that we do not find in the South Asians and Papuans," she says. "This Denisovan ancestry in East Asians seems to be something they acquired themselves."

After studying more than 5,600 whole-genome sequences from individuals from Europe, Asia, America, and Oceania and comparing them to the Denisovan genome, Browning and colleagues determined that the Denisovan genome is more closely related to the modern East Asian population than to modern Papuans. "We analyzed all of the genomes searching for sections of DNA that looked like they came from Denisovans," says Browning, whose team relied on genomic information from the UK10K project, the 1000 Genomes Project, and the Simons Genome Diversity Project.

"When we compared pieces of DNA from the Papuans against the Denisovan genome, many sequences were similar enough to declare a match, but some of the DNA sequences in the East Asians, notably Han Chinese, Chinese Dai, and Japanese, were a much closer match with the Denisovan," she says.

What is known about Denisovan ancestry comes from a single set of archaic human fossils found in the Altai mountains in Siberia. That individual's genome was published in 2010, and other researchers quickly identified segments of Denisovan ancestry in several modern-day populations, most significantly with individuals from Oceania but also in East and South Asians.

"The assumption is that admixing with Denisovans occurred fairly quickly after humans moved out of Africa, around 50,000 years ago,

but we do not know where in terms of location," Browning says. She theorizes that perhaps the ancestors of Oceanians admixed with a southern group of Denisovans while the ancestors of East Asians admixed with a northern group.

Going forward, the researchers plan on studying more Asian populations and others throughout the world, including Native Americans and Africans. "We want to look throughout the world to see if we can find evidence of interbreeding with other archaic humans," says Browning. "There are signs that intermixing with archaic humans was occurring in Africa, but given the warmer climate no one has yet found African archaic human fossils with sufficient DNA for sequencing."

This work was supported by the National Institute of General Medical Sciences of the National Institutes of Health.

Cell, Browning, SR, et al: "Analysis of Human Sequence Data Reveals Two Pulses of Archaic Denisovan Admixture" http://www.cell.com/cell/fulltext/S0092-8674(18)30175-2

http://bit.ly/2GCPQ3k

Evidence of major environmental and technological changes in East Africa, as Homo sapiens evolved

Studies highlight environmental factors that may have spurred a change in human behavior

Three new studies[1,2,3] highlight major environmental, ecological and technological changes that occurred in East Africa preceding the Middle Stone Age roughly 300,000 years ago, around the time that anatomically modern humans were evolving. The results hint that environmental factors may have spurred a change in human behavior, encouraging more widespread dispersal, trade and novel tool-making.

First, a study by Rick Potts *et al*. analyzes well-preserved sediments in the Olorgesailie Basin, in Kenya, finding that beginning around 800,000 years ago the region underwent a transformation. The sediments suggest that the Olorgesailie Basin was mostly floodplains until roughly 800,000 years ago, when it increasingly exhibited fluctuations between moist and arid states. Furthermore, carbon isotopes of soil samples suggest that the region developed into a vast grassland. Around this time, the mammalian fauna experienced dramatic turnover, with many large-bodied, specialized grazing lineages, including some elephant and horse species, going extinct; in their stead, related taxa with smaller body sizes emerged - which the authors say is another sign of climate variability. They note that such climate variability makes food availability unpredictable for human hunter-gatherers, in turn driving greater mobility, information gathering, and perhaps trade. Such changes are evident in archeological evidence, Potts *et al*. note; whereas previously 98% of rock used to manufacture tools was from a tiny localized area of the Olorgesailie Basin (spanning just 5 kilometers), by about 320,000 years ago, tools were replaced with obsidian from regions farther away, an indication of travel and potentially trade. This represents a significant revision in African hominin behavior at or near the time of origin of *Homo sapiens*, the authors say.

A separate study by Alison Brooks *et al*. provides more detail on human-made artifacts excavated from the Olorgesailie Basin, including weapons (and also pigments) that shed life on early technology and trade. Notably, the authors base their work on evaluations at five sites spanning the period between approximately 500,000 and 298,000 years ago, finding distinct differences in the types of tools at older and younger sites. Whereas the older sites yielded larger, bulkier weapons such as hand axes, which were made from localized volcanic rock, one of the more recent sites contained much smaller and more refined weapons of a different style. About 42% of the latter tools were crafted from obsidian, of which there is no local source, the authors note. Furthermore, about 46,000 obsidian flakes were recovered from the site, indicating that obsidian was brought in as raw material and manipulated onsite rather than imported as finished artifacts. As well, the researchers found that the second-most common exotic raw material was green, brown, or white chert (colored rock). Of particular interest is a lump of ochre pigment with two perforated holes, which makes it among the oldest-known clearly worked pigments, the authors say, noting that

exotic bright red and black rocks may have been valued, and worth transporting, for their intense color - used as symbolic communicators of identity or status.

Lastly, Brooks *et al*. also discuss animal remains found within the vicinity of the sites, which suggest that early modern humans may have in part subsisted on small animals. A third study, by Alan Deino *et al*., provides detailed dating of sites within the Olorgesailie Basin, work that helps elucidate the critical transition between the Acheulean period and the Middle Stone Age. The researchers used argon and uranium dating techniques to determine the timeline of sites within the basin, confirming that older Acheulean sites contained larger tools; beginning around 320,000 years ago, sites lacked Acheulean-like tools, the authors report, noting that these results establish the oldest repository of Middle Stone Age artifacts identified in eastern Africa to date.

1. Potts, R. et al. Science http://dx.doi.org/10.1126/science.aao2200 (2018).Article Google Scholar

2. Deino, A. L. et al. Science http://dx.doi.org/10.1126/science.aao2216 (2018). Article Google Scholar

3. Brooks, A. S. et al. Science http://dx.doi.org/10.1126/science.aao2646 (2018). Article Google Scholar

http://bit.ly/2IyM1MX

Scientific misconduct harms prior collaborators

Guilt by association in science

While there has always been anecdotal evidence of this being the case, a study by Prof. Katrin Hussinger (University of Luxembourg) and Dr Maikel Pellens (ZEW, Mannheim and KU Leuven, Belgium) now provides empirical evidence. "Guilt by Association: How Scientific Misconduct Harms Prior Collaborators" was based on the U.S. Office of Research Integrity's 1993 to 2008 misconduct filings. A group of 856 prior research collaborators of the fraudulent scientists was identified by using publication records dating back five years before the case of misconduct. Only cases where a retraction or correction of the research processed for scientific misconduct was published were taken into account.

Compared to a control group, the results showed an average drop in citations of 8 to 9 percent for previous colleagues. Citations play an important role in science as they show the impact of research in the scientific community. Researchers with a high citation count are usually also more successful in attracting funding and receive more lucrative job offers. The reduced citation count could therefore have significant implications for their career.

"The results of the study are worrisome," explained Prof. Hussinger. "Our research shows that guilt by association stretches back to projects prior to the fraud case and thereby to unsuspecting and uninvolved co-workers."

While stigmatization by association has been observed in different settings and contexts, the results from the field of academia are problematic in their own ways, according to Prof. Hussinger: "Trust is a crucial aspect of communicating science and conveying research results to the public. The ripple effects of one misconduct case can put at risk the reputation of a much larger group of scientists and even institutions."

Even though the researchers cannot provide a simple solution to the issue, guilt by association should be treated seriously, Prof. Hussinger and Dr. Pellens argue. An unwanted implication, Prof. Hussinger concluded, could be the underreporting of actual fraud causes: "Knowing that they might be penalised for mere association might make researchers think twice before speaking out."

http://bit.ly/2FQkmWm

Major study shows x5 greater suicide rate in patients with urological cancers

Patients with urological cancer such as prostate, bladder or kidney cancer are five times more likely to commit suicide

A major UK survey has shown that patients with urological cancer such as prostate, bladder or kidney cancer are five times more likely to commit suicide than people without cancer. The analysis also shows that cancer patients generally are around three times more likely to

commit suicide than the general population, and that the proportion of attempted suicides which result in a completed or successful suicide was higher in cancer patients, with a higher proportion still in patients with urological cancers.

Severe psychological stress is one of the main side-effects of both a diagnosis of cancer and cancer treatment, with depression affecting between 5 and 25% of cancer patients1, 2: many are also affected by Post-Traumatic Stress Disorder (PTSD)3. Previous research has shown that the vast majority of cancer patients who have symptoms of depression often go untreated2. This study shows a substantial increase in suicide attempts and successful suicides in cancer patients. The work is presented at the European Association of Urology conference in Copenhagen.

This is the largest UK study looking at suicide in cancer patients (see below). The research team led by Mr Prashant Patel at the University of Birmingham retrospectively examined the records from the England and Wales Hospital Episode Statistics database, from the period 2001 to 2011. They linked this with cause of death statistics from the Office of National Statistics.

This is also the first time that a major study has examined suicidal intent in cancer patients - which they defined as the ratio of successful suicides to the rate of attempted suicides. They found that this rate was far higher (1 to 7) in patients with prostate cancer than in the general population (1 to 25), which may show a greater determination to commit suicide in cancer patients. "This is important" said first author Dr Mehran Afshar (St George's Hospital, London), "as we know that people who attempt suicide are at higher risk of subsequently being successful in completing a suicide, and we have shown this 'intent' to commit to be far higher in our cancer population, thus confirming a real need to address psychological issues early on in the management of these patients".

Dr Afshar continued: "Our data confirms research from other countries that suicide rates are higher in cancer patients, and we show this to be higher particularly in patients with urological cancers. There are particular issues which are specific to this cancer group - for example, men with prostate cancer undergo treatment which can affect their bladder function, their bowel function, erectile function and libido, can result in symptoms similar to the female menopause, and entirely alter the personality, leading to relationship problems, anxiety, depression and post-traumatic stress disorder.

We know from a 2014 study2 by Cancer Research UK that the vast majority of cancer patients who have symptoms of depression go untreated. We can see from the results of our study that although all cancers have a higher suicide rate, inferring a higher level of psychological distress, there are disparities between cancers. This needs to be addressed within our healthcare systems, and more focus is needed on integrating the robust and specialist assessment and treatment of mental health needs in cancer care".

The study also showed significant differences between the time to a successful suicide, which means that some cancer patients are more vulnerable in certain periods.

The numbers

- ***The researchers identified a total of 980,761 (493,234 males and 487,094 female) cancer patients which meant that 13.4 million-person years were included in the final data analysis. The team identified 162 suicides and 1222 suicide attempts.***
- ***In the general population, the suicide rate is 10 per 100,000 people. The team found that the all-cancer suicide rate was 30 per 100,000 people. In the urological cancers the figures are 36 per 100,000 people in kidney cancer, 48 suicides per 100,000 in bladder cancer, and 52 per 100,000 people in prostate cancer.***
- ***In the general population, there is an average of 25 suicide attempts for each successful suicide. In kidney cancer this ratio is 1 suicide for every 10 attempts. In bladder and prostate cancer, this ratio drops to one suicide for every 7 attempts.***

- ***The time taken to commit suicide also varies substantially: median time to suicide is 175 days from diagnosis for kidney cancer, 846 days for prostate cancer, and 1037 days for bladder cancer.***

Commenting, EAU Adjunct Secretary General, Prof Hein van Poppel (Leuven) said: "This important work shows just how distressing cancer can be, but it also shows that there may be special factors associated with urological cancers which make them even more stressful than other cancers. It looks like urological cancers can affect patients' sense of self in a way that many cancers don't.

The work implies that some urological cancers, such as kidney cancer, can lead to fairly immediate distress, whereas the distress associated with prostate and bladder cancer may take a while to hit home - perhaps when patients begin to take up some of the problems associated with returning to normal life.

We also need to put things in context: many patients recover well, and don't reach the stage of despair or distress which brings them to think of suicide. Nevertheless, this is a real problem. We need to recognise that the figures presented here are for suicides, which means that they are at the 'sharp end of emotional distress'. For every suicide or attempted suicide, there will be many more patients who find difficulty in coping.

This distress does not stop when the cancer is removed or contained, and we owe it to patients to ensure that ongoing emotional support and mental health care is fully integrated in cancer care".

(Professor van Poppel was not involved in this work. He is a specialist in urological cancers).

The team noted a limitation of the study: they looked at the general suicide rate, not at the rate of suicides according to age (age-standardised suicide rate), however a comparison to baseline population suicide rates could only be made using crude suicide rates per 100,000 as this is population level data available.

There was no specific funding for this research.

http://bit.ly/2GClHkv

Medicinal cannabis is safe and effective -- it's time to reboot research

New special issue of the European Journal of Internal Medicine aims to bring cannabis into mainstream medicine

Amsterdam - Medicinal cannabis is safe and effective in pain relief, and researchers are calling for the treatment to be properly established in our modern medical arsenal. A new special issue of the *European Journal of Internal Medicine* provides a comprehensive overview of current evidence for the use of cannabis and derived products in medicine, and calls for more research to improve the evidence base for its use.

"We feel it is absolutely imperative to not only present the current state of affairs, but also propose the development of the scientific research program within the paradigm of evidence-based medicine," said Prof. Victor Novack, guest editor of the special issue and a professor at Ben-Gurion University of the Negev in Israel. "Our ultimate aim should be to scientifically establish the actual place of medical cannabis derived products in the modern medical arsenal."

Cannabis has been used for centuries in pain relief, as a sleep aid and for many other purposes, yet there is little evidence on its safety and effectiveness. This is in part due to relatively recent legal restrictions on its use, which have hampered research efforts and resulted in doctors having little to no understanding of its use.

However, there has been an explosion in the number of studies published since 2012. The new special issue provides two major studies on the use of cannabis in cancer patients and the elderly, as well as a comprehensive overview of the evidence, regulations, ethics and practical use. The authors and editors call for more research to improve the evidence base.

In a study led by Prof. Novack, a team of researchers from Israel analyzed data collected during the medicinal cannabis treatment of 2,970 cancer patients between 2015 and 2017. The two main problems

patients were hoping to overcome were sleep problems and pain, and cannabis has been shown to be effective in alleviating both. 95.9 percent of the patients reported an improvement in their condition.

The same team also analyzed the effectiveness of medical cannabis in elderly patients who were being treated in 2015-2017 for a variety of issues, including pain and cancer. The researchers conclude in their paper: "Our study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative."

In a review in the special issue, Prof. Donald Abrams at University of California San Francisco Ward in the US covers the recent review conducted by the National Academies of Sciences, Engineering and Medicine, *The Health Effects of Cannabis and Cannabinoids*. The report, which considered 10,000 scientific abstracts, "concluded that there was conclusive or substantial evidence that Cannabis or cannabinoids are effective for the treatment of pain in adults; chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis."

Yet the report also highlighted the barriers to research in the US, which may explain the lack of strong evidence for the therapeutic use of cannabis. This dearth of research has also led to numerous ethical issues in prescribing cannabis, not least because many doctors do not understand the treatment enough to advise dosage and use. An article by researchers at the University of British Columbia, Canada and International Cannabis and Cannabinoids Institute, Prague, Czech Republic provides practical guidance for doctors, with data on cannabis pharmacology.

"This Medical Cannabis special issue covers everything you wanted to know about medical cannabis," said Prof. Novack. "We hope that it will provide physicians with a contemporary summary of different aspects related to the medical cannabis and guide the choice of an appropriate for the indications where the evidence is sufficient to initiate the treatment. We also hope the articles will facilitate the conversation on the future of medical cannabis research and its accommodation into mainstream medicine."

Notes for editors

The article is "Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer," by Lihi Bar-Lev Schleider, Raphael Mechoulam, Violeta Lederman, Mario Hilou, Ori Lencovsky, Oded Betzalel, Liat Shbiro, and Victor Novack.

The review is "The therapeutic effects of Cannabis *and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report," by Donald I. Abrams.*

The article is "Practical considerations in medical cannabis administration and dosing," by Caroline A. MacCallum and Ethan B. Russo.

The above articles appear in the European Journal of Internal Medicine *Special Issue: Cannabis in Medicine, volume 49 (March, 2018), published by Elsevier.*

http://bit.ly/2tTw9S2

Planting GMOs kills so many bugs that it helps non-GMO crops

Bt corn protects neighboring peppers and green beans, cuts pesticide use.

Diana Gitig - 3/15/2018, 10:54 PM

One of the great purported boons of GMOs is that they allow farmers to use fewer pesticides, some of which are known to be harmful to humans or other species. Bt corn, cotton, and soybeans have been engineered to express insect-killing proteins from the bacterium *Bacillus thuringiensis*, and they have indeed been successful at controlling the crops' respective pests. They even protect the non-Bt versions of the same crop that must be planted in adjacent fields to help limit the evolution of Bt resistance.

But new work shows that Bt corn also controls pests in other types of crops planted nearby, specifically vegetables. In doing so, it cuts down on the use of pesticides on these crops, as well.

Entomologists and ecologists compared crop damage and insecticide use in four agricultural mid-Atlantic states: New Jersey, Delaware, Maryland, and Virginia. Their data came from the years before Bt corn was widespread (1976-1996) and continued after it was adopted (1996-

2016). They also looked at the levels of the pests themselves: two different species of moths, commonly known as the European corn borer and corn earworm. They were named as scourges of corn, but their larvae eat a number of different crops, including peppers and green beans.

After Bt corn was planted in 1996, the number of moths captured for analysis every night in vegetable fields dropped by 75 percent. The drop was a function of the percentage of Bt corn planted in the area and occurred even though moth populations usually go up with temperature. So the Bt corn more than counteracted the effect of the rising temperatures we've experienced over the quarter century covered by the study.

As the number of moths has gone down, the number of recommended and actual pesticide applications has dropped as well. Green beans and peppers used to require three to six pesticide applications per crop cycle "to ensure marketable quality." Between 1992 and 2016, the total amount of insecticide applied to New Jersey pepper fields decreased by 85 percent.

Granted, this coincided with the introduction of more effective pesticides that didn't need to be applied quite as liberally as their forebears. But this study still suggests that much of the decline can be attributed to Bt corn.

There are a couple of practical applications of this work besides vindicating that Bt crops are at least doing what they were engineered to do. One is planning plantings so that that other crops known to be attacked by these same pests—popcorn, potatoes, and sorghum—end up near fields of Bt corn. Another is using these vegetables, rather than non-Bt corn or soy, as the refuges for Bt resistance management that are currently mandated by the EPA.

Pests who eat the non-Bt crops in these refuges have no reason to evolve resistance to the toxin. When they mate with any of their rare colleagues that manage to survive after eating the Bt corn in the next field over, they will likely make baby moths that are still susceptible. This should help preserve the effectiveness of Bt technology—for a while, at least. But now that the widespread benefits of Bt crop use are known, farmers can plant to both minimize resistance and maximize the benefits.

PNAS, *2018. DOI: 10.1073/pnas.1720692115 (About DOIs).*

http://nyti.ms/2IvY79K

What's Behind Many Mystery Ailments? Genetic Mutations, Study Finds

A new study suggests that many Mendelian disorders go undetected

Carl Zimmer

Gregor Mendel discovered fundamental rules of genetics by raising pea plants. He realized that hidden factors — we now know them to be genes — were passed down from parents to offspring.

It wasn't until the early 1900s, long after Mendel's death, that doctors discovered that humans weren't so very different. Some diseases, it turns out, are inherited — they're Mendelian.

Today, scientists have identified over 7,000 Mendelian diseases, and many are discovered with screenings of children and adults. But a new study suggests that many disorders go undetected.

With a database of electronic health records and DNA samples, a team of scientists has found that 3.7 percent of patients in a hospital system carried a genetic variant linked to a disease. It's possible that as many as 4.5 percent of cases of apparently nongenetic diseases, from infertility to kidney failure, are the result of such mutations.

The study also suggests that it may be possible to catch more of these hidden disorders with a computer program that flags suspicious clusters of symptoms in groups of patients. That would be an enormous step forward for patients coping with unexplained ailments.

The study, published Thursday in Science, represents the first large-scale search of electronic health records for hidden Mendelian diseases. But Dr. Joshua C. Denny, a biomedical informatics researcher at the Vanderbilt University School of Medicine and co-author of the new study, suspected that it only revealed the tip of a genetic iceberg. Much

larger databases including DNA and records for hundreds of thousands of people are being built, and searching them may uncover many more hidden mutations. “I’m sure there’s a whole bunch else out there that we will discover,” Dr. Denny said.

He and his colleagues gathered data from Vanderbilt’s massive electronic health records system, which includes more than two million patients. More than 225,000 have signed up as volunteers for genetic research, allowing scientists to analyze their DNA.

The researchers picked out 21,701 patients from the database and surveyed all the symptoms recorded for each one. They then compared the symptoms to those seen in 1,204 Mendelian diseases.

It was a difficult task. These disorders can produce a number of symptoms, and each patient may have a different combination of them. And some symptoms linked to a Mendelian disease may also be signs of other diseases. Cystic fibrosis can cause asthma and recurrent infections, for instance — but those symptoms alone aren’t enough to diagnose the disease.

Dr. Denny and his colleagues developed a scoring system to determine how likely it was that each patient in their study suffered each Mendelian disease. If a patient had a rare symptom linked to a disease, she scored a lot of points. A common symptom earned her far fewer points.

The researchers identified groups of people with symptoms strongly suggesting they shared a Mendelian disease. The researchers went on to examine the DNA of these patients to see if they also shared a mutation.

Dr. Denny would have been happy just to find a few undiagnosed patients. Instead, the team found 807 patients carrying mutations in genes linked to 17 different diseases, such as cystic fibrosis or hemochromatosis, a disorder that causes iron to build up in the blood.

Only eight of these patients had gotten a test that revealed the mutation. In other cases, doctors had tested for the wrong disease and gotten a negative result. Many times, the doctors hadn’t ordered any genetic tests at all.

Typically, these disorders can be passed down in one of two ways. A dominant disease, like Huntington’s, requires inheriting just one defective copy of a gene from a parent. Recessive diseases, such as sickle cell anemia, usually require two defective copies of the same gene.

The mutations that the scientists discovered often didn’t fit the standard profile for the diseases. Many of the patients had conditions that are considered recessive, yet they carried a just single defective copy of the gene.

A single defective copy may cause milder versions of Mendelian diseases, Dr. Denny suspects.

The researchers identified 36 people, for example, who carried only one defective version of a gene called AGXT. Two copies of the gene cause a disease known as primary hyperoxaluria, which can result in kidney failure in toddlers. The patients identified in the new study also suffered kidney problems — but not in the first few years of life.

One patient who turned up in their search had kidney stones at age 15. That’s unusual — but apparently not enough to lead the patient’s doctors to suspect primary hyperoxaluria. “It’s not as simple as what we learned in high school genetics,” Dr. Denny said.

These results are all the more surprising given how modest Dr. Denny’s search was. He only looked for a limited number of mutations in a relatively small group of people, all of whom were of European descent. (Much of what is known about gene variants that cause disease was discovered by researching predominantly white populations.)

“I’m kind of surprised we found anything. The fact that we did means there’s maybe a lot out there that we don’t know,” Dr. Denny said.

Heidi L. Rehm, a molecular geneticist at Brigham and Women’s Hospital who was not involved in the study, said many doctors do not suspect that their patients are suffering from a Mendelian disorder unless they suffer severe textbook symptoms.

"They simply never order any genetic testing, and then you never develop an understanding that it's genetic to begin with," she said.

Overlooking the genetic causes of diseases can seriously harm patients. "There are people here who had kidney and liver transplants that could potentially have been avoided," Dr. Denny said.

Undiagnosed hemochromatosis, for example, can lead to liver failure. Of the 40 people Dr. Denny and his colleagues identified with hemochromatosis, four needed liver transplants.

Yet hemochromatosis can be readily treated by having patients donate blood on a regular basis, which helps rid them of excess iron.

The strategy employed by the research team was startlingly effective at identifying potential causes of disease. In the long run, Dr. Denny and Dr. Rehm agreed, the best solution might be to sequence the entire genome of every patient — in childhood, or even at birth.

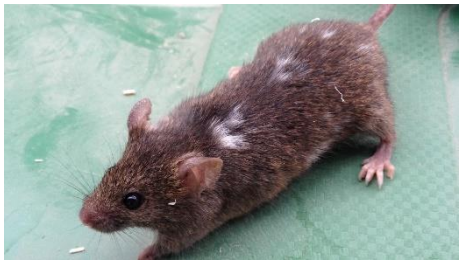
But such a policy would create an unmanageable glut of genetic data. "I don't think we're ready to do that," Dr. Denny said.

http://bit.ly/2FSckMC

Mice change their appearance as a result of frequent exposure to humans

Mice show traits signifying domestication syndrome

Dogs, cows, sheep, horses, pigs, and birds - over the past 15,000 years, our ancestors domesticated dozens of wild animals to keep them as farm animals or pets. To make wild wolves evolve into tame dogs, the least aggressive animals, or most gentle ones, were selected for breeding.



The white patches in the brown fur of the house mice are a sign of self-domestication. **Linda Heeb**

Tameness was therefore the key criterion for selection. Over time, it wasn't only the animals' behavior that changed, but their appearance as well - with the same changes emerging across various species. For example, domestic rabbits, dogs, and pigs all have white patches, floppy ears, smaller brains, and shorter snouts. In science, this suite of traits is referred to as the domestication syndrome.

Regular exposure to humans results in white patches in the fur

A team of researchers led by Anna Lindholm from the Department of Evolutionary Biology and Environmental Studies at UZH has now also observed this phenomenon in wild mice (Mus musculus domesticus) that live in a barn near Zurich. Within a decade, this population of mice developed two of the distinct phenotypic changes: white patches in their otherwise brown-colored fur as well as shorter snouts. "The mice gradually lost their fear and developed signs of domestication. This happened without any human selection, solely as a result of being exposed to us regularly," says Anna Lindholm. The evolutionary biologist has been studying the mice that live in the empty barn for about 15 years. These animals are regularly provided with food and water, and investigated by the researchers.

Experimental taming of wild foxes provides the key

Scientists' knowledge about the domestication syndrome comes from a remarkable experiment that began in Siberia in 1959. Soviet geneticist Dmitry Belyaev tamed wild foxes and investigated their evolutionary changes. He selected the tamest animals from among every new generation. Over time, the foxes began to change their behavior: They not only tolerated people, but were outright friendly. At the same time, their appearance also changed: Their fur featured white patches, their snouts got shorter, their ears drooped, and their tails turned curly.

Neural crest stem cells provide link

It appears that a small group of stem cells in the early embryo - the neural crest - is responsible for these behavioral and physical changes that take place in parallel. The ear's cartilage, the teeth's dentine, the melanocytes responsible for the skin's pigmentation, as well as the adrenal glands which produce stress hormones are all derived from these stem cells. The selection of less timid or aggressive animals results in smaller adrenal glands that are less active, and therefore leads

to tamer animals. Changes in the color of fur and head size can thus be considered unintended side effects of domestication, as these traits can also be traced back to stem cells in the neural crest that were more passive in the early stages of development.

How wild mice became tame without selection

The observations of the study's first author Madeleine Geiger increases the understanding of how house mice began to live in closer proximity to humans, attracted by their food, some 15,000 years ago. As a result of this proximity alone, the rodents got used to people and became tamer. "This self-domestication resulted in the gradual changing of their appearance - incidentally and inadvertently," says Geiger. Evolutionary biologists assume that the development from wild wolf to domestic dog also initially began without the active involvement of humans. Wolves that lived near humans became less timid and aggressive - the first step in becoming domesticated.

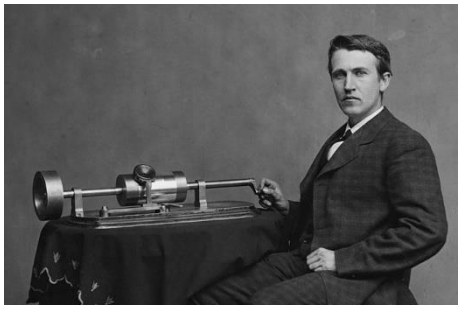
http://bit.ly/2FK2O22

Thomas Edison Was an Early Adopter of the Word 'Bug'

In an 1878 letter, he uses the term to refer to a technological glitch.

by Sarah Laskow

In 1878, Thomas Edison's star was on the rise. A few years before, when he sold his quadruplex telegraph design—an industry-changing innovation that allowed four signals to go over one wire—he had used the proceeds to build his lab in Menlo Park, New Jersey. Soon enough, he would start work on his lightbulb and the motion-picture camera, the work that would make him one of America's most lauded scientists. But already newspapers had started hailing him as a genius, after he debuted the phonograph in 1877.

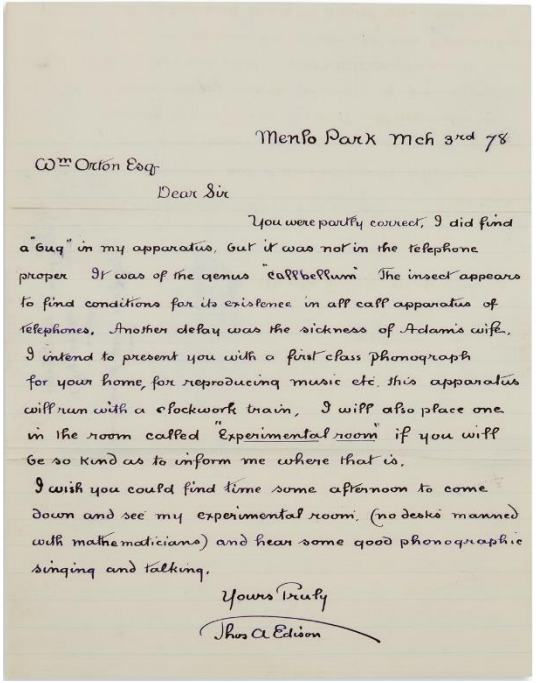


Thomas Edison and his early phonograph, circa 1877. **Library of Congress/Public Domain**

Now, though, Edison was focused on improving the telephone—a job he took on for Western Union, which was eager to rival Alexander Graham Bell's new communications company. In March, Edison wrote to William Orton, Western Union's president, updating him on a conversation they'd had in person about a new telephone design:

"You were partly correct, I did find a 'bug' in my apparatus, but it was not in the telephone proper. It was of the genus 'callbellum.' The insect appears to find conditions for its existence in all call apparatus of telephones."

This letter, at auction next week at Swann Galleries, is one of the earliest examples of this use of "bug," to describe a problem with technology.



Menlo Park Mch 3rd 78

Wm Orton Esqr

Dear Sir

You were partly correct, I did find a "bug" in my apparatus, but it was not in the telephone proper. It was of the genus "callbellum" The insect appears to find conditions for its existence in all call apparatus of telephones. Another delay was the sickness of Adams wife. I intend to present you with a first class phonograph for your home, for reproducing music etc. this apparatus will run with a clockwork train, I will also place one in the room called "Experimental room" if you will be so kind as to inform me where that is.

I wish you could find time some afternoon to come down and see my experimental room, (no desks manned with mathematicians) and hear some good phonographic singing and talking.

Yours Truly

Thos A Edison

Thomas A. Edison's letter to Western Union President William Orton, 1878. Courtesy of Swann Auction Galleries

That coinage is sometimes attributed to U.S. Navy Rear Admiral Grace Hopper, who in 1947 found an actual bug (a moth) in a Mark II computer. She taped the moth in a log book and wrote beside it, "First actual case of a bug being found."

But by the 1940s this type of bug was already well-known. Edison started using the term in the 1870s, while working on the quadruplex telegraph, which needed a "bug trap" to work properly. By 1878, it had become part of his lexicon: He used it often in his notebooks and had started spreading the term outside his own lab, to people like Orton.

Orton kept the 1878 letter; it came to Swann Galleries as part of a larger estate that included, as well, the draft of a contract between Edison and

Western Union. The “callbellum” bug that Edison was referring to was likely in the wires that connected the receiver and transmitter, says Marco Tomaschett, a Swann Galleries specialist.

At this point in his career, Edison was invested in maintaining a strong relationship with Western Union, a major source of income for him.

“He didn’t write this way always, but he was trying to give a good impression—he’s about to renegotiate his contact,” says Tomaschett. “He wants to make a good impression. But he’s famous, so it’s not as if he’s groveling. He’s got quite a bit of clout.”

Eventually, Edison worked out the bug in the telephone. Western Union used his work, along with designs from other inventors, to try to challenge Bell Telephone’s hold on this new technology. The two communications companies fought over the telephone for years in court, until Bell Telephone walked away triumphant. By then, Edison was onto a new battle—the so-called “War of Currents” that determined how electricity would flow over wires into households across America.

http://bit.ly/2IztrED

Exposure to low levels of BPA during pregnancy can lead to altered brain development

Explaining how exposure bisphenol A during pregnancy, even at safe levels can later lead to altered brain development and behavior

CHICAGO -- New research in mice provides an explanation for how exposure to the widely used chemical bisphenol A (BPA) during pregnancy, even at levels lower than the regulated "safe" human exposure level, can lead to altered brain development and behavior later in life. The research will be presented Monday, March 19 at ENDO 2018, the 100th annual meeting of the Endocrine Society in Chicago, Ill.

BPA is a chemical that is added to many commercial products, including water bottles, paper receipts, can liners and food storage containers. It is known as an endocrine-disrupting chemical--a chemical that interferes with the body's hormones.

"Decades of research in over 1,000 animal and 100 human epidemiological studies have demonstrated a link between BPA exposure and adverse health outcomes," said lead researcher Deborah Kurrasch, Ph.D., Associate Professor at the University of Calgary in Calgary, Canada. "This is especially true for the developing brain, which is particularly sensitive to the estrogen-promoting effects of BPA during gestation. Indeed, several human studies have now correlated early life BPA exposure with behavioral problems later in childhood, suggesting BPA permanently alters brain development that leads to lasting effects on neural functioning."

Governmental agencies around the world, including the U.S. Food and Drug Administration, Health Canada, and European Food Safety Authority, declare BPA to be safe. "One reason for this disparity is the absence of a smoking gun: if BPA is so toxic to developing brains, then where is the evidence of defective brains?" Kurrasch said. "Our study is the first to use environmentally relevant doses of BPA and show exposure to the chemical during brain development can affect the timing of the birth of nerve cells, or neurons."

The researchers studied three groups of pregnant mice. One group ate food without BPA; a second group at food with high doses of BPA; and a third ate low-dose BPA food. They found an increase in the number of neurons created during early development in mouse pups exposed to high and low doses of BPA during pregnancy, compared with those not exposed to BPA.

"This is important because specific neurons are known to be born at a very distinct time points, and if they are born early--as is the case here--then presumably these early neurons will migrate to the wrong place and form the wrong connections. These findings start to provide a rationale as to how BPA might affect developing brains," Kurrasch said.

Siblings to these pups were given behavioral tests to assess whether the early birth of neurons led to changes that affected brain function later in life. The researchers found mice that were exposed to BPA-high and BPA-low food during gestation exhibited some behaviors that match

those observed in human children whose mothers had high levels of BPA during pregnancy. "These findings suggest that gestational exposure to BPA can lead to lasting and permanent changes in the brain," Kurrasch said.

"The public is becoming well educated on the debate surrounding BPA safety, as well as other chemicals," she noted. "Although there is still work to be done to translate these rodent effects to human pregnancy, this research could provide expectant mothers with important information on what to avoid to best protect their babies."

http://bit.ly/2tXIPHN

Chemicals in lavender and tea tree oil appear to be hormone disruptors

More evidence of a suspected link between abnormal breast growth in young boys and regular exposure to lavender or tea tree oil

CHICAGO--A new study lends further evidence to a suspected link between abnormal breast growth in young boys--called prepubertal gynecomastia--and regular exposure to lavender or tea tree oil, by finding that key chemicals in these common plant-derived oils act as endocrine-disrupting chemicals. The study results will be presented Monday at ENDO 2018, the Endocrine Society's 100th annual meeting in Chicago.

Lavender and tea tree oil are among the so-called essential oils that have become popular in the United States as alternatives for medical treatment, personal hygiene and cleaning products, and aromatherapy. Various consumer products contain lavender and tea tree oil, including some soaps, lotions, shampoos, hair-styling products, cologne and laundry detergents.

"Our society deems essential oils as safe," said study lead investigator J. Tyler Ramsey, a postbaccalaureate research fellow at the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health. "However, they possess a diverse amount of chemicals and should be used with caution because some of these chemicals are potential endocrine disruptors."

An endocrine-disrupting chemical is a chemical in the environment that interferes with hormones and their actions in the body.

Male gynecomastia occurring before puberty is relatively rare, but a growing amount of cases have been reported to coincide with topical exposure to lavender and tea tree oil, and the condition went away after the boys stopped using the oil-containing products, Ramsey said. Researchers at the NIEHS, including Kenneth Korach, Ph.D., a co-investigator for the new study, previously found laboratory evidence that lavender and tea tree oil have estrogenic (estrogen-like) properties and anti-androgenic (testosterone inhibiting-like) activities, meaning they compete or hinder the hormones that control male characteristics, which could affect puberty and growth.

Under Korach's direction, Ramsey and his NIEHS colleagues went a step further. From the hundreds of chemicals that comprise lavender and tea tree oil, they selected for analysis eight components that are common and mandated for inclusion in the oils. Four of the tested chemicals appear in both oils: eucalyptol, 4-terpineol, dipentene/limonene and alpha-terpineol. The others were in either oil: linalyl acetate, linalool, alpha-terpinene and gamma-terpinene. Using in vitro, or test tube, experiments, the researchers applied these chemicals to human cancer cells to measure changes of estrogen receptor- and androgen receptor-target genes and transcriptional activity.

All eight chemicals demonstrated varying estrogenic and/or anti-androgenic properties, with some showing high or little to no activity, the investigators reported. Ramsey said these changes were consistent with endogenous, or bodily, hormonal conditions that stimulate gynecomastia in prepubescent boys.

"Lavender oil and tea tree oil pose potential environmental health concerns and should be investigated further," he said.

Of further concern, according to Ramsey, is that many of the chemicals they tested appear in at least 65 other essential oils. Essential oils are available without a prescription and are not regulated by the U.S. Food

and Drug Administration. Thus, the public should be aware of these findings and consider all evidence before deciding to use essential oils. The NIEHS Division of Intramural Research funded this study through its support of Korach.

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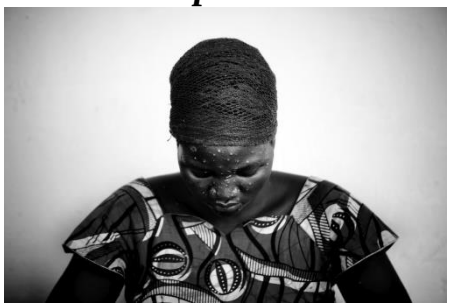
Health authorities issue warning on monkeypox outbreak

Pandemic fears arise as smallpox relative spreads.

Andrew Masterson reports.



A monkeypox patient, photographed during an outbreak in the Democratic Republic of Congo in 2008. **Jeff Hutchens / Contributor / Getty Images**

Labelling it a "concern for global health security", the US Centres for Disease Control and Prevention (CDC) have sounded the alarm about a surge in cases of a sometimes-fatal close relative of smallpox called monkeypox.

In its *Morbidity and Mortality Weekly Report*, the CDC notes a "recent apparent increase in human monkeypox cases across a wide geographic area", and calls for urgent public health action and international collaboration to head off the threat of a pandemic.

Monkeypox is described by the World Health Organisation as being similar to smallpox. Primary infection is caused by contact with the bodily fluids of sick animals, but cases of human-to-human transmission have also been documented.

The disease presents in two phases. After an incubation period of up to three weeks, victims experience up to five days of intense fever, headache and muscle pain. This is followed by a rash, typically on the face, palms and soles of the feet, and sometimes across the entire body. The rash period lasts for around three weeks, after which recovery or death occurs.

Monkeypox is fatal in about 10% of cases.

The CDC warning targets several countries in Africa, many of which had not until recently reported a single case in decades. The Democratic Republic of Congo is experiencing more than 1000 cases a year, with, since 2016, additional cases reported in the Central African Republic (19), Liberia (two), Nigeria (more than 80), Republic of the Congo (88) and Sierra Leone (one).

There has also been an outbreak among captive chimpanzees in Cameroon.

Altogether, the CDC says, there have been monkeypox cases reported in more countries during the past decade than in the preceding 40 years.

Describing the disease as an "emerging zoonosis", the organisation flags multiple concerns, including the fact that many of the countries affected lack the knowledge, experience and facilities to respond quickly to outbreaks, thus increasing the likelihood that the virus will continue to spread.

In calling for an increase in resources to tackle the disease – a call echoed by WHO, which this year identified monkeypox as a developing threat – the CDC draws comparisons with smallpox.

While closely related, the two viruses differ in one crucial aspect. Smallpox is an entirely human disease, a crucial factor in its vaccine-led eradication. Monkeypox, however, is zoonotic – meaning that it exists outside humans in one or more animal species that serve as reservoirs.

These reservoirs have not been identified, meaning attempts at a smallpox-style eradication will be much harder, if not impossible. (A similar problem besets Ebola researchers. During the 2013 to 2016 West African outbreak, which killed over 11,000 people, the animal species reservoir was never conclusively identified. The search continues today, with candidates ranging from bats to snakes.)

There is, however, some good news. Although there is no specific treatment available for monkeypox, the smallpox vaccination offers cross-protection, meaning that, in theory at least, large-scale prevention is possible.

http://bit.ly/2DE4pQW

New diabetes drug may help people with obesity lose weight

Compound similar to the hormone glucagon-like peptide 1 may help people who have obesity but not diabetes to lose weight

CHICAGO--A compound that mimics a naturally occurring hormone that regulates appetite may help people who have obesity but not diabetes to lose weight, a new study suggests. The research will be presented Sunday, March 18, at ENDO 2018, the Endocrine Society's 100th annual meeting in Chicago, Ill.

The compound, semaglutide, has a chemical structure that is very (GLP-1), which regulates both insulin secretion and appetite. In December, the U.S. Food and Drug Administration approved the semaglutide injection Ozempic as a once-weekly adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

"This randomized study of weight loss induced with semaglutide in people with obesity but without diabetes has shown the highest weight reductions yet seen for any pharmaceutical intervention," said lead author Patrick M. O'Neil, Ph.D., Director of the Weight Management Center and Professor of Psychiatry and Behavioral Sciences at the Medical University of South Carolina in Charleston, S.C.

The new study included 957 participants, 35 percent of whom were male. All participants had a body mass index (BMI) of at least 30, but did not have diabetes. They were randomly assigned to seven different groups. Five groups received different doses of semaglutide (between 0.05 mg and 0.4 mg) via injection once daily; a sixth group received a placebo, and a seventh group received 3 mg of the diabetes drug liraglutide. All participants received monthly diet and exercise counseling.

After one year, all participants receiving semaglutide had lost significantly more weight than those receiving placebo. The higher the dose participants received, the greater their average weight loss. Participants who received 0.05 mg of semaglutide daily lost an average of 6.0 percent of their body weight; the 0.1 mg group lost an average of 8.6 percent; the 0.3 mg group lost an average of 11.2 percent; and those receiving a daily dose of 0.4 mg lost an average of 13.8 percent. Those receiving liraglutide lost an average of 7.8 percent of their body weight, while those in the placebo group lost only 2.3 percent on average.

Sixty five percent of participants who received 0.4 mg of semaglutide per day lost at least 10 percent of their body weight, compared with 10 percent of those in the placebo group and 34 percent of the liraglutide group.

The most common adverse events in those taking semaglutide were mild/moderate nausea, as seen previously with GLP-1 receptor agonists. O'Neil noted that further studies of semaglutide for obesity are underway.

http://bit.ly/2tYvVZQ

Even dinosaurs had parasites

Fossilised faeces and holes in ancient jawbones show that dinosaurs, like modern animals, were plagued by parasites.

Even mighty dinosaurs such as *Tyrannosaurus rex* were not immune from being pestered by parasites, as this video from PBS's Gross Science explains.

By examining fossilised dinosaur droppings – known as coprolites – palaeontologists have found evidence of internal parasites including eggs from flatworms and roundworms, and cysts that look like those formed by modern amoebas. A 100-million-year-old fly has also been found preserved in amber that hosted a malaria-like parasite in its own guts, indicating that dinosaurs too may have been prey to the tiny infectious organism. Distinctive

holes in *T. rex* jawbones may also be signs of a parasite that caused invasive ulcers in the mouth and throat.

It just goes to show that strength and size are no defence against parasites. For that, you need hygiene and – if all else fails – modern medicine.

http://bit.ly/2pnUAS9

A small, daily dose of Viagra may reduce colorectal cancer risk

A small, daily dose of Viagra significantly reduces colorectal cancer risk in an animal model that is genetically predetermined to have the third leading cause of cancer death, scientists report.

AUGUSTA, Ga. - A small, daily dose of Viagra significantly reduces colorectal cancer risk in an animal model that is genetically predetermined to have the third leading cause of cancer death, scientists report.

Viagra cut in half the formation of polyps, an abnormal and often asymptomatic clump of cells on the lining of the intestines that may become cancer, says Dr. Darren D. Browning, cancer researcher at the Georgia Cancer Center and Department of Biochemistry and Molecular Biology at the Medical College of Georgia at Augusta University.

Next steps should include a clinical trial for the drug in patients considered at high risk of colorectal cancer, such as those with a strong family history, multiple previous polyps and chronic intestinal inflammation like colitis, Browning says.

Viagra has been used safely for years in a wide range of doses and age groups, from premature infants with pulmonary hypertension to the elderly with erectile dysfunction, he notes.

When placed in the drinking water, Browning's team found that Viagra reduced polyps in a mouse model with a genetic mutation that occurs in humans, causing them to produce hundreds of polyps starting as teenagers and essentially always resulting in colorectal cancer, says Browning, corresponding author of the study in the journal Cancer Prevention Research.

"Giving a baby dose of Viagra can reduce the amount of tumors in these animals by half," Browning says.

Viagra is best known for its ability to relax the smooth muscle cells around blood vessels so the vessels can more easily fill with blood, which is how it helps both erectile dysfunction and pulmonary hypertension. But Browning's lab is showing it also increases levels of the chemical cyclic GMP, which is known to affect the intestinal lining, called the epithelium.

While the details of just how remain unclear, Browning and his team have seen that the results of increased cyclic GMP include suppression of some of the excessive cell proliferation that occurs in the gut and an increase in normal cell differentiation as well as the natural elimination of abnormal cells, through a process called apoptosis.

"When we give Viagra, we shrink the whole proliferating compartment," says Browning, in an area of our body that directly deals with whatever we put in our mouths and normally experiences high cell turnover "Proliferating cells are more subject to mutations that cause cancer."

Existing polyps were not affected, more evidence that targeting cyclic GMP signaling appears to be a good prevention strategy in high-risk patients, he says.

Viagra is known to inhibit PDE5, a naturally occurring enzyme in colon cells - and other tissues - that breaks down cyclic GMP so there is more of it available to reduce cell proliferation and improve differentiation into cells like the goblet cells that secret protective mucus.

Guanylyl-cyclase C, or GCC, is the primary source of cyclic GMP in the intestinal lining. Mice like those in his study with the genetic predisposition for polyps, were found to have reduced levels of GCC-activating peptides, which are also commonly lost in human colon cancers.

The mice have mutations in the APC - adenomatous polyposis coli - gene, a known tumor suppressor. Like these mice, people with mutations in the APC gene can develop hundreds of polyps in the colon

and rectum and are considered at highest risk for colorectal cancer, says Browning of the inherited disorder called familial adenomatous polyposis. The average age at which individuals develop colon cancer is 39, according to the National Institutes of Health.

The scientists also looked at the prescription drug linaclotide, which is used to treat constipation and irritable bowel syndrome with constipation and, like Viagra, is known to increase cyclic GMP. While linaclotide was also effective at significantly reducing polyp formation, the common side effect of diarrhea at pretty much any dose makes it unlikely that patients would find it tolerable to use long term, even to reduce their cancer risk, Browning says. The low doses of Viagra used by humans and in the lab, on the other hand, have no known side effects, Browning notes.

Browning's lab published a paper in July in Cancer Prevention Research that showed Viagra cut polyp formation in half in a mouse model of colitis, an inflammation of the colon and risk factor for colorectal cancer. But in this model as well, they found the drug targeted problems from the genetic mutations, although inflammation also was reduced.

He notes that inflammation is the driver in less than 5 percent of colorectal cancers. About 80 percent form spontaneously when cells in this high-cell turnover area divide and develop a mutation that may support uncontrolled proliferation. Mutations occur most often when we consume carcinogens like those found in processed or over-cooked meats.

The research was supported by the National Cancer Institute.