http://bit.ly/2I8kHco

Spinal cord is 'smarter' than previously thought

Research shows our spinal cords contribute to sophisticated hand function

We often think of our brains as being at the centre of complex motor function and control, but how 'smart' is your spinal cord?

Turns out it is smarter than we think.

It is well known that the circuits in this part of our nervous system, which travel down the length of our spine, control seemingly simple things like the pain reflex in humans, and some motor control functions in animals.

Now, new research from Western University has shown that the spinal cord is also able to process and control more complex functions, like the positioning of your hand in external space.

"This research has shown that a least one important function is being done at the level of the spinal cord and it opens up a whole new area of investigation to say, 'what else is done at the spinal level and what else have we potentially missed in this domain?'" said the study's senior and supervising researcher Andrew Pruszynski, PhD, assistant professor at Western's Schulich School of Medicine & Dentistry and Canada Research Chair in Sensorimotor Neuroscience.

The study, "Spinal stretch reflexes support efficient hand control," will be published online in the high impact journal *Nature Neuroscience*. (LINK to follow)

This kind of hand control requires sensory inputs from multiple joints - mainly the elbow and the wrist - and these inputs was previously thought to be processed and converted into motor commands by the brain's cerebral cortex.

Using specialized robotic technology, a three degree of freedom exoskeleton at Western's Brain and Mind Institute, subjects were asked to maintain their hand in a target position and then the robot bumped it away from the target by simultaneously flexing or extending the wrist and elbow. The researchers measured the time that it took for the muscles in the elbow and wrist to respond to the bump from the robot and whether these responses helped bring the hand back to the initial target.

By measuring the latency, or 'lag', in the response, they were able to determine whether the processing was happening in the brain or the spinal cord.

"We found that these responses happen so quickly that the only place that they could be generated from is the spinal circuits themselves," said the study's lead researcher Jeff Weiler, PhD, a post-doctoral fellow at Schulich Medicine & Dentistry. "What we see is that these spinal circuits don't really care about what's happening at the individual joints, they care about where the hand is in the external world and generate a response that tries to put the hand back to where it came from."

This response generated by the spinal cord is called a 'stretch reflex,' and has previously been thought to be very limited in terms of how it helps movement. "Historically it was believed that these spinal reflexes just act to restore the length of the muscle to whatever happened before the stretch occurred," said Pruszynski. "We are showing they can actually do something much more complicated - control the hand in space."

This finding adds immensely to our understanding of neuroscience and neurocircuitry, and provides new information and targets for rehabilitation science.

"A fundamental understanding of the neurocircuits is critical for making any kind of progress on rehabilitation front," said Pruszynski who is also a scientist at Western's Robarts Research Institute and the Brain and Mind Institute. "Here we can see how this knowledge could lead to different kinds of training regimens that focus on the spinal circuitry."

http://bit.ly/2N2trzt

Do you like Earth's solid surface and life-inclined climate? Thank your lucky (massive) star

Earth's solid surface and moderate climate may be due, in part, to a massive star in the birth environment of the Sun, according to new computer simulations of planet formation.

ANN ARBOR- Without the star's radioactive elements injected into the early solar system, our home planet could be a hostile ocean world covered in global ice sheets.

"The results of our simulations suggest that there are two qualitatively different types of planetary systems," said Tim Lichtenberg of the National Centre of Competence in Research PlanetS in Switzerland. "There are those similar to our solar system, whose planets have little water, and those in which primarily ocean worlds are created because no massive star was around when their host system formed."

Lichtenberg and colleagues, including University of Michigan astronomer Michael Meyer, were initially intrigued by the role the potential presence of a massive star played on the formation of a planet.

Meyer said the simulations help solve some questions, while raising others.

"It is great to know that radioactive elements can help make a wet system drier and to have an explanation as to why planets within the same system would share similar properties," Meyer said.

"But radioactive heating may not be enough. How can we explain our Earth, which is very dry, indeed, compared to planets formed in our models? Perhaps having Jupiter where it is was also important in keeping most icy bodies out of the inner solar system."

Researchers say while water covers more than two-thirds of the surface of Earth, in astronomical terms, the inner terrestrial planets of our solar system are very dry--fortunately, because too much of a good thing can do more harm than good.

All planets have a core, mantle (inside layer) and crust. If the water content of a rocky planet is significantly greater than on Earth, the mantle is covered by a deep, global ocean and an impenetrable layer of ice on the ocean floor. This prevents geochemical processes, such as the carbon cycle on Earth, that stabilize the climate and create surface conditions conducive to life as we know it.

The researchers developed computer models to simulate the formation of planets from their building blocks, the so-called planetesimals--rocky-icy bodies of probably dozens of kilometers in size. During the birth of a planetary system, the planetesimals form in a disk of dust and gas around the young star and grow into planetary embryos.

Radioactive heat engine

As these planetesimals are heated from the inside, part of the initial water ice content evaporates and escapes to space before it can be delivered to the planet itself.

This internal heating may have happened shortly after the birth of our solar system 4.6 billion years ago, as primeval traces in meteorites suggest, and may still be ongoing in numerous places.

Right when the proto-Sun formed, a supernova occurred in the cosmic neighborhood. Radioactive elements, including aluminium-26, were fused in this dying massive star and got injected into our young solar system, either from its excessive stellar winds or via the supernova ejecta after the explosion.

The researchers say the quantitative predictions from this work will help near-future space telescopes, dedicated to the hunt for extrasolar planets, to track potential traces and differences in planetary compositions, and refine the predicted implications of the Al^{26} dehydration mechanism.

They are eagerly awaiting the launch of upcoming space missions with which Earth-sized exoplanets outside our solar system will be observable. These will bring humanity ever-closer to understanding whether our home planet is one of a kind, or if there are "an infinity of worlds of the same kind as our own."

Their study appears in Nature Astronomy. Other researchers include those from the Swiss Federal Institute of Technology, University of Bayreuth and University of Bern.

Study: A water budget dichotomy of rocky protoplanets from ^{26}Al-heating (will be live when embargo lifts)

http://bit.ly/2S17npQ

Could energy overload drive cancer risk?

An over-abundance of energy in cells might super-charge their growth and cause them to become cancerous

It's well-known that obesity, diabetes and chronic inflammation are major risk factors for cancer. But just how cancer evolves in people with these diseases -- and why a healthy diet and exercising regularly can help prevent it -- is poorly understood. New research published in *Evolution, Medicine and Public Health* offers an intriguing theory: By providing an over-abundance of energy to cells, these diseases might super-charge their growth and cause them to become cancerous.

Much of the research that explores how cancer develops focuses on mutations that arise in non-reproductive cells, meaning that they are not passed down from parent to offspring; instead, they are only passed on to new "daughter" cells when a mutated cell divides within a tissue.

But a number of recent studies have suggested that these "driver mutations" are surprisingly common in normal cells, not just in cancers. "This led me to believe that cancer driver mutations cannot be a complete explanation for why some tissues give rise to cancer, while others do not," says lead author John Pepper, a biologist with the National Cancer Institute's Division of Cancer Prevention and an External Professor at the Santa Fe Institute. "A small collection of papers in the last few years made me go 'wait a minute, suddenly that explanation is not adequate anymore.'"

Healthy tissue has a built-in limiter that keeps cell proliferation in check. But an energy overload -- common in diabetes, obesity, and inflammation -- can overwhelm those guardrails. "One question is, how abundant are the resources cells need for proliferation? If they are more abundant in some tissues, that might be what evolves into cancer," Pepper says.

He and his colleagues, Daniel Wu of Stanford University and C. Athena Aktipis of Arizona State University, building on previous work by French researchers and others that suggested an oversupply of energy may be one of those proliferation resources, used a computer model of cell evolution to simulate what happens when a tissue is flooded with energy.

They found that such an overload did indeed cause a cell production boom. The study hints at a new explanation for how cancer evolves, particularly in the obese and other high-risk populations.

It may also help explain the inverse: why following a healthy diet and exercising regularly can reduce that risk. "One of the pieces that's been missing is, when these lifestyle changes are made it has to be through some kind of physiological mechanism," Pepper says.

While empirical studies are needed to confirm the findings, the study lays the groundwork for what could be an important advance in cancer prevention research -- an area that deserves increased attention, he adds.

Pepper credits conversations with other Santa Fe Institute faculty -- Michael Hochberg, Chris Kempes, Jim Brown, and Geoffrey West -- for inspiring him to consider the connection between energy supply and cancer cell proliferation.

http://bit.ly/2TIzfks

Mosquitoes that carry malaria may have been doing so 100 million years ago

New research shows mosquitoes that carry malaria were present 100 million years ago

***Priscoculex burmanicus, a newly identified genus and species of anopheline mosquito, preserved in amber.* George Poinar Jr.**

CORVALLIS, Ore. - The anopheline mosquitoes that carry malaria were present 100 million years ago, new research shows, potentially shedding fresh light on the history of a disease that continues to kill more than 400,000 people annually.

"Mosquitoes could have been vectoring malaria at that time, but it's still an open question," said the study's corresponding author, George Poinar Jr. of Oregon State University's College of Science. "Back then anopheline mosquitoes were probably biting birds, small mammals and reptiles since they still feed on those groups today."

In amber from Myanmar that dates to the mid-Cretaceous Period, Poinar and co-authors described a new genus and species of mosquito, which was named *Priscoculex burmanicus*. Various characteristics, including those related to wing veins, proboscis, antennae and abdomen indicate that *Priscoculex* is an early lineage of the anopheline mosquitoes.

"This discovery provides evidence that anophelines were radiating - diversifying from ancestral species - on the ancient megacontinent of Gondwana because it is now thought that Myanmar amber fossils originated on Gondwana," said Poinar, an international expert in using plant and animal life forms preserved in amber to learn more about the biology and ecology of the distant past.

Findings were published in *Historical Biology*.

Most malaria, especially the species that infect humans and other primates, is caused primarily by one genus of protozoa, *Plasmodium*, and spread mainly by anopheline mosquitoes. Ancestral forms of the disease may literally have determined animal survival and evolution, according to Poinar.

In a previous work, he suggested that the origins of malaria, which today can infect animals ranging from humans and other mammals to birds and reptiles, may have first appeared in an insect such as a biting midge that was found to be vectoring a type of malaria some 100 million years ago. Now he can include mosquitoes as possible malaria vectors that existed at the same time.

In a 2007 book, "What Bugged the Dinosaurs? Insects, Disease and Death in the Cretaceous," Poinar and his wife, Roberta, showed insect vectors from the Cretaceous with pathogens that could have contributed to the widespread extinction of the dinosaurs some 65 million years ago.

"There were catastrophic events that happened around that time, such as asteroid impacts, climatic changes and lava flows," the Poinars' wrote. "But it's still clear that dinosaurs declined and slowly became extinct over thousands of years, which suggests other issues must also have been at work. Insects, microbial pathogens such as malaria, and other vertebrate diseases were just emerging around that time."

Scientists have long debated about how and when malaria evolved, said Poinar, who was the first to discover malaria in a 15- to 20-million-year-old fossil mosquito from the New World, in what is now the Dominican Republic.

It was the first fossil record of *Plasmodium* malaria, one type of which is now the strain that infects and kills humans.

Understanding the ancient history of malaria, Poinar said, might offer clues on how its modern-day life cycle evolved and how to interrupt its transmission. Since the sexual reproductive stage of malaria only occurs in the insect vectors, Poinar considers the vectors to be the

primary hosts of the malarial pathogen, rather than the vertebrates they infect.

The first human recording of malaria was in China in 2,700 B.C., and some researchers say it may have resulted in the fall of the Roman Empire. In 2017 there were 219 million cases of malaria worldwide, according to the World Health Organization. Immunity rarely occurs naturally and the search for a vaccine has not yet been successful.

http://bit.ly/2S0o6ti

Stonehenge, other ancient rock structures may trace their origins to monuments like this

Findings demonstrate absolutely that Brittany is the origin of the European megalithic phenomenon

By Michael Price

Stonehenge may be the most famous example, but tens of thousands of other ancient sites featuring massive, curiously arranged rocks dot Europe.

The famed megalith Carnac in the Brittany region of northwestern France

Andia/UIG/Getty Images

A new study suggests these megaliths weren't created independently but instead can be traced back to a single hunter-gatherer culture that started nearly 7000 years ago in what is today the Brittany region of northwestern France. The findings also indicate societies at the time were better boaters than typically believed, spreading their culture by sea.

"This demonstrates absolutely that Brittany is the origin of the European megalithic phenomenon," says Michael Parker Pearson, an archaeologist and Stonehenge specialist at University College London.

The origins of the megalith builders have haunted Bettina Schulz Paulsson since she excavated her first megalithic monument in Portugal nearly 20 years ago. Early on, most anthropologists thought megaliths originated in the Near East or the Mediterranean, whereas many modern thinkers back the idea they were invented independently in five or six different regions around Europe. The major hurdle, she says, has been sorting through the mountains of archaeological data to find reliable dates for the 35,000 sites, including carved standing stones, tombs, and temples.

"Everyone told me, 'You're crazy, it can't be done,'" says Schulz Paulsson, a prehistoric archaeologist at the University of Gothenburg in Sweden and the study's sole author. "But I decided to do it anyway."

What she did was sift through radiocarbon dating data from 2410 ancient sites across Europe to reconstruct a prehistoric archaeological timeline. The radiocarbon dates came mostly from human remains buried within the sites. The study looked not just at megaliths, but also at so-called premegalithic graves that featured elaborate, earthen tombs but no huge stones. Schulz Paulsson also factored in information on the sites' architecture, tool use, and burial customs to further narrow the dates.

The very earliest megaliths in Europe, she found, come from northwestern France, including the famous Carnac stones, a dense collection of rows of standing stones, mounds, and covered stone tombs called dolmens. These date to about 4700 B.C.E., when the region was inhabited by hunter-gatherers. Engravings on standing stones from the region depict sperm whales and other sea life, which suggests the precocious masons may also have been mariners, Schulz Paulsson says.

Northwestern France is also the only megalithic region that also features gravesites with complex earthen tombs that date to about 5000 B.C.E., which she says is evidence of an "evolution of megaliths" in the region. That means megalith building likely

originated there and spread outward, she reports today in the *Proceedings of the National Academy of Sciences*.

By about 4300 B.C.E., megaliths had spread to coastal sites in southern France, the Mediterranean, and on the Atlantic coast of the Iberian Peninsula. Over the next few thousand years, the structures continued to pop up around Europe's coasts in three distinct phases.

Stonehenge is thought to have been erected around 2400 B.C.E., but other megaliths in the British Isles go back to about 4000 B.C.E. The abrupt emergence of specific megalithic styles like narrow stone-lined tombs at coastal sites, but rarely inland, suggests these ideas were being spread by prehistoric sailors. If so, it would push back the emergence of advanced seafaring in Europe by about 2000 years, Schulz Paulsson says.

Dolmen Sa Coveccada on northeastern Sardinia in the Mediterranean Sea **Bettina Schulz Paulsson**

"This seems quite plausible," says Gail Higginbottom, an archaeologist at the University of Adelaide in Australia.

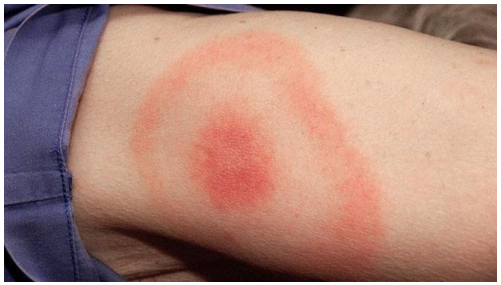
Parker Pearson says the study does a good job establishing that megaliths first arose in northwestern France, but it doesn't quite rule out the possibility that some later cultures independently developed the idea.

Karl-Göran Sjögren, a fellow archaeologist at the University of Gothenburg, says he accepts that northwest France was among the first builders. But he isn't fully convinced there aren't still earlier megaliths yet to be uncovered, or more evidence that might push back the dates of some known megaliths. Future studies that include ancient DNA and other bioarchaeological evidence on population movements could clear things up, he says.

https://bbc.in/2SM9lif

Lyme disease can be diagnosed by 'bull's eye' rash alone

Lyme disease can be diagnosed by the rash alone, new advice for the NHS says.



The rash is raised around the edges **CDC**

People with the "bull's eye" circular rash do not need a blood test and should be treated immediately to avoid complications, the National Institute for Health and Care Excellence says.

Waiting for lab results is unnecessary and can cause delays in patients being prescribed the antibiotics they need.

Lyme disease is spread by tick bites and can be debilitating.

A blood tests can check for it but may not give a positive result until eight weeks after the patient is bitten.

Prof Gillian Leng, deputy chief executive and director of health and social care at the National Institute for Health and Care Excellence (NICE), said for most people with Lyme disease, a course of antibiotics would be an effective treatment, "so it is important we diagnose and treat people as soon as possible".

"A person with Lyme disease may present with a wide range of symptoms, so we have clear advice for professionals about the use of lab tests for diagnosis and the most appropriate antibiotic treatments," she said.

"If a characteristic bull's eye rash is present, healthcare professionals should feel confident in diagnosing Lyme disease."

Lyme disease can be difficult to diagnose. It has similar symptoms to other conditions and there is not always an obvious rash. The rash

can also appear in a number of different ways, as these images from the NICE guidance show.

Symptoms can also include:

- ***a high temperature or feeling hot and shivery***
- ***headaches***
- ***muscle and joint pain***
- ***tiredness***
- ***loss of energy***

But if there is a delay in treatment, more severe symptoms can develop months or years later, including:

- ***pain and swelling in joints***
- ***nerve problems - such as pain or numbness***
- ***heart problems***
- ***loss of memory or concentration***

Lyme Disease

- ***Ticks that may cause Lyme disease are found all over the UK***
- ***High-risk areas include grassy and wooded areas in southern England and the Scottish Highlands***
- ***To reduce the risk of being bitten, cover your skin, tuck your trousers into your socks, use insect repellent and stick to paths***
- ***If you are bitten, remove the tick with fine-tipped tweezers or a tick-removal tool found in chemists***
- ***Clean the bite with antiseptic or soap and water***
- ***The risk of getting ill is low as only a small number of ticks are infected with the bacteria that cause Lyme disease***
- ***You don't need to do anything else unless you become unwell***
- ***You should go to your GP if you've been bitten by a tick or visited an area in the past month where infected ticks are found and you get flu-like symptoms or a circular red rash***
- ***These symptoms can include feeling hot and shivery, headaches, aching muscles or feeling sick***

A growing number of high profile people have spoken out about their experiences of the problems of living with Lyme disease due to delayed diagnosis.

American model Bella Hadid has spoken of the challenges of continuing to work with the disease because she's often exhausted and needs to take regular medication. Her mother, who starred in The Real Housewives of Beverly Hills, and Bella's brother also have the disease.

Singer Avril Lavigne said it had taken months for her to be diagnosed with the disease, which had left her bedridden for two years. She got the first symptoms on tour, when she was achy, fatigued and couldn't get out of bed. She said she had felt so bad at one point she had "accepted that I was dying".

Former England rugby player Matt Dawson got the disease after being bitten by a tick in a London park in 2015. It caused a bacterial infection to spread through his body and eventually left him needing heart surgery.

Phones 4U founder John Caudwell funds a charity Caudwell LymeCo that funds research he hopes "will lead to a truly reliable test and cure via the NHS for every Lyme disease patient". He and 14 other members of his family have the disease.

Veronica Hughes, chief executive of Caudwell LymeCo, said she hoped the new NICE draft guidance would increase the number of doctors who felt confident diagnosing a Lyme disease rash on sight.

"Caudwell LymeCo Charity hears regularly from people whose doctors have diagnosed an erythema migrans but decide to check with a blood test, not realising that the rash is the more reliable of the two," she said.

"Waiting for blood test results always delays treatment. When a patient has the rash, this delay is unnecessary and reduces the likelihood of total cure."

https://nyti.ms/2tnFzSO

A.I. Shows Promise Assisting Physicians

Doctors competed against A.I. computers to recognize illnesses on magnetic resonance images of a human brain during a competition in Beijing last year. The human doctors lost.

By Cade Metz

Each year, millions of Americans walk out of a doctor's office with a misdiagnosis. Physicians try to be systematic when identifying illness and disease, but bias creeps in. Alternatives are overlooked.

Now a group of researchers in the United States and China has tested a potential remedy for all-too-human frailties: artificial intelligence.

In a paper published on Monday in Nature Medicine, the scientists reported that they had built a system that automatically diagnoses common childhood conditions — from influenza to meningitis — after processing the patient's symptoms, history, lab results and other clinical data.

The system was highly accurate, the researchers said, and one day may assist doctors in diagnosing complex or rare conditions.

Drawing on the records of nearly 600,000 Chinese patients who had visited a pediatric hospital over an 18-month period, the vast collection of data used to train this new system highlights an advantage for China in the worldwide race toward artificial intelligence.

Because its population is so large — and because its privacy norms put fewer restrictions on the sharing of digital data — it may be easier for Chinese companies and researchers to build and train the "deep learning" systems that are rapidly changing the trajectory of health care.

On Monday, President Trump signed an executive order meant to spur the development of A.I. across government, academia and industry in the United States. As part of this "American A.I. Initiative," the administration will encourage federal agencies and universities to share data that can drive the development of automated systems.

Pooling health care data is a particularly difficult endeavor. Whereas researchers went to a single Chinese hospital for all the data they needed to develop their artificial-intelligence system, gathering such data from American facilities is rarely so straightforward.

"You have go to multiple places," said Dr. George Shih, associate professor of clinical radiology at Weill Cornell Medical Center and co-founder of MD.ai, a company that helps researchers label data for A.I. services. "The equipment is never the same. You have to make sure the data is anonymized. Even if you get permission, it is a massive amount of work."

After reshaping internet services, consumer devices and driverless cars in the early part of the decade, deep learning is moving rapidly into myriad areas of health care. Many organizations, including Google, are developing and testing systems that analyze electronic health records in an effort to flag medical conditions such as osteoporosis, diabetes, hypertension and heart failure.

Similar technologies are being built to automatically detect signs of illness and disease in X-rays, M.R.I.s and eye scans.

The new system relies on a neural network, a breed of artificial intelligence that is accelerating the development of everything from health care to driverless cars to military applications. A neural network can learn tasks largely on its own by analyzing vast amounts of data.

Using the technology, Dr. Kang Zhang, chief of ophthalmic genetics at the University of California, San Diego, has built systems that can analyze eye scans for hemorrhages, lesions and other signs of diabetic blindness. Ideally, such systems would serve as a first line of defense, screening patients and pinpointing those who need further attention.

Now Dr. Zhang and his colleagues have created a system that can diagnose an even wider range of conditions by recognizing patterns in text, not just in medical images. This may augment what doctors can do on their own, he said. “In some situations, physicians cannot consider all the possibilities,” he said. “This system can spot-check and make sure the physician didn’t miss anything.”

The experimental system analyzed the electronic medical records of nearly 600,000 patients at the Guangzhou Women and Children’s Medical Center in southern China, learning to associate common medical conditions with specific patient information gathered by doctors, nurses and other technicians.

First, a group of trained physicians annotated the hospital records, adding labels that identified information related to certain medical conditions. The system then analyzed the labeled data.

Then the neural network was given new information, including a patient’s symptoms as determined during a physical examination. Soon it was able to make connections on its own between written records and observed symptoms.

When tested on unlabeled data, the software could rival the performance of experienced physicians. It was more than 90 percent accurate at diagnosing asthma; the accuracy of physicians in the study ranged from 80 to 94 percent.

In diagnosing gastrointestinal disease, the system was 87 percent accurate, compared with the physicians’ accuracy of 82 to 90 percent.

Able to recognize patterns in data that humans could never identify on their own, neural networks can be enormously powerful in the right situation. But even experts have difficulty understanding why such networks make particular decisions and how they teach themselves. As a result, extensive testing is needed to reassure both doctors and patients that these systems are reliable.

Experts said extensive clinical trials are now needed for Dr. Zhang’s system, given the difficulty of interpreting decisions made by neural networks. “Medicine is a slow-moving field,” said Ben Shickel, a researcher at the University of Florida who specializes in the use of deep learning for health care. “No one is just going to deploy one of these techniques without rigorous testing that shows exactly what is going on.”

It could be years before deep-learning systems are deployed in emergency rooms and clinics. But some are closer to real-world use: Google is now running clinical trials of its eye-scan system at two hospitals in southern India.

Deep-learning diagnostic tools are more likely to flourish in countries outside the United States, Dr. Zhang said. Automated screening systems may be particularly useful in places where doctors are scarce, including in India and China.

The system built by Dr. Zhang and his colleagues benefited from the large scale of the data set gathered from the hospital in Guangzhou. Similar data sets from American hospitals are typically smaller, both because the average hospital is smaller and because regulations make it difficult to pool data from multiple facilities.

Dr. Zhang said he and his colleagues were careful to protect patients’ privacy in the new study. But he acknowledged that researchers in China may have an advantage when it comes to collecting and analyzing this kind of data. “The sheer size of the population — the sheer size of the data — is a big difference,” he said.

http://bit.ly/2DGq1yp

Testosterone limits for female athletes based on 'flawed' research

As sprinter Caster Semenya prepares to challenge the new rules in court, a new study suggests they are scientifically unsound

New regulations requiring certain female athletes to medically lower their testosterone levels in order to compete internationally are based on "fatally flawed" data, according to new research led by the University of Colorado Boulder.

The paper, published this month in the *Asser International Sports Law Journal*, comes as South African Olympic sprinter Caster Semenya prepares to challenge the controversial new rules in an international court in Switzerland.

The authors have called for a retraction of the original research and asked the International Association of Athletics Federations - the global governing body for track and field - to reconsider the rule change.

"In almost any other setting of science, errors of this magnitude would lead to a paper being retracted," said lead author Roger Pielke Jr., director of the Center for Sports Governance at CU Boulder. "And it certainly would not be the basis for broad regulations that have a profound impact on people's lives."

In April 2018, the IAAF announced new regulations requiring certain female athletes with naturally high testosterone levels to take testosterone-lowering hormones if they want to continue to compete in the women's category for the 400-meter, the 400-meter hurdles, the 800-meter, the 1,500-meter and the mile.

The rule, which applies to IAAF-sanctioned international competitions, requires that they maintain serum testosterone levels below 5 nanomoles per liter (nmol/L) for at least six months prior to competition. Most females have testosterone levels ranging from 1.12 to 1.79 nmol/L while the normal adult male range is 7.7 - 29.4 nmol/L. About seven in every 1,000 elite female athletes have high testosterone levels, according to IAAF.

The association had attempted to put forth similar regulations in 2011 , but that rule was thrown out when the Swiss-based Court of Arbitration for Sport (CAS) - the highest court for international sport - concluded in 2015 that there was a lack of evidence linking high testosterone to "a real competitive advantage" in women.

In 2017, the IAAF came back with that research, publishing a paper in the British Journal of Sports Medicine (BJSM), which claimed that elite women runners with the highest testosterone levels performed as much as 3 percent better than those with the lowest levels in several events.

Pielke and co-authors Erik Boye, a professor emeritus of molecular biology at the University of Oslo, and Ross Tucker, a University of Cape Town exercise physiologist, challenge those results.

"We found problematic data throughout the study and consequently, the conclusions can't be seen as reliable," Pielke said.

When the three tried to replicate the original findings using data from the study's authors and publicly available results from four of the races included, they uncovered "significant anomalies and errors."

For instance, they found performance times that were erroneously duplicated and "phantom times" that did not exist in official IAAF competition results. In addition, some athletes disqualified for doping were included in the study dataset - a fact that could confound the results.

In all, from 17 to 32 percent of the data used in the study was found to be in error. The researchers also note that IAAF researchers themselves conducted the *BJSM* study.

"We would not find it appropriate for cigarette companies to provide the scientific bases for the regulation of smoking, or oil companies to provide the scientific bases for regulation of fossil fuels. Sport regulation should be held to the same high standards," they write.

The IAAF researchers did correct what they characterized as "data capture errors" and re-ran their analysis in a subsequent letter to the journal. But flaws remain in that revision, Pielke said.

The research will be at issue later this month when Pielke is expected to serve as an expert witness at the Court of Arbitration for Sport, where Semenya and Athletics South Africa have brought a case against the IAAF calling the rules "discriminatory, irrational, and unjustifiable."

Under the new regulations, those who decline to medically reduce their testosterone levels must relinquish their right to compete as females.

Originally set to take effect in November, implementation of the rules has been postponed until after the outcome of the case.

"Fundamentally, the issues that we raise with our paper are about the integrity of science in regulation," said Pielke. "Any agency, in sport or beyond, should be expected to produce science that can withstand scrutiny and which actually supports the justification for proposed regulations. That simply did not happen here."

http://bit.ly/2GrkiQu

Couples creating art or playing board games release 'love hormone'

But men painters release most, Baylor University study finds

WACO, Texas - When couples play board games together or take a painting class with each other, their bodies release oxytocin -- sometimes dubbed the "hugging hormone." But men wielding paintbrushes released twice as much or more as the level of women painters and couples playing games, a Baylor University study has found.

Couples in the Baylor University "love hormone " study were asked to paint this scene -- inserting their own initials --in the art class. **Karen Melton**

"We were expecting the opposite -- that couples playing the board games would interact more because they were communicating about the games and strategies, or because they were competing, and with more interaction, they would release more oxytocin," which is associated with bonding and family cohesiveness, said Karen Melton, Ph.D., assistant professor of child and family studies in Baylor's Robbins College of Health and Human Sciences.

The study -- "Examining Couple Recreation and Oxytocin Via the Ecology of Family Experiences Framework" -- is published in the *Journal of Marriage and Family*, the journal of the National Council on Family Relations.

Researchers also expected that painting couples would be more attentive to the instructor and to the canvas than to their partners -- but instead, couples in the art class reported more partner-touching than couples playing board games.

"Typically, an art class is not seen as an interactive date with your partner. But sometimes couples that were painting turned the activity into a bonding time by choosing to interact -- putting an arm around their partner or simply saying, 'Good job,'" Melton said.

The study is the first to examine how distinct types of leisure are associated with oxytocin release, researchers said.

"Our big finding was that all couples release oxytocin when playing together -- and that's good news for couples' relationships," Melton said.

"But men in the art class released 2 to 2.5 times more oxytocin than the other groups. This suggests that some types of activities may be more beneficial to males than females, and vice versa."

Of the four groups, the release of oxytocin increased most for the men in the art class, followed by women playing board games; women in the art class; and last, men playing board games. But the last three groups did not differ significantly from one another, the study found.

Researchers also identified a significant environmental impact, in that couples in a novel setting and activity released more oxytocin than in a familiar home-like environment.

That suggests that novelty can be an important factor to consider when planning date nights with our partners.

For the study, Melton and Maria Boccia, Ph.D., professor of child and family studies, recruited 20 couples ranging in age from 25 to 40.

Couples were randomly assigned to participate in one of two couple dates -- game night or couple art class -- for one hour.

One group played board games in a familiar home-like setting. Couples were alone. These couples chose familiar games that would not require them to read instructions. Among the games were cards, checkers, chess, puzzles, dominoes, Monopoly and word games.

Meanwhile, the other group participated in painting classes for couples at a community art studio. These couples participated in two groups of five couples.

They painted a simple beach scene with their initials in the sand. The art instructor had prepared the canvases to reduce interactions between the couples.

To measure participants' oxytocin levels, researchers took urine samples before and after the activities.

They also administered a six-item survey about the couple's familiarity with the activities and about their communication, touch and eye contact with their partners during the sessions, which lasted for about an hour.

In the future, Melton and Boccia want to explore further what role the environment may play in oxytocin release.

The researchers noted that their study differs from others, in which participants have been asked to perform specific actions as cuddling, hand-holding or massage, sometimes for an assigned period. The physical interactions in Melton and Boccia's study took place without prompting and lasted briefly.

"This has implications for the everyday family - to find those small, meaningful ways to interact when they're eating dinner together or going for a walk or doing homework with a child or sitting on their couches with their iPad," Melton said.

"While, yes, this advice is simple, we also have to make sure we're doing the hard work ... This is the hard advice: we have to make time for our families if we want to have families."

http://bit.ly/2SvI0Sl

Seven moral rules found all around the world

Anthropologists at the University of Oxford have discovered what they believe to be seven universal moral rules.

The rules: ***help your family, help your group, return favours, be brave, defer to superiors, divide resources fairly, and respect others' property***. These were found in a survey of 60 cultures from all around the world.

Previous studies have looked at some of these rules in some places – but none has looked at all of them in a large representative sample of societies. The present study, published in *Current Anthropology*, is the largest and most comprehensive cross-cultural survey of morals ever conducted.

The team from Oxford's Institute of Cognitive & Evolutionary Anthropology (part of the School of Anthropology & Museum Ethnography) analysed ethnographic accounts of ethics from 60 societies, comprising over 600,000 words from over 600 sources.

Dr. Oliver Scott Curry, lead author and senior researcher at the Institute for Cognitive and Evolutionary Anthropology, said: "The debate between moral universalists and moral relativists has raged for centuries, but now we have some answers. People everywhere face a similar set of social problems, and use a similar set of moral rules to solve them. As predicted, these seven moral rules appear to be universal across cultures. Everyone everywhere shares a common moral code. All agree that cooperating, promoting the common good, is the right thing to do."

The study tested the theory that morality evolved to promote cooperation, and that – because there are many types of cooperation – there are many types of morality. According to this theory of 'morality as cooperation," kin selection explains why we feel a special duty of care for our families, and why we abhor incest. Mutualism explains why we form groups and coalitions (there is

strength and safety in numbers), and hence why we value unity, solidarity, and loyalty. Social exchange explains why we trust others, reciprocate favours, feel guilt and gratitude, make amends, and forgive. And conflict resolution explains why we engage in costly displays of prowess such as bravery and generosity, why we defer to our superiors, why we divide disputed resources fairly, and why we recognise prior possession.

The research found, first, that these seven cooperative behaviours were always considered morally good. Second, examples of most of these morals were found in most societies. Crucially, there were no counter-examples – no societies in which any of these behaviours were considered morally bad. And third, these morals were observed with equal frequency across continents; they were not the exclusive preserve of 'the West' or any other region.

So, among the Amhara, 'flouting kinship obligation is regarded as a shameful deviation, indicating an evil character." In Korea, there exists an 'egalitarian community ethic [of] mutual assistance and cooperation among neighbors [and] strong in-group solidarity." "Reciprocity is observed in every stage of Garo life [and] has a very high place in the Garo social structure of values." Among the Maasai, "Those who cling to warrior virtues are still highly respected," and 'the uncompromising ideal of supreme warriorhood [involves] ascetic commitment to self-sacrifice…in the heat of battle, as a supreme display of courageous loyalty." The Bemba exhibit 'a deep sense of respect for elders' authority." The Kapauku 'idea of justice' is called 'uta-uta, half-half…[the meaning of which] comes very close to what we call equity." And among the Tarahumara, 'respect for the property of others is the keystone of all interpersonal relations."

The study also detected "variation on a theme"—although all societies seemed to agree on the seven basic moral rules, they varied in how they prioritised or ranked them. The team has now developed a new moral values questionnaire to gather data on modern moral values, and is investigating whether cross-cultural variation in moral values reflects variation in the value of cooperation under different social conditions.

According to co-author Professor Harvey Whitehouse, anthropologists are uniquely placed to answer long-standing questions about moral universals and moral relativism. "Our study was based on historical descriptions of cultures from around the world; this data was collected prior to, and independently of, the development of the theories that we were testing. Future work will be able to test more fine-grained predictions of the theory by gathering new data, even more systematically, out in the field.

"We hope that this research helps to promote mutual understanding between people of different cultures; an appreciation of what we have in common, and how and why we differ," added Curry.

The full paper, "Is it good to cooperate? Testing the theory of morality-as-cooperation in 60 societies," can be read in *Current Anthropology*.

More information: *Oliver Scott Curry et al. Is It Good to Cooperate? Testing the Theory of Morality-as-Cooperation in 60 Societies, Current Anthropology (2019). DOI: 10.1086/701478*

http://bit.ly/2UYxW0S

Polio returns to Papua New Guinea

Low vax rates blamed for a slew of new cases in recent months.

Andrew Masterson reports.

Almost two decades after being declared free of the disease, Papua New Guinea (PNG) is battling an outbreak poliomyelitis.

The re-emergence of the disease – the first cases seen in the country since 1996 – has been traced to the strain of poliovirus used in the standard vaccine administered to protect against the illness.

But the real cause, reports a team of medicos writing for the Centres for Disease Control and Prevention (CDC), is not the vaccine itself, but the fact that not enough people have received it.

The country was officially certified free of polio by the World Health Organisation in 2000.

Researchers led by Mathias Bauri of PNG's National Department of Health report 26 confirmed cases of polio occurring between April and October 2018. The cases have been recorded in nine of the country's 22 provinces.

The first, or index, case of the current outbreak is identified as a boy aged six from Lae in Morobe Province, who succumbed to paralysis on April 25. Investigating doctors discovered he had received two doses of the standard Sabin oral poliovirus vaccine (OPV). Genetic testing revealed the cause of his illness was a variant of vaccine-derived poliovirus type 1 (cVDPV1). The virus differed from the vaccine type across 14 nucleotides, leading researchers to conclude that it had been circulating in the community for more than a year.

Of the subsequent cases, all have been young, with 19 of them under five years old.

Two-thirds of the cases have arisen in areas containing mines or plantations, which have highly transient populations.

Bauri and colleagues say the outbreak is because vaccination rates across the country remain too low, meaning cVDPV1 can be extensively transmitted person-to-person in conditions that allow it to mutate and turn virulent.

Because of a multitude of factors including inadequate access to healthcare, infant vaccination against polio was as low as 44% in 2017, and never climbed about 70% during the preceding decade.

http://bit.ly/2Nc91o4

Man Who Led FDA Team to Approve LASIK Now Says It Was a Mistake

Pushing for more transparent warnings on the risks of the procedures and the number of adverse events

Marcia Frellick

Morris Waxler, PhD, who led the US Food and Drug Administration (FDA) team that approved LASIK in 1999, has since said that decision was a mistake and is pushing for more transparent warnings on the risks of the procedures and the number of adverse events.

He's been fighting this fight for more than 12 years with little to no response from the FDA, he told *Medscape Medical News*. In 2007, 7 years after he left the FDA, he said he began to meet people who had been hurt personally or had family members who had suffered after LASIK surgeries, and set out to convince the FDA to add warnings.

In his latest correspondence to the FDA on January 30, Waxler references Jessica Starr, a *Fox 2* meteorologist in Detroit who died by suicide last December 12 at age 35.

As the *Detroit Free Press* reports, a month before the suicide, she publicly shared in a video her struggle with her recovery during the 4 weeks she took off work after a LASIK-type procedure, SMILE, in October. The procedure's role, if it is connected to the suicide, is unclear but it set off a wave of news reports on the potential risks of the procedure.

Waxler, who now has his own regulatory consulting business in Madison, Wisconsin, addressed the letter to Malvina Eydelman, director of FDA's Division of Ophthalmic and Ear, Nose and Throat Devices, in the wake of the suicide, writing that the "FDA deceived the public about problems with SMILE. You deceptively say, 'No AE (adverse events) occurred at a rate of 1% or greater per type of event.' Your statement is true ONLY for your narrow definition of adverse events (AE) as loss of distance acuity greater than 20/40. In addition, your statement is limited to 'per type of event,' falsely assuming SMILE does NOT induce multiple eye problems simultaneously. You deceptively understate the risks by not cumulating complication rates for different types of events."

FDA Clarifies Its Role

A spokesperson for the FDA told *Medscape Medical News* in a statement, "Whether or not to undergo LASIK is a decision made between a patient and a health care provider. The FDA's role is to determine whether there is reasonable assurance of the safety and effectiveness of a device for a given use based on scientific data.

"Lasers used for LASIK are class III devices, meaning they potentially pose a high risk to patients. Class III devices are reviewed through the Pre-Market Approval (PMA) process, which is the most stringent and rigorous review process at the FDA's Center for Devices and Radiological Health.

The PMA process includes a scientific and regulatory review to evaluate the safety and effectiveness of class III medical devices. In addition, our review process includes a thorough review of the product labeling for both patients and providers.

"In our own continued assessment of the literature and medical device reports, the FDA continues to believe that based on all the available scientific evidence, there is a reasonable assurance of the safety and effectiveness of the approved devices used in LASIK procedures when used according to the FDA-approved instructions for use.

"The FDA has extensive information for consumers and health care professionals on the benefits and risks of LASIK on its website, including patient labeling (information booklet), which discloses visual symptoms as potential risks of LASIK devices, and a summary of safety and effectiveness data for each LASIK device detailing information about the visual symptoms observed in the clinical studies. The FDA will continue to monitor postmarket data related to LASIK devices. We also encourage researchers to use robust questionnaires to elucidate the impact of visual symptoms on daily functioning," the spokesperson said.

ASCRS: "LASIK Is Safe and Effective"

A spokesperson for the American Society of Cataract and Refractive Surgery (ASCRS) also said in a statement, "After 20 years and more than 19 million procedures in the U.S., we know LASIK is safe and effective. To be clear, there is a vast body of scientific evidence supporting laser vision correction as a both safe and effective option for vision correction.

"The results of the clinical trial conducted to support the FDA approval of the use of excimer lasers for LASIK surpassed the goals set by Dr. Waxler and his office. It is important to point out that the work on laser vision correction didn't stop upon LASIK's approval in the late 1990s or when Dr. Waxler left the FDA.

Since the first studies were presented to the FDA, scientific investigation into laser vision correction has continued to both improve the procedure and to better understand and monitor postoperative complications. To date, laser vision correction technologies have received more than 50 FDA approvals."

As to why complication rates are not stated cumulatively, the ASCRS responds that "Cumulative complication rates are misleading and may overstate the proportion of patients who experienced symptoms because one patient may report experiencing several symptoms."

The ASCRS acknowledges that LASIK is not for everyone.

"It's important for patients to work with an experienced refractive surgeon and clearly understand the risks and benefits of any procedure so that they can make the decision that's right for them," the statement reads.

According to Market Scope estimates, surgical volume globally for refractive surgery is expected to increase from 4.3 million to 5.5 million procedures a year from 2018 to 2023.

Waxler is a former employee of the FDA. He has disclosed no other relevant financial relationships.

http://bit.ly/2SC3X27

Chimp communication gestures found to follow human linguistics rules

A team of researchers with members from the U.K., Switzerland and Spain has found that chimpanzees use communication gestures in ways that follow human linguistic rules.

By Bob Yirka, Phys.org

In their paper published in *Proceedings of the Royal Society B*, the group describes their study of chimps communicating with one another in the wild, and compares their observations against human communication rules.

Over the years, linguistic researchers have discovered that human language conforms to specific rules regardless of the language in which it is spoken. Such rules have names to make them more easily discussed. One such rule, Zipf's law of abbreviation, holds that words that are used frequently tend to be short. Another rule is called Menzerath's law—it says that large language structures tend to be made up of multiple short segments (syllables) when spoken. In this new effort, the researchers wondered if such rules might apply to other animals. To find out, they obtained and studied video footage of wild chimpanzees living and communicating in Uganda's Budongo Forest Reserve.

The researchers were able to identify approximately 2,000 examples of 58 unique gestures used by the chimps when communicating with one another. Since chimps cannot speak, they communicate by using hand gestures, body posture, facial expressions and they make various noises. By combining gestures that are available to them, chimps are able to convey a wide variety of messages to one another. The researchers found that human language rules do apply to the chimpanzees' use of gestures—the most commonly used gestures tended to be quite short, for example, and longer gestures tended to be broken up by multiple shorter gestures. They suggest that this indicates that despite the major differences in the mode of communication, the underpinnings of the two communications systems follow the same basic mathematical principles. Interestingly, an international team of researchers found just last year that human toddlers and chimps have very similar communications systems.

The researchers plan to continue their research by expanding their analysis to include other species—they expect to focus on bonobos next because they are known to use many of the same gestures as chimpanzees.

More information: *Raphaela Heesen et al. Linguistic laws in chimpanzee gestural communication, Proceedings of the Royal Society B: Biological Sciences (2019). DOI: 10.1098/rspb.2018.2900*

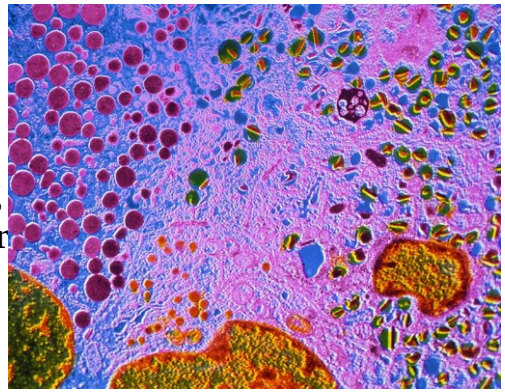
https://go.nature.com/2twrO4t

Human cells reprogrammed to create insulin

Pancreatic cells that don't normally produce insulin can be modified to do so, and to help control blood sugar levels in diabetic mice.

Matthew Warren

The destruction of a single kind of insulin-producing cell in the pancreas can lead to diabetes — but a study suggests that other cells could be modified to take its place and help to control blood sugar levels.



Cells in islets of Langerhans in the pancreas secrete hormones such as insulin. **CNRI/SPL**

The results raise hopes that 'reprogrammed' insulin-producing cells could be used as treatment for diabetes, but the approach has so far only been tested with human cells in mice studies.

In a study published on 13 February in *Nature*[1], researchers report coaxing human pancreatic cells that don't normally make insulin, a

hormone that regulates the amount of glucose in the blood, to change their identity and begin producing the hormone.

When implanted in mice, these reprogrammed cells relieved symptoms of diabetes, raising the possibility that the method could one day be used as a treatment in people.

"I think this has got huge potential," says Terence Herbert, a biologist at the University of Lincoln, UK. But it is still early days, he says, with several hurdles to overcome before the technique can be used in the clinic.

System breakdown

When blood sugar levels rise after eating, cells in the pancreas called β-cells normally respond by releasing insulin, which in turn stimulates cells to start absorbing sugars. In people with diabetes, this system breaks down, leading to high blood sugar levels that can damage the body and cause illness.

In type 1 diabetes, the immune system attacks and destroys β-cells; in type 2, the β-cells do not produce enough of the hormone, or the body becomes resistant to insulin.

Scientists have previously shown in mouse studies that if β-cells are destroyed, another type of pancreatic cell, called α-cells become more β-like and start making insulin[2]. These α-cells normally produce the hormone glucagon, and are found alongside β-cells in clumps of hormone-secreting cells called pancreatic islets or islets of Langerhans.

Previous studies showed that two proteins that control gene expression seemed to have an important role in coaxing α-cells to produce insulin in mice: Pdx1 and MafA.

The human factor

So Pedro Herrera at the University of Geneva, Switzerland, and colleagues wondered whether producing more of these proteins in human α-cells would have a similar effect.

They first took islet cells from human pancreases, and separated out the individual cell types. They then introduced DNA that encoded Pdx1 and MafA proteins into the α-cells, before clumping them back together.

After one week in culture, almost 40% of the human α-cells were producing insulin, whereas control cells that hadn't been reprogrammed were not. The reprogrammed cells also showed an increase in the expression of other genes related to β-cells. "They have a hybrid personality," says Herrera.

The team then implanted the mass of cells into diabetic mice, which had their β-cells destroyed, and found that blood-sugar levels went down to normal levels. When the cell grafts were removed, the mice's blood sugar shot back up.

Switching identity

Herrera says that if α-cells — or other kinds of islet cells — could be made to start producing insulin in this way in people with diabetes, their quality of life might be greatly improved. The dream, Herrera says, is to find a drug that can switch the identity of α-cells.

But he acknowledges that any kind of treatment is still far away. First, his team will need to work out what is going on at the molecular level when α-cells become more β-like.

Other teams are also trying to create new insulin-producing cells in the pancreas: some have sought to generate β-cells from stem cells. But in type 1 diabetes, the immune system attacks β-cells, posing a challenge for such strategies.

Herrera and his team present some evidence that their hybrid cells are less prone to this kind of attack, notes Herbert, suggesting that their method could be a more feasible way of generating β-cells than the stem-cells approach.

But Herbert adds that, before the authors can draw strong conclusions about the efficacy of their approach, they will need to test the hybrid

cells with other antibodies present in type-1 diabetes that could potentially attack those cells.

Pancreatic plasticity

Inês Cebola, an islet biologist at Imperial College London, is intrigued that pancreatic cells can be convinced to produce insulin without actually becoming proper β-cells. “That’s quite striking.”

Diego Balboa Alonso, an islet biologist at the Centre for Genomic Regulation in Barcelona, agrees. The latest work demonstrates that there is much more plasticity in the hormonal system of the human pancreas than was previously thought, he says. “I think it’s a beautiful study showing this idea.”

doi: 10.1038/d41586-019-00578-z

http://bit.ly/2SC7mhd

Future of US citrus may hinge on consumer acceptance of genetically modified food

Tiny insect, threatens to topple the multibillion-dollar citrus industry in the U.S.

CHAMPAIGN, Ill. -- A tiny insect, no bigger than the head of a pin, is threatening to topple the multibillion-dollar citrus industry in the U.S. by infecting millions of acres of orchards with an incurable bacterium called citrus greening disease.

The battle to save the citrus industry is pitting crop producers and a team of agriculture researchers - including agricultural communications professor Taylor K. Ruth of the University of Illinois - against a formidable brown bug, the Asian citrus psyllid, which spreads the disease.

Trees infected with the disease, also called Huanglongbing or HB, bear small, misshapen, bitter-tasting green fruit and often die within five years. Currently, there's no known cure for the disease, which has cost the U.S. citrus industry billions of dollars in crop production and thousands of jobs since it was first identified in Florida in 2005, according to agriculture experts.

Among other solutions, scientists are exploring the possibility of breeding genetically modified trees that are resistant to the disease.

But given the controversy over the safety of genetically modified food, scientists need to know whether producers will adopt this technology and whether shoppers will buy and consume GM citrus fruit.

A recent study, funded by the U.S. Department of Agriculture, provides some encouraging answers.

Ruth was on a team of scientists from several universities that surveyed a representative sample of U.S. consumers and conducted focus groups to better understand American consumers' attitudes about GM food and agriculture.

About half of the 1,050 people who responded to the survey had positive attitudes toward GM science, the researchers found. Nearly 37 percent of the consumers surveyed felt neutral about GM science and 14 percent had negative perceptions of it.

Most of the people who were receptive to GM science were white males who were millennials or younger, the data indicated. They were highly educated - most held a bachelor's degree or higher - and affluent, with annual incomes of $75,000 or greater.

Women, on the other hand, constituted 64 percent of the group with negative feelings about GM science. Baby boomers and older adults were nearly twice as likely to fall into this group. People in this group also were less educated - about half reported some college but no degree.

The findings were published recently in the journal *Science Communication*. Co-authors of the paper were Joy N. Rumble, of Ohio State University; Alexa J. Lamm, of the University of Georgia; Traci Irani, of the University of Florida; and Jason D. Ellis, of Kansas State University.

Since social contexts influence public opinion on contentious issues, the survey also assessed respondents' willingness to share their

opinions about GM science, their current perceptions of others' views on the topic and what they expected public opinion about it to be in the future.

The research team was particularly interested in exploring the potential impact of the "spiral of silence" theory, a hypothesis on public opinion formation that states in part that people who are highly vocal about their opinions in public encourage others with similar views to speak out while effectively silencing those who hold opposite views.

"If people believe the majority of others disagree with them on a topic, they will feel pressure to conform to the majority opinion," Ruth said.

"People aren't going to be supportive of something if nobody else is supportive of it - no one wants to feel like they are different from the group. That's the reality of the world that we live in today."

By contrast, people surveyed who rejected GM science were more likely to express their opinion when they believed others held the opposite view. But people with positive feelings about GM technology were less likely to speak out when they believed others supported it too.

"The way others express their attitude has an indirect effect on what our attitude ends up being," Ruth said. "We might fall in the actual majority opinion about some of these complex topics, but if other people aren't vocalizing their opinions, we don't know that others out there are like-minded.

"Then we start to think 'Well, maybe I should realign my attitude to what I'm seeing in the media.' What we see in the media is just reflective of the most dominant voice in the conversation, not necessarily the majority opinion. And I think sometimes people don't quite understand that."

Like climate change, GM science is among the complex challenges that some researchers call "wicked issues" - societal problems that are often poorly understood and fraught with conflict, even when the public is provided with relevant science and facts, Ruth, Rumble, Lamm and Ellis wrote in a related study.

That paper was published recently in the Journal of Agricultural Education.

"We must have these conversations about these wicked issues," Ruth said. "If scientists let other people who don't have a scientific background fill the void, we're not going to be a part of that conversation and help people make decisions based upon all of the facts."

http://bit.ly/2tqpBrc

Study helps solve mystery of how sleep protects against heart disease

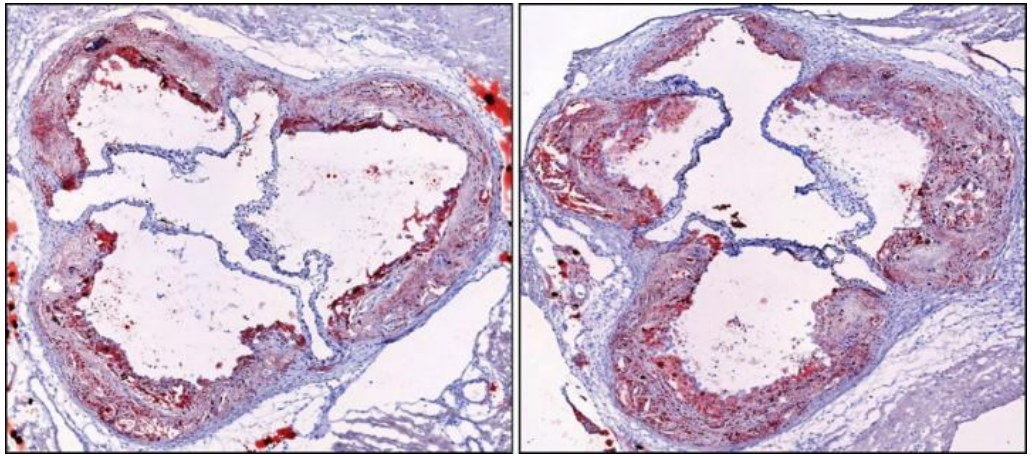
Solving the mystery of how a good night's sleep protects against heart disease

Researchers say they are closer to solving the mystery of how a good night's sleep protects against heart disease. In studies using mice, they discovered a previously unknown mechanism between the brain, bone marrow, and blood vessels that appears to protect against the development of atherosclerosis, or hardening of the arteries--but only when sleep is healthy and sound. The study, funded by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, will appear in the journal Nature.

The discovery of this pathway underscores the importance of getting enough, quality sleep to maintain cardiovascular health and could provide new targets for fighting heart disease, the leading cause of death among women and men in the United States, the researchers said.

"We've identified a mechanism by which a brain hormone controls production of inflammatory cells in the bone marrow in a way that helps protect the blood vessels from damage," explained Filip Swirski, Ph.D., the study's lead author who also is an associate

professor at Harvard Medical School and Massachusetts General Hospital, Boston. "This anti-inflammatory mechanism is regulated by sleep, and it breaks down when you frequently disrupt sleep or experience poor sleep quality. It's a small piece of to a larger puzzle." Swirski noted that while other similar mechanisms may exist, the findings are nonetheless exciting. Recent research has linked sleep deficiency and certain sleep disorders, such as sleep apnea, to an increased risk of obesity, diabetes, cancer, as well as heart disease. But scientists have known little about the cellular and molecular underpinnings that could help explain the link between sleep and cardiovascular health.



Images of plaque from the artery of a mouse model of atherosclerosis that experienced a normal sleeping pattern (left) and an image of arterial plaque from a mouse model that underwent sleep fragmentation (right). The amount of arterial plaque in the sleep-fragmented mouse is significantly larger. **Filip Swirski, Ph.D., Harvard Medical School**

Poor or insufficient sleep is a major public health problem affecting millions of people of all ages. Studies show that getting enough quality sleep at the right times is vital for health, but fewer than half of adults in the United States get the recommended seven to eight hours per day.

To learn more about the impact of this deficiency on cardiovascular disease, the researchers focused on a group of mice that were genetically engineered to develop atherosclerosis. They disrupted the sleep patterns of half the mice and allowed the other half to sleep normally.

Over time, the mice with disrupted sleep developed progressively larger arterial lesions compared to the other mice. Specifically, the sleep-disrupted mice developed arterial plaques, or fatty deposits, that were up to one-third larger than the mice with normal sleep patterns. The sleep-disrupted mice also produced twice the level of certain inflammatory cells in their circulatory system than the control mice--and also lower amounts of a hypocretin, a hormone made by the brain that is thought to play a key role in regulating sleep and wake states.

The researchers also showed that sleep-deficient, atherosclerotic mice that received hypocretin supplementation tended to produce fewer inflammatory cells and develop smaller atherosclerotic lesions when compared to mice that did not get the supplementation. These results, they said, demonstrate that hypocretin loss during disrupted sleep contributes to inflammation and atherosclerosis. But they cautioned that more studies are needed, particularly in humans, to validate these findings and especially before experimenting with hypocretin therapeutically.

Still, health experts say, targeting the newly discovered biological mechanism--a so-called neuro-immune axis--could be a breakthrough that one day leads to new treatments for heart disease, sleep, and other disorders.

"This appears to be the most direct demonstration yet of the molecular connections linking blood and cardiovascular risk factors to sleep health," said Michael Twery, Ph.D., director of the National Center on Sleep Disorders Research at NHLBI. Circadian biology refers to the 24-hour internal body clock that governs the expression

of many genes in most every tissue and the regulation of sleep and wake cycles.

"Understanding the potential impact of poor sleep and circadian health on blood cell formation and vascular disease opens new avenues for developing improved treatments," Twery added.

This work was supported in part by NHLBI grants R35 HL135752, R01 HL128264, P01 HL131478, and NIH grant R35 HL139598. The study was also supported by additional institutions outside of NIH, including the American Heart Association. For a more complete funding disclosure, please see the full research article.

Study: Sleep modulates hematopoiesis and protects against atherosclerosis. DOI: 10.1038/s41586-019-0948-2

http://bit.ly/2GswsJ5

IU School of Medicine makes breakthrough toward developing blood test for pain

Can objectively tell doctors if the patient is in pain, and how severe that pain is

INDIANAPOLIS--A breakthrough test developed by Indiana University School of Medicine researchers to measure pain in patients could help stem the tide of the opioid crisis in Indiana, and throughout the rest of the nation.

A study led by psychiatry professor Alexander Niculescu, MD, PhD and published this week in the high impact Nature journal *Molecular Psychiatry* tracked hundreds of participants at the Richard L. Roudebush VA Medical Center in Indianapolis to identify biomarkers in the blood that can help objectively determine how severe a patient's pain is. The blood test, the first of its kind, would allow physicians far more accuracy in treating pain--as well as a better long-term look at the patient's medical future.

"We have developed a prototype for a blood test that can objectively tell doctors if the patient is in pain, and how severe that pain is. It's very important to have an objective measure of pain, as pain is a subjective sensation. Until now we have had to rely on patients self-reporting or the clinical impression the doctor has," said Niculescu, who worked with other Department of Psychiatry researchers on the study. "When we started this work it was a farfetched idea. But the idea was to find a way to treat and prescribe things more appropriately to people who are in pain."

During the study, researchers looked at biomarkers found in the blood--in this case molecules that reflect disease severity. Much like as glucose serves as a biomarker to diabetes, these biomarkers allow doctors to assess the severity of the pain the patient is experiencing, and provide treatment in an objective, quantifiable manner. With an opioid epidemic raging throughout the state and beyond, Niculescu said never has there been a more important time to administer drugs to patients responsibly.

"The opioid epidemic occurred because addictive medications were overprescribed due to the fact that there was no objective measure whether someone was in pain, or how severe their pain was," Niculescu said. "Before, doctors weren't being taught good alternatives. The thought was that this person says they are in pain, let's prescribe it. Now people are seeing that this created a huge problem. We need alternatives to opioids, and we need to treat people in a precise fashion. This test we've developed allows for that."

In addition to providing an objective measure of pain, Niculescu's blood test helps physicians match the biomarkers in the patient's blood with potential treatment options. Like a scene out of CSI, researchers utilize a prescription database--similar to fingerprint databases employed by the FBI--to match the pain biomarkers with profiles of drugs and natural compounds cataloged in the database.

"The biomarker is like a fingerprint, and we match it against this database and see which compound would normalize the signature," said Niculescu, adding that often the best treatment identified is a non-opioid drug or compound. "We found some compounds that have been used for decades to treat other things pair the best with the biomarkers. We have been able to match biomarkers with existing

medications, or natural compounds, which would reduce or eliminate the need to use the opioids."

In keeping with the IU Grand Challenge Precision Health Initiative launched in June 2016, this study opens the door to precision medicine for pain. By treating and prescribing medicine more appropriately to the individual person, this prototype may help alleviate the dilemmas that have contributed to the current opioid epidemic.

"In any field, the goal is to match the patient to the right drug, which hopefully does a lot of good and very little harm," Niculescu said. "But through precision health, by having lots of options geared toward the needs of specific patients, you prevent larger problems, like the opioid epidemic, from occurring."

Additionally, study experts discovered biomarkers that not only match with non-addictive drugs that can treat pain, but can also help predict when someone might experience pain in the future--helping to determine if a patient is exhibiting chronic, long-term pain which might result in future emergency room visits.

"Through precision medicine you're giving the patient treatment that is tailored directly to them and their needs," Niculescu said. "We wanted first to find some markers for pain that are universal, and we were able to. We know, however, based on our data that there are some markers that work better for men, some that work better for women. It could be that there are some markers that work better for headaches, some markers that work better for fibromyalgia and so on. That is where we hope to go with future larger studies."

The study was supported by an NIH Director's New Innovator Award and a VA Merit Award. Moving forward, Niculescu's group looks to secure more funding through grants or outside philanthropy to continue and accelerate these studies--with the hopes of personalizing the approach even more and moving toward a clinical application. A self-described longshot at the start, Niculescu said that the work his group has done could have a major impact on how doctors around the world treat pain in the future.

"It's been a goal of many researchers and a dream to find biomarkers for pain," Niculescu said. "We have come out of left field with an approach that had worked well in psychiatry for suicide and depression in previous studies. We applied it to pain, and we were successful. I give a lot of credit for that to my team at IU School of Medicine and the Indianapolis VA, as well as the excellent environment and support we have."

Other investigators involved in the study were Helen Le-Niculescu, PhD, Daniel Levey, Kyle Roseberry, Katherine Soe, MD, Jordan Rogers, Faisal Khan, MD, Tammy Jones, Seth Judd, Morgan McCormick, MD, Ann Wessel, Andrea Williams, Sunil Kurian and Fletcher White, MS, PhD.

The study supports an initiative established in 2017 by Indiana University. To build on IU's existing expertise and research regarding addictions, IU President Michael McRobbie, along with Indiana Gov. Eric Holcomb and IU Health President and CEO Dennis Murphy, announced the Responding to the Addictions Crisis Grand Challenge initiative. This Grand Challenge initiative engages a broad array of IU's world-class faculty, as well as IU's business, nonprofit and government partners. The initiative aims to implement a collaborative, applied and comprehensive plan to reduce deaths from addiction, ease the burden of drug addiction on Hoosier communities, and improve health and economic outcomes. This statewide initiative is one of the nation's largest and most comprehensive state-based responses to the opioid addiction crisis--and the largest led by a university.

The research was supported by the National Institutes of Health under Award Number IDP20D007363 and VA Merit Award 2I01CX000139. The content is solely the responsibility of Indiana University School of Medicine and does not necessarily represent the official views of the National Institutes of Health or the VA.

https://wb.md/2tmyu4K

A Drug-by-Drug Guide to Treating Insomnia

Question: Which drugs and supplements commonly used for the treatment of insomnia are supported by clinical evidence and practice guidelines?

Response from Expert Alyson P. Lozicki, PharmD*

Unmanaged sleep disorders are creating a public health epidemic. So says the Centers for Disease Control and Prevention and the American Academy of Sleep Medicine (AASM).[1] An estimated

30%-50% of people suffer acute or transient symptoms at some point in their lifetime, and in 5%-10% of cases, these symptoms persist and develop into a chronic condition.[2,3] Poor sleep is increasingly recognized to have broadly negative effects on a range of health outcomes, including mortality, accidents, injury, and disability.

Insomnia is broadly defined as subjective difficulty with initiating or maintaining sleep that results in some form of daytime impairment. However, several types and subtypes of insomnia exist and are differentiated by etiology and pathophysiology. Primary insomnia may be idiopathic in nature or the result of conditioned sleep difficulty/heightened arousal (psychophysiologic insomnia).[3] More commonly, insomnia presents secondary to an acute or chronic medical condition (eg, obstructive sleep apnea, chronic obstructive pulmonary disease, allergies), medications (eg, decongestants, opioids, stimulants), substances (eg, caffeine, alcohol, nicotine), or other environmental factors and life changes.[4] The goals of treatment are to improve both sleep quality and insomnia-related daytime impairment. Patients should be re-evaluated periodically until symptoms have stabilized or resolved.

For all patients suffering from symptoms of insomnia, the initial management should include counseling and assessment of any precipitating or perpetuating factors, education about proper sleep hygiene and techniques, and management of contributing comorbidities.

When behavioral therapy and nonpharmacologic interventions are insufficient, or when the duration of treatment is expected to be short (eg, in acute settings of stress), pharmacologic management should be considered.[3] Several classes of medications and natural supplements are used in the treatment of insomnia, and selection of drug therapy will vary depending on etiology, symptoms, treatment goals, past treatment responses, patient preference, cost and availability, comorbid conditions, contraindications, drug interactions, and adverse-effect profiles.

The agents and recommendations for use, according to the AASM clinical practice guidelines (most recently updated in 2017), are summarized in the Table. It is important to note that these recommendations are based on moderate- to low-quality evidence, with the caveat that most patients would use a particular treatment over no treatment.[5]

Table. Summary of AASM Recommendations for the Pharmacologic Treatment of Insomnia[5]

Drug	Sleep-Onset Insomnia	Sleep Maintenance Insomnia	NOT Recommended*
Diphenhydramine (Benadryl)			X
Doxepin (Silenor)		X	
Eszopiclone (Lunesta)	X	X	
L-tryptophan			X
Melatonin			X
Ramelteon (Rozerem)	X		
Suvorexant (Belsomra)		X	
Temazepam (Restoril)	X	X	
Tiagabine (Gabitril)			X
Trazodone (Desyrel)			X
Triazolam (Halcion)	X		
Valerian			X
Zaleplon (Sonata)	X		
Zolpidem (Ambien)	X	X	

**Little to no improvement in quality of sleep compared with placebo*

Pharmacologic Treatment of Insomnia

While pharmacologic management has many advantages, a thorough understanding of the unique pharmacokinetic and pharmacodynamic properties of sleep aids is critical for the development of individual treatment plans to optimize therapeutic benefit and to ensure the safe

use of these medications. The guidelines from the AASM also emphasize the importance of patient education and close monitoring to assess efficacy of treatment, risk factors for and emergence of adverse drug reactions, and the need for ongoing medication.[3]

The sleep aids recommended for treatment of insomnia include benzodiazepines, benzodiazepine receptor agonists ("Z-drugs"), orexin receptor antagonists, tricyclic antidepressants, and melatonin receptor agonists. These agents have demonstrated short-term efficacy (ie, 4-6 weeks) compared with placebo in clinical trials, and there is no specific agent that is preferred. Timing of administration and duration of use can have a significant impact on the therapeutic effect of sleep aids, and some agents have the potential to cause rebound insomnia or rebound anxiety if not managed appropriately. Patients should be maintained on the lowest effective dose, and the medication should be tapered/discontinued when conditions allow.

Long-term (eg, nightly, intermittently, or as needed) use of these medications may be indicated for those with severe or refractory insomnia or chronic comorbidities, and chronic use of pharmacologic treatment should be supplemented by cognitive-behavioral therapy when possible.[3,5] The safety and efficacy of long-term use of these agents also have not been established.

In general, over-the-counter agents (eg, diphenhydramine) and herbal/dietary supplements (eg, melatonin, valerian) are not recommended, owing to the relative lack of evidence supporting efficacy and safety.[5]

Clinical Pearls in Insomnia

Clinical pearls regarding dosing and potentially serious adverse side effects in the pharmacologic treatment of insomnia include[6,7]:

- ***Administer on an empty stomach at least 30 minutes before bedtime; administration with food can delay onset.***
- ***Patients should not take a dose if they plan to get less than 7-8 hours of sleep, and middle-of-the-night dosing is not recommended.***
- ***Benzodiazepine use, short- or long-term, has the potential to cause physical dependence. Rapid dose decreases or abrupt discontinuation can produce withdrawal symptoms, including rebound insomnia and rebound anxiety.***
- ***Agents with long half-lives (eg, eszopiclone, temazepam) are associated with a greater risk for next-day impairment.***
- ***High doses of hypnotics with both short and long half-lives are more likely to cause symptoms of sedation and next-day impairment.***
- ***All agents have the potential to cause significant cognitive impairment, including abnormal thinking and behavior changes, memory impairment, and central nervous system (CNS) depression.***
- ***There is an additive effect on psychomotor performance with concomitant CNS depressants or alcohol use.***
- ***Sleepwalking, sleep-driving, sleep-eating, sleep-sex, night terrors, and other abnormal sleep-related behaviors are most frequently associated with the use of zolpidem. However, these concerning side effects have also been reported with the other "Z-drugs" and, more rarely, benzodiazepines.***

Special Populations

Pharmacologic treatment for chronic insomnia in the elderly should be initiated with caution. Evidence demonstrates a minimally improved quality of sleep with pharmacologic agents and a significantly increased risk for adverse events.[8,9] The American Geriatrics Society 2019 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends avoiding benzodiazepines due to a significant risk for adverse effects (eg, cognitive impairment, delirium, falls, fractures). Avoidance of benzodiazepine receptor agonists ("Z-drugs") in older adults is also recommended due to their minimal efficacy in treating insomnia and an adverse-effect profile similar to that of benzodiazepines.[10]

Benzodiazepines and "Z-drugs" are generally not recommended for the management of insomnia during pregnancy or in women who are breastfeeding.[3]

Efficacy and safety of the medications and supplements discussed above for the treatment of insomnia in pediatric patients have not been established, and use is not recommended.[5]

Additionally, for patients receiving pharmacologic therapy for the management of comorbid psychiatric conditions (eg, depression, anxiety, mood disorder), medication regimens may be optimized on the basis of the clinical effects of an agent. For example, antidepressant or antipsychotic agents with sedating properties may be administered at night or before bedtime to facilitate sleep, and it may be recommended to administer agents with greater activating properties in the morning to avoid interference with sleep.[5]

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http://bit.ly/2SF4L68

You know kilo, mega, and giga. Is the metric system ready for ronna and quecca?

Fresh from redefining the kilogram and other fundamental measures, the guardians of the metric system have set their sights on another upgrade: new prefixes for outrageously large and small numbers.

By David Adam Feb. 14, 2019 , 9:00 AM

A proposal lodged with the International Bureau of Weights and Measures (BIPM) in Paris recommends new names—ronna and quecca—as prefixes for 10^{27} and 10^{30}, respectively. They would be joined by their microscopic counterparts, ronto for 10^{-27}, and quecto for 10^{-30}. If approved, the new terms could be formally introduced in 2022. They would be the first prefixes added since 1991.

The planned update responds to the massive growth in global data storage, which by the early 2030s is forecast to reach 1 yottabyte (10^{24})—the top of the existing scale.

Without new prefixes, computer scientists will have no way to officially talk about what comes next. At the other end of the scale, quantum physicists have measured atomic forces as small as 42 yoctonewtons. Much smaller and they run out of metrological road.

By the 2030s, computer data storage may surpass 1 yottabyte (10^{24}), the largest number with an official metric prefix. **Uwe Moser Moser/Alamy Stock Photo**

"Where there is a need that is not met, there is also a risk that unofficial units can take hold and that can cause confusion," says Richard Brown, head of metrology at the National Physical Laboratory near London, who came up with the new names. He says

unofficial terms beyond yotta, including brontobyte and geobyte, are already becoming popular. Although mathematicians sometimes use the prefix googol (10^{100}), a name coined a century ago by a 9-year-old girl, it, too, is unofficial.

Brown prefers to follow tradition. The new prefixes should relate etymologically to nine and 10, to represent the ninth and 10th powers of 10^3. He also wanted to continue the reverse alphabetical trend set by zetta and yotta, but needed to avoid letters such as X, W, and V that could be confused with other terms. And so, drawing from the Latin and Greek words for nine (*novem*, *ennea*) and 10 (*decem*, *deka*), with some poetic license to make the terms more easily pronounced, he came up with ronna, quecca, ronto, and quecto. "It's supposed to be a conversation starter," says Brown, who published his proposal last month in the journal *Measurement.*

Prefix	Symbol	Power
quecca	Q	10^{30}
ronna	R	10^{27}
yotta	Y	10^{24}
zetta	Z	10^{21}
exa	E	10^{18}
peta	P	10^{15}
tera	T	10^{12}
giga	G	10^{9}
mega	M	10^{6}
kilo	k	10^{3}
milli	m	10^{-3}
micro	μ	10^{-6}
nano	n	10^{-9}
pico	p	10^{-12}
femto	f	10^{-15}
atto	a	10^{-18}
zepto	z	10^{-21}
yocto	y	10^{-24}
ronto	r	10^{-27}
quecto	q	10^{-30}

A whole lotta yottas

Metrologists are proposing to extend metric prefixes beyond yotta and yocto.

The terms are due to be discussed at the October meeting of BIPM's Consultative Committee for Units. If the committee approves the idea, it could make a formal recommendation to BIPM. The organization's general conference, which includes government representatives and is due to next meet in 2022, would have the final vote—as it did late last year when it approved a new definition of the kilogram based on fundamental physical constants.

It's too early to say whether the prefixes will be adopted, says Estefanía de Mirandés, executive secretary of the units committee and a physicist with BIPM. "It would be premature to mention a possible outcome of the discussion," she wrote in an email.

Other proposals to extend the measurement scale have fizzled. In 2010, a physics student in California suggested "hella" as a prefix for 10^{27}, and thousands of people signed an online petition in support. (Contrary to reports, the idea did not reach the BIPM units committee for formal discussion.) In 2008, an article in *The New York Times* on supercomputers referred to a xeraflop, and a 2015 paper on cosmic engineering used the symbols X, W, and V to describe the gargantuan energy levels, beyond the yotta scale, that could be seen if aliens turned a black hole into a particle accelerator. One prankster hacked a Wikipedia article in 2008 to introduce a new technical term for a computer that could attempt 10^{48} operations per second: a gonnaflop. It lasted 7 minutes before being deleted.

Ronna, quecca, and their partners could fare better. Emilio Prieto, who represents the Spanish Metrology Center in Madrid on the units committee, says he would vote for the names because they are simple and memorable. "Once people start using the wrong prefix names it is impossible to go back," he says.

If those four are approved, Brown says, only a single good letter would remain that could be used on its own for 10^{33} and 10^{-33} in future: B (and b). Brown already has names at the ready: bundecca and bundecto, based on the Latin for 11, *undecim.*

http://bit.ly/2GtZVT6

'Lack of cleaning' in brain cells is central to Alzheimer's disease

Targeting the cleaning process in the brain may aid in preventing Alzheimer's

Scientists around the world are still struggling to understand Alzheimer's better in order to be able to treat and potentially prevent

the development of the debilitating disease in the future. No new medications have been approved during recent years.

In a new study in the scientific journal Nature Neuroscience, an international team of researchers from the University of Copenhagen, National Institutes of Health and the University of Oslo among others have come closer to a new way of attacking the disease. They target the efforts towards the cleaning process in the brain cells called mitophagy.

'When the cleaning system does not work properly, there will be an accumulation of defective mitochondria in the brain cells. And this may be really dangerous. At any rate, the poor cleaning system is markedly present in cells from both humans and animals with Alzheimer's. And when we improve the cleaning in live animals, their Alzheimer's symptoms almost disappear,' says Vilhelm Bohr, author of the study and affiliate professor at the Center for Healthy Aging and National Institutes of Health.

Defect Energy Factories

The researchers have looked more closely at the cleaning process in brain cells from deceased Alzheimer's patients, in Alzheimer's-induced stem cells and in live mice and roundworms with Alzheimer's. In addition, they have also tested active substances targeted at the cleaning process in the animal models.

'It significantly strengthens our results that the cleaning process seems to be important in both human cells and across different animal species. And then it is encouraging that in living animals we are able to improve the central Alzheimer's symptoms, memory and learning,' says Vilhelm Bohr.

The mitochondria lie inside the cell and can be seen as the cell's energy factories. Mitophagy breaks down defective mitochondria and reuses the proteins that they consist of. It is known from previous research that dysfunctional mitophagy is associated with poor function and survival of nerve cells, but so far, no connection with Alzheimer's has been shown.

Slowing Down the Accumulation

In both Alzheimer's and other states of dementia, there is an accumulation of the proteins tau and beta amyloid in the brain, leading to cell death. In the new animal models, the researchers show that when boosting the mitophagy, such accumulation will slow down.

The researchers believe that altogether their findings indicate that the cleaning process is a potential target for the treatment of Alzheimer's, which should be further investigated. They therefore plan to start clinical trials in humans in the near future.

The study is supported by Helse Sør Øst RHF (the Southern and Eastern Norway Regional Health Authority), the Research Council of Norway, the ERC and the Olav Thon Foundation. The research at the Center for Healthy Aging is supported by Nordea-Fonden.

The researchers behind the study have a research and development agreement with ChromaDex and Elysium Health.

Read the entire study 'Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease' in Nature Neuroscience.

http://bit.ly/2SYOFne

Antidepressant could stop deadly sepsis, study suggests

Previous FDA approval could fast-track new treatment

An antidepressant drug used to treat obsessive-compulsive disorder could save people from deadly sepsis, new research from the University of Virginia School of Medicine suggests.

Sepsis is a significant cause of death around the world. The federal Centers for Disease Control and Infection calls it "the body's extreme response to an infection." Essentially, the body's immune response spirals out of control, and the normally beneficial inflammation becomes harmful. The result can be tissue damage, organ failure or even death.

"Sepsis is very dangerous. In the U.S., 1.7 million get it every year, and 270,000 people die," said researcher Alban Gaultier, PhD, of

UVA's Department of Neuroscience and its Center for Brain Immunology and Glia (BIG). "Once you get diagnosed, you have a high chance of mortality. And there is no good treatment. Basically, we will try to keep you alive and monitor you as much as we can. So clearly there is a critical need for treatment."

Gaultier and his team have identified a drug that could offer that treatment - and previous safety testing of the drug could fast-track it into use in hospitals around the country.

A Simple Solution for Sepsis?

The UVA researchers were looking at a little-studied biological process inside our cells when they determined it has an important role in regulating inflammation. They began studying it partly because there are already drugs that can affect players in the process. "Inflammation, most of the time, is good. It's when it gets out of control that we need to modulate it," Gaultier said. "Inflammation is a very precisely controlled reaction. When we need it and have too much, it's a problem, but when we don't have enough, it's also a problem."

To evaluate the potential of one drug, the antidepressant fluvoxamine, to stop sepsis, Gaultier's team tested it in a mouse model of the disease. The drug worked very effectively, they found.

While the drug will need to be tested in people to determine its effectiveness at battling human sepsis, previous testing to determine its safety should accelerate that process.

Gaultier hypothesizes that the same biological process could be targeted to generate beneficial inflammation when needed, such as in immunocompromised people. "By inhibiting the receptor, we could activate inflammation in conditions where patient don't have a proper inflammatory response," he said.

He plans to continue his research, including testing that hypothesis.

Sepsis Findings Published

The researchers have published their findings in Science Translational Medicine. The research team consisted of Dorian A Rosen, Scott M. Sek,, Anthony Fernández-Castañeda, Rebecca M. Beiter, Jacob D. Eccles, Judith A. Woodfolk and Gaultier.

The work was supported by the National Institutes of Health, grants R01 NS083542, R21 NS101281 and T32 GM007055; and the Owens Family Foundation.

http://bit.ly/2tlGJhI

Simple bile acid blood test could tell risk of stillbirth

Clinical researchers at Guy's and St Thomas' and King's College London have found a better way to measure the risk of stillbirth for women with a common liver disorder through a simple blood test.

The discovery will help doctors identify the small number of women at most risk who require intervention to prevent stillbirth. This will allow the majority of women with intrahepatic cholestasis of pregnancy (ICP) who are at a low risk to carry on their pregnancy normally.

The researchers estimate that implementing this test could prevent hundreds of women having unnecessary early deliveries.

ICP is a liver disorder affecting approximately 5,300 pregnancies annually in the UK - more than 14 every day. The condition causes build-up of bile acids in the blood, and symptoms include itching. It was previously thought that small increases in bile acid concentration are associated with higher risks of stillbirth. Pregnant women showing symptoms of ICP, therefore, are often offered early induction of labour at around 37 weeks in order to prevent stillbirth.

To understand the link between ICP, bile acid levels and stillbirth, the authors analysed more than 170,000 pregnancies from 40 international studies. The work was funded by ICP Support, Tommy's, Genesis Research Trust, Wellcome Trust and the NIHR.

The results, published in *The Lancet*, show that the likelihood of stillbirth as a result of ICP is related to the concentration of bile acids in a pregnant woman's blood. This can be determined by a simple blood test.

Professor Catherine Williamson, Consultant Obstetric Physician and Chair in Women's Health at Guy's and St Thomas' and King's College London, who led the study said:

"We are grateful to our collaborators worldwide who have helped us perform the largest study to date, the results of which will enable doctors to personalise treatment for women with ICP.

"We can now identify those women at the highest risk of stillbirth and consider interventions to specifically prevent stillbirth in this group. We will also be able to reassure a large number of women, who may have previously been concerned, that they are not at increased risk of stillbirth."

At the moment more than 15% of women with bile acids below the 100 micromole per litre threshold are delivered early: at least 700 a year in the UK and 18,500 globally.

Actress Helen George, Patron of ICP Support, believes that this will be reassuring news for many women with ICP. She said: "My own ICP pregnancy would have been less anxiety-provoking with this latest information but I believe that it's also incredibly important that women who itch continue to let their midwife or doctor know so that they can be tested for the condition."

The results of the study show that for the majority of women with ICP, who have bile acid concentration below 100 micromoles per litre, the risk of stillbirth is not significantly greater than that of pregnant women without ICP. This means they need no further treatment other than regular bile acid blood tests for the remainder of their pregnancy.

Dr Caroline Ovadia, Chadburn Clinical Lecturer at King's College London, said: "This marks a real step forward in the diagnosis and management of liver disorders during pregnancy. Being able to measure the risks to women and their babies by simple tests allows doctors to concentrate treatment on those who really need it.

"It also means that women will not have to be offered preterm birth unnecessarily which comes with associated risks to their babies including admission to neonatal units, breathing problems and jaundice.

"We are hopeful our findings will help to improve pregnancy outcomes in high risk women and allow thousands of pregnant women to be reassured that their ICP does not pose a significant risk to themselves or their baby."

Jenny Chambers, CEO of ICP Support who suffered two stillbirths because of the condition said: "We welcome the news that most women with ICP will now be spared the anxiety of worrying about the possibility of stillbirth. However, it important that health professionals realise that regular bile acid testing until birth is vital to ensure that those women who are at greater risk aren't missed."

Jane Brewin, Chief Executive of Tommy's said: "Stillbirth devastates parents' lives and Tommy's believes that too many babies still die at full term. This study means that we can detect more otherwise healthy babies who are at risk of sudden death because of their mother's liver condition. This study has the potential to save lives if practice is revised immediately and implemented nationally. Importantly it will prevent babies from being induced early, which carries a risk of lifelong negative consequences for them, and prevent the distress and concern caused to parents who wrongly believe that their baby is at risk."

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Note to editors:

The paper, 'Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses', will be published at http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31877-4/fulltext at 23:30 on 14 February 2019

https://bbc.in/2SIGWdO

Chemicals 'repair damaged neurons in mice'

New results suggest ageing brains can potentially be rejuvenated, at least in mice, according to researchers.

By Pallab Ghosh Science correspondent, BBC News, Washington DC

Very early-stage experiments indicate that drugs can be developed to stop or even reverse mental decline.

The results were presented at the 2019 meeting of the American Association for the Advancement of Science.

The US and Canadian researchers took two new approaches to trying to prevent the loss of memory and cognitive decline that can come with old age.

One team, from the University of California, Berkeley, showed MRI scans which indicated that mental decline may be caused by molecules leaking into the brain.

Blood vessels in the brain are different from those in other parts of the body. They protect the organ by allowing only nutrients, oxygen and some drugs to flow through into the brain, but block larger, potentially damaging molecules. This is known as the blood-brain barrier.

The scans revealed that this barrier becomes increasingly leaky as we get older. For example, 30-40% of people in their 40s have some disruption to their blood-brain barrier, compared with 60% of 60-year-olds.

The scans also showed that the brain was inflamed in the leaky areas.

Prof Daniela Kaufer, who leads the Berkeley group, said that young mice altered to have leaky blood-brain barriers showed many signs of aging. She discovered a chemical that stops the damage to the barrier from causing inflammation to the brain.

Prof Kaufer told BBC News that not only did the chemical stop the genetically altered young mice from showing signs of aging, it reversed the signs of aging in older mice.

"When you think of brain aging you think about the degeneration of cells and losing what we have," she said.

"What these results show is that you are not losing anything. The cells are still there and they just needed to be 'unmasked' by reducing the inflammation."

Brain's weak link

In another study, Canadian researchers also said they could reverse cognitive decline in mice using an alternative approach.

They targeted a brain cell known to be a "weak link" in many brain disorders. The so-called somatostatin-positive neurons, which are involved in coding information, are the first to fail. The signals from these cells are too weak to be received by surrounding neurons, which would relay the information to other parts of the brain.

Prof Etienne Sibille, from the University of Toronto, identified a chemical that essentially amplifies the signal. He presented results that showed that older mice who could not find their way around mazes were able to do this after they were given the chemical, just as well as younger mice not given the drug.

Prof Sibille said he was hoping to begin clinical trials on human patients in two years' time.

"If people have a cognitive deficit we would potentially be able to bring them back to higher functioning."

The big caveat is that the vast majority of treatments that show promise in mice don't work on humans. But both scientists believe that this time it might be different.

Prof Sibille said he was heartened by the fact that the chemical repaired damaged neurons when it was given to mice. And Prof Kaufer said she believed that such work really could lead to a brain rejuvenation pill.

"People get jaded when they hear that things work on mice and then it is tried on humans," she said. "But I think there is something

different and exciting about this story in that it explains a new biology.

"It looks at brain function in a different way. It is about mechanisms that have been neglected and not thought about before."

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

The vaporized rock and extreme heat at a huge landslide's heart

An entire mountainside came crashing down after a devastating earthquake in China's Sichuan Province.

A gargantuan landslide in China generated enough heat to vaporize some of the sliding material, creating superheated steam that helped the avalanche of rock to barrel downhill.

In 2008, the magnitude-8.2 Wenchuan earthquake shook loose more than a cubic kilometre of soil and stone from the summit and flank of Daguangbao mountain in central China. A team led by Runqiu Huang at Chengdu University of Technology in China analysed rock samples from the landslide to study conditions within the flow.

An expanse of soil and rock measuring 2.4 kilometres long and 1.2 kilometres wide tumbled down Daguangbao mountain in China after a massive earthquake. **W. Hu et al./Earth Planet. Sci. Lett.**

By comparing rock samples with the results of friction experiments in the laboratory, the scientists concluded that temperatures at the boundary between the slide and the intact slope reached at least 850°C.

That would have partially vaporized a mineral called dolomite in the rock, releasing high-pressure, high-temperature carbon dioxide and steam that would have allowed the landslide to flow. At the same time, the immense pressure on the minerals would have caused them to recrystallize, lubricating the sliding surface and helping the debris to hurtle more than 4 kilometres from its original location.

The work offers clues to how big landslides travel long distances.

Earth Planet. Sci. Lett. (2019)

http://bit.ly/2Ni038R

Brain discovery explains a great mystery of Alzheimer's, Parkinson's

One of the great mysteries of neuroscience may finally have an answer:

Scientists at the University of Virginia School of Medicine have identified a potential explanation for the mysterious death of specific brain cells seen in Alzheimer's, Parkinson's and other neurodegenerative diseases.

The new research suggests that the cells may die because of naturally occurring gene variation in brain cells that were, until recently, assumed to be genetically identical. This variation - called "somatic mosaicism" - could explain why neurons in the temporal lobe are the first to die in Alzheimer's, for example, and why dopaminergic neurons are the first to die in Parkinson's.

"This has been a big open question in neuroscience, particularly in various neurodegenerative diseases," said neuroscientist Michael McConnell, PhD, of UVA's Center for Brain Immunology and Glia (BIG). "What is this selective vulnerability? What underlies it? And so now, with our work, the hypotheses moving forward are that it could be that different regions of the brain actually have a different garden of these [variations] in young individuals and that sets up different regions for decline later in life."

A Most Unexpected Outcome

The finding emerged unexpectedly from McConnell's investigations into schizophrenia. It was in that context that he and his collaborators

first discovered the unexpected variation in the genetic makeup of individual brain cells. That discovery may help explain not just schizophrenia but depression, bipolar disorder, autism and other conditions.

Continuing his investigations, McConnell expected that this mosaicism would increase with age - that mutations would accumulate over time. What he and his collaborators at Johns Hopkins found is exactly the opposite: Younger people had the most mosaicism and older people had the least.

"We wound up building an atlas that contained neurons from 15 individuals. None of these individuals had disease," said McConnell, of UVA's Department of Biochemistry and Molecular Genetics and UVA's Department of Neuroscience. "They ranged in age from less than a year to 94 years, and it showed a perfect correlation - a perfect anti-correlation - with age."

Based on the finding, McConnell believes that the neurons with significant genetic variation, known as CNV neurons, may be the most vulnerable to dying. And that could explain the idiosyncratic death of specific neurons in different neurodegenerative diseases. People with the most CNV neurons in the temporal lobe, for example, might be likely to develop Alzheimer's.

More work needs to be done to fully understand what's occurring, McConnell said. So far, he has only looked at neurons in the frontal cortex of the brain, and his studies are limited by the fact that neurons can be examined only after death, so it can be hard to make direct comparisons. But he is excited to expand the scope of his research.

"Because I'm collaborating with the Lieber Institute and they have this fantastic brain bank, now I can look at individuals' frontal cortex [for the schizophrenia research] and I can look at the temporal lobe in those same individuals," McConnell said. "So now I can really start to map things out more carefully, building an atlas of different brain regions from many individuals."

That research could greatly advance our understanding of both neurodegenerative diseases and the cognitive decline that besets us with age, potentially leading to new treatments.

"What's really interesting about mosaicism is that it is fundamentally tweaking our assumptions about what nature is, because we've kind of always assumed that every cell in any given individual had the same genome, the same DNA in every cell," McConnell said. "And now we're showing that it's different and what that might mean."

Findings Published

The researchers have published their findings in the scientific journal Cell Reports*. The research team consisted of William D. Chronister, Ian E. Burbulis, Margaret B. Wierman, Matthew J. Wolpert, Mark F. Haakenson, Aiden C.B. Smith, Joel E. Kleinman, Thomas M. Hyde, Daniel R. Weinberger, Stefan Bekiranov and McConnell.*

The work was supported by the National Institutes of Health, grants U01 MH106882, U01 MH106893, U01 MH106882-03S1 and T32 GM008136-30; and the McDonnell Foundation.

https://nyti.ms/2Efiqbk

Dialysis Is a Way of Life for Many Older Patients. Maybe It Shouldn't Be.

So-called conservative management can ease symptoms without dialysis in some people with kidney disease. But many of them are never given the option.

By Paula Span

John Everdell had lived most of his life with kidney disease. As a young man awaiting a transplant, he had briefly undergone dialysis. That's how he knew, when the prospect of kidney failure loomed again in his late 60s, that he would refuse dialysis this round.

"He was a very independent man, with an idea of how he was going to live his life," said Trix Oakley, his partner of 22 years.

"He didn't want to be tied down to the routine, having to report to the dialysis clinic every other day. He didn't like the ups and downs — feeling good but washed-out, then feeling crummy. He didn't like being attached to the machine."

A woodworker and furniture maker, Mr. Everdell had been in his 30s when he was first diagnosed with kidney disease. By his 60s, he had received two transplants, with kidneys donated by his siblings.

But in recent years, living in Cambridge, Mass., he and Ms. Oakley could see that his second transplanted kidney was faltering. The readings on his monthly blood tests grew troubling; he felt cold and tired; his hands and feet began to swell. His doctors again suggested dialysis.

Instead, with Ms. Oakley's help, he relied on what's often called "conservative management," which helps slow the disease's progression and treats its symptoms and complications. He followed a careful diet, controlled his blood pressure, avoided weight gain and gave himself hormone injections to ward off anemia. A sister offered her kidney for a third transplant, when needed.

In the meantime, he and Ms. Oakley enjoyed road trips, particularly seeking out ferry routes from Canada to Florida. Mr. Everdell, who had once sailed across the Atlantic, was no longer strong enough to handle a boat, Ms. Oakley said. "So we took as many ferries as we could, because he loved being on the water."

Developed as a temporary measure to keep patients with kidney disease alive until they could receive transplants, dialysis instead often becomes a way of life. More than 104,000 people over age 75 were receiving dialysis in 2016, the United States Renal Data System has reported; so were more than 130,000 patients aged 65 to 74.

It's a safe bet most never learned about an alternative: managing their disease and its symptoms medically, with frequent physician monitoring and consultation — but without dialysis.

Dialysis prolongs survival, but it also imposes burdens — like traveling to a clinic three times a week for four-hour sessions of hemodialysis, or doing multiple fluid exchanges daily for peritoneal dialysis, which can be performed at home. Conservative management can help patients avoid those routines.

Moreover, while some studies show that older patients undergoing dialysis survive longer than those using conservative management, those differences fade among people over age 75 who also contend with other serious health problems, as most do.

And survival, of course, is not the only thing patients value. Conservative management may allow greater freedom to pursue what matters to them, even if they live fewer weeks or months.

"Dialysis is a life-changing event," Dr. Susan Wong, a nephrologist at the Veterans Affairs Health Services Research and Development Center in Seattle, and lead author of a new study in JAMA Internal Medicine. "It's a very demanding form of treatment. It involves medical issues, spiritual issues, quality of life. It's a big decision."

Yet patients often tell researchers that they don't recall making a decision, or even discussing one. Physicians frequently present dialysis as inevitable; in a small study of nephrologists, only a third routinely informed patients about conservative management.

"Patients didn't recognize it as a choice — 'My doctor told me I'd die if I didn't do dialysis,'" said Keren Ladin, director of an aging and ethics program at Tufts University, who has interviewed both patients and nephrologists. "Or they'd say that it wasn't their choice, that their doctor made the choice."

Those patients might have wanted to know, for example, that at the end of life, patients using conservative management were less likely to be hospitalized than dialysis patients, less apt to undergo aggressive procedures, and less likely to die in a hospital.

Yet doctors frequently doubt that decision, according to Dr. Wong's new study of 851 Veterans Affairs patients who declined dialysis. Medical records showed doctors questioning patients' competence, pushing them to change their minds.

"Most were skeptical," Dr. Wong said of the doctors' response. "It's a relatively unusual decision, and providers find it suspect."

Other developed countries take a different approach, especially at advanced ages. Among patients over age 85 with failing kidneys, fewer than 7 percent received dialysis in Canada, a large retrospective study has shown, and fewer than 5 percent in Australia and New Zealand.

In the United States, by contrast, a 2016 study of Veterans Affairs patients found more than 40 percent of those over age 85 with advanced kidney disease received dialysis.

Lyman Dally was nearly 92 when a fall in his South Orange, N.J., home led to kidney failure in 2013. In the emergency room, doctors started dialysis.

"After a week or two, he decided, 'This is not the way I want to live. It's painful and it's tiring,'" said his son, also Lyman Dally.

The elder Mr. Dally discontinued dialysis, telling his son that he'd had a wonderful life. He died two weeks later.

Medicare and other insurers help propel reliance on this treatment. "Our financial incentives are all about putting people on dialysis," said Dr. Alvin Moss, a nephrologist and palliative care specialist at West Virginia University School of Medicine.

Low reimbursement for monthly office visits to supervise conservative management might doom a practice financially. But Dr. Moss and other researchers also suspect that "conservative management" implies lack of care.

Perhaps, they've suggested, the approach needs rebranding as "active medical management" or "comprehensive supportive care."

For now, patients interested in conservative management, or whatever we decide to call it, won't find supportive doctors easy to locate. A few nephrologists have launched programs at New York University, the University of Washington, the University of Rochester and U.P.M.C. in Pittsburgh, among other medical centers.

Elsewhere, Dr. Moss suggests seeking out palliative care specialists. Patients should also document their preferences for conservative measures in advance directives, including state P.O.L.S.T. (Physician Orders for Life Sustaining Treatment) forms.

Organizations like the Coalition for Supportive Care of Kidney Patients and the American Association of Kidney Patients have useful websites. Dr. Moss also recommends a Canadian site, Conservative Kidney Management.

Conservative management helped John Everdell take a lot of ferry rides. But last spring, after years of managing his disease conservatively, Mr. Everdell, 69, was hospitalized with heart failure, a common illness in kidney patients. That ruled out a third transplant as his donated kidney failed.

He agreed to give peritoneal dialysis a try. "If you hate it, you can stop," Ms. Oakley told him.

But Mr. Everdell developed a serious infection. When his doctors advised switching to daily hemodialysis, "He said no, he didn't want to live that way," Ms. Oakley said. He explained his decision to his doctors, his sisters and his best friend.

He died at Tufts Medical Center in May, two months after entering the hospital and two days after refusing dialysis for the final time. His partner said he had no regrets.

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Drug combination may become new standard treatment for advanced kidney cancer

Combination of two drugs could become a new standard, first-line treatment for patients with metastatic kidney cancer

BOSTON - A combination of two drugs - one of them an immunotherapy agent - could become a new standard, first-line treatment for patients with metastatic kidney cancer, says an investigator from Dana-Farber Cancer Institute, reporting results from a phase 3 clinical trial.

Patients who received the immunotherapy drug avelumab plus axitinib, a targeted agent, had a significant advantage in progression-

free survival compared with those who received sunitinib (Sutent), a targeted drug that has been a standard treatment for advanced clear cell renal cell carcinoma - the most common form of kidney cancer.

"Patients receiving the drug combination also had a higher response rate - meaning their tumors shrank - than the sunitinib-only group," said Toni K. Choueiri, MD, senior and co-corresponding author of the report on the JAVELIN Renal 101 trial in the New England Journal of Medicine and Director of the Lank Center for Genitourinary Oncology at Dana-Farber.

"This is certainly better than sunitinib -- hopefully this will lead to Food and Drug Administration approval soon," said Choueiri, The Jerome and Nancy Kohlberg Professor of Medicine at Harvard Medical School

While progression-free survival was improved with the combination treatment, additional follow-up is needed to show whether the two-drug therapy extends overall survival compared to the standard regimen.

The trial is the first pivotal study to combine avelumab with a drug that targets the vascular endothelial growth factor receptor (VEGFR). VEGFR blockers like sunitinib and axitinib are designed to starve tumors by disrupting their blood supply. Immunotherapy drugs such as avelumab - which blocks an immune checkpoint called PD-L1 - work by activating "exhausted" immune T cells so they can more effectively attack cancer cells.

The clinical trial involved 886 patients with previously untreated, advanced renal cell carcinoma who were randomized to receive the drug combination or sunitinib alone.

The results from this study showed that the median progression-free survival (PFS) - the length of time before the cancer began to worsen - was 13.8 months in the combination group and 7.2 months in patients receiving only sunitinib. These results specifically applied to patients whose cancer cells tested positive for the PD-L1 checkpoint that is blocked by avelumab. The PFS for the overall population (PD-L1 positive or negative) was similar - 13.8 months versus 8.4 months.

The proportion of patients whose tumors shrank was 55.2 percent with avelumab plus axitinib and 25.5 percent with sunitinib in the patients who were positive for PD-L1.

"Interestingly, the analysis showed that all subgroups - good, intermediate, and poor-risk patient - benefited from the combination treatment," said Choueiri. This was the topic of an oral presentation Choueiri has just given at the 2019 Genitourinary Cancers Symposium in San Francisco. The results were simultaneously published in the *New England Journal of Medicine*.

Nearly all patients in both treatment groups experienced some side effects. In the combination treatment group, 38.2 percent of patients experienced immune-related adverse events, the most frequent being thyroid disorders, observed in 107 patients.

Choueiri said that for patients with advanced disease, "this is an important option. What we're doing in advanced kidney cancers is pushing the envelope - these treatments may not be curative, but patients are living longer, and the disease is becoming more chronic."

The clinical trial is sponsored by Pfizer, Inc., and is part of an alliance between Pfizer and Merck KGaA.

Dr. Choueiri reports grants, personal fees and non-financial support from Pfizer, during the conduct of the study; grants and personal fees from Astra Zeneca, grants and personal fees from Bayer, grants and personal fees from BMS, grants and personal fees from Cerulean, grants and personal fees from Esai, grants and personal fees from Foundation Medicine Inc., grants and personal fees from Exelixis, grants and personal fees from Genentech, grants and personal fees from Roche, grants and personal fees from GlaxoSmithKline, grants and personal fees from Merck, grants and personal fees from Novartis, grants and personal fees from Peloton, grants and personal fees from Pfizer, grants and personal fees from Prometheus Labs, grants and personal fees from Corvus, grants and personal fees from Ipsen, grants from Tracon, personal fees from Alligent, personal fees from Up-to-Date, personal fees from NCCN, personal fees from Analysis Group, personal fees from Michael J. Hennessy (MJH) Associates, Inc. (Healthcare Communications Company and several brands such as OnClive and PER), personal fees from L-path, personal fees from Kidney Cancer Journal, personal fees from Clinical Care

Options, personal fees from Platform Q, personal fees from Navinata Healthcare, personal fees from Harborside Press, personal fees from American Society of Medical Oncology, personal fees from NEJM, personal fees from Lancet Oncology, grants from Calithera, grants from Takeda, outside the submitted work

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Genetic engineering promises improved bone marrow transplants

First clinical trial shows partial donors can be used in blood cancer treatments.

Andrew Masterson reports.

More people may soon be able to receive bone marrow transplants for the treatment of bone cancer, following a successful clinical trial carried out in Australia.

For people with certain high-risk forms of blood cancers, such as leukaemia and lymphoma, bone marrow transplants are the only clinical option with a chance of success.

Sadly, however, many patients never have the opportunity to undergo the procedure because a suitably matched donor cannot be found.

The main criteria for matching bone marrow content is the immune cell profiles of both parties.

"The key to bone marrow transplantation is the immune cells. Immune cells are a double-edged sword – they are necessary for fighting cancer and infection but they can also cause unwanted tissue damage, known as graft-versus-host disease," explains Siok-Keen Tey of the QIMR Berghofer medical research institute in Queensland, Australia, who led the latest trial.

Searching for a way to reduce the risk of incompatibility, Tey and her colleagues turned to genetic engineering.

Using cells derived from partially matched donors, they inserted an extra gene which functions essentially as a kill-switch. If the transplanted bone marrow starts to cause graft-versus-host disease, the extra gene kills them off.

In a Phase 1 clinical trial – to ascertain the safety of the procedure – blood cancer patients first received a transplant from a part-matched donor, followed by the genetically engineered immune cells.

The results, which appear in the journal *Clinical Cancer Research*, were impressive, the researchers believe.

"What we found really amazing was that these immune cells can massively grow in number in the patients," Tey says.

"We were able to show, using two independent molecular techniques that a single genetically modified immune cell, when challenged by a cancer, could split into millions and millions of cells within a few days.

"This immense capacity for rapid expansion was something that had not been shown before and really demonstrates the 'power of one': One cell, if it is the right cell, can grow rapidly and help control cancer or infection."

The researchers are now planning a larger clinical trial.

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Common gut virus linked to coeliac disease

Researchers identify a possible connection between a childhood illness and later autoimmune disease.

Lyndal Byford reports.

A group of common intestinal viruses may be a trigger for coeliac disease in children who have a genetic predisposition for the disease, according to research published in *The BMJ* journal.

The research details the results of a 15-year study, led by Christian Kahrs of the Østfold Hospital Trust, Grålum, in Norway, that included 220 children with genes that made them more susceptible to the condition. Of these, 25 went on to develop the disease.

The scientists found that these participants were more likely than non-coeliacs to test positive for a group of gut bugs known as enteroviruses.

Enterovirus infections are common and often produce mild symptoms such as runny noses, vomiting and illnesses including hand, foot and mouth disease.

“We found a significant association between exposure to enterovirus and subsequent risk of coeliac disease,” the researchers write.

“This study suggests that infections with enterovirus in early life could be one among several key risk factors for development of a disease with lifelong consequences.”

The authors add they were more likely to find enterovirus before the children developed coeliac disease, suggesting there may be a link between the two.

They also tested for another group of bug, adenoviruses, which cause common cold symptoms, but these did not show the same link.

Katie Allen from the Murdoch Children’s Research Institute in Melbourne, Australia, who was not involved in the study, says coeliac disease is one of the most common autoimmune conditions in Western countries, where it affects around one in every 100 children.

"We still don't know why it occurs in some kids who eat gluten but not others,” she notes.

She tells *Cosmos* the study provides an interesting lead in hunting down the cause of coeliac disease, which is a lifelong condition.

Kahrs and colleagues say the link between enteroviruses and the condition is consistent with the idea that viruses may disrupt the mucous barrier in the gut, allowing more gluten to enter and triggering a loss of tolerance.

Jason Tye-Din from the Walter and Eliza Hall Institute, also in Melbourne, says the Norwegian researchers are highly regarded and their science is sound. However, he points to the small number of children in the study who actually developed coeliac disease, saying this could lead to incorrect associations.

Enteroviruses are also unlikely to be the complete answer. Only 20% of the infants who developed coeliac disease in the study showed evidence of an enterovirus infection beforehand, compared to the control group where the rate of infection was 15%.

“Enterovirus was not present in most children who developed coeliac disease,” he says. “Other factors are important in disease development.”

Tye-Din adds that the research supported a growing body of evidence suggesting that micro-organisms may be important triggers for a range of autoimmune diseases.

If enterovirus is confirmed as a trigger factor, Kahrs and colleagues say a vaccine could be developed that may reduce the high numbers of those with coeliac disease.

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Pass the antidote

From paracetamol to pesticides – not to mention nerve agents – there are many toxic compounds that doctors need to be able to counteract. Nina Notman investigates

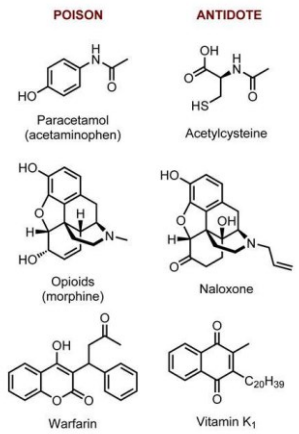
By Nina Notman12 February 2019

The word ‘poisoning’ might conjure up thoughts of Agatha Christie novels or defected Russian spies on a Kremlin hit-list. But poisonings are more common than you might think. The World Health Organization estimated that 193,460 people died worldwide from unintentional poisoning in 2012. Each year, around 160,000 people visit UK hospitals seeking help for exposure to toxic compounds, accidental and otherwise. Many more ask doctors or NHS helplines for guidance. The number of possible poisons is also far larger than the infamous few used by Christie and the KGB , with around 17,000 substances listed on ToxBase – a database for healthcare professionals run by the UK’s National Poisons Information Service. Paracetamol overdoses are the most common type of poisoning in the UK. Between April 2017 and March 2018, approximately 65% of National Poisons Information Service enquires related to paracetamol (also known as acetaminophen) and other pharmaceuticals. A further 15% were regarding household poisons such as washing and dishwasher tablets, cleaning products, essential oils and synthetic fragrances.

‘Patients are often found with circumstantial evidence of poisoning – such as a syringe, powder or tablets – or they come to the hospital and tell us they’ve taken certain substances,’ explains Arvind Veiraiah, a clinical toxicologist at the Royal Infirmary of Edinburgh in Scotland. In the absence of these clues, a patient’s symptoms will often direct medics towards what caused them. Blood tests can help too.

Treating the symptoms

The treatment for most poisons is largely supportive, says Ruben Thanacoody, clinical toxicologist at the Royal Victoria Infirmary in Newcastle in the UK. He and Veiraiah are members of a team of consultants that provide telephone advice on complex poisonings through the National Poisons Information Service. ‘We decide, based on how the drug works, what the likely toxicity is and then manage the complications accordingly. If they have low blood pressure, we manage the low blood pressure; if they have low heart rate, we manage the low heart rate,’ Thanacoody explains.



Source: © Royal Society of Chemistry

It is possible to reduce exposure to some substances by using activated charcoal to reduce absorption in the gut. ‘If a patient presents within one hour of ingestion, we can use activated charcoal to bind to some drugs and prevent them from being absorbed into the circulation to cause toxicity,’ Thanacoody says.

For some of the most toxic poisons, antidotes are available if the poisoning is severe enough. ‘The most commonly used antidotes are naloxone and acetylcysteine,’ says Veiraiah. These treat opioid and paracetamol overdoses, respectively. The National Poisons Information Service recommends about 30 antidotes that should be held by all hospitals with emergency departments in the UK.

This must-have list includes vitamin K, an antidote for warfarin, and idarucizumab for reversing dabigatran, a similar drug. Warfarin, originally developed as a *rat poison*, has been the UK’s staple oral anticoagulant for around 70 years. The past decade has seen a handful of new oral blood thinners approved, the first of which was dabigatran. Haemorrhage is a potentially serious side effect of all

anticoagulants, making an antidote crucial. Idarucizumab was approved in 2015 as the first, and currently only, antidote for the novel anticoagulant drugs in the UK. The US has two, idarucizumab and andexanet alfa, approved in May 2018 for reversing rivaroxaban and apixaban. The EC is expected to decide on andexanet alfa in early 2019. A third reversal agent against the novel oral anticoagulant agents is in Phase II trials. 'Ideally we would have an antidote for all these newer anticoagulant drugs,' says Thanacoody.

There are many other extremely toxic drugs for which there are no antidotes and supportive treatment isn't always enough, he adds, giving gout treatment colchicine and malaria medicine quinine as examples. 'The difficulty in developing antidotes is the market is very small and doing clinical trials is very difficult,' he says. 'And even if you do develop them, they could be prohibitively expensive because those poisonings happen so rarely.' According to the UK's National Institute for Health and Care Excellence, in 2016 a single dose of idarucizumab was £2400.

Mass casualty threats

Countermeasures for chemical and biological weapons and toxic industrial chemicals are the most active areas of antidote development. Global awareness of the potential for these to be used deliberately against civilians has risen in recent decades. In 1995, for example, the nerve agent sarin killed 12 people in a Tokyo subway.

Source: © STR/AFP/Getty Images

In 2001, five people were killed in the US when anthrax was posted to media offices and senators shortly after the September 11 attacks. Sarin and chlorine continue to be used as weapons in the Syrian civil war. And in 2018, a Novichok nerve agent was used against civilians in Salisbury..

A methy isocyanate leak from a pesticide plant in Bhopal caused one of the worst industrial accidents in history

Antidotes could also prove useful in the accidental large-scale release of toxic industrial chemicals. In December 1984, for example, a methyl isocyanate gas leak from a Union Carbide pesticide plant in the Indian city of Bhopal killed thousands of people. And in August 2015, a chemical storage warehouse containing, among other chemicals, 700 tonnes of sodium cyanide exploded in China killing at least 160 people. Scores of smaller chemical releases have been reported around the world too. The US Chemical Safety Board, for example, has declared the accidental releases of a number of toxic industrial chemicals including ammonia, chlorine and phosgene in recent years.

In the US, the National Institutes of Health's Countermeasures Against Chemical Threats (CounterACT) programme (which is part of its Chemical Countermeasures Research Programme, CCRP) is a key funding source for efforts to develop improved antidotes against chemical weapons and toxic industrial chemicals for civilian use.

Toxic gases

Paediatric pulmonologist Carl White, from the University of Colorado in the US, is funded by CounterACT to study how toxic gases harm the respiratory tract and how it might be possible to counteract these effects. 'We have been studying the pathogenesis of methyl isocyanate airway toxicity and testing several relevant interventions,' White explains. 'We have some encouraging leads for therapies.'

One approach, being developed in collaboration with Sven Eric Jordt at Duke University in North Carolina, US, is to target the transient receptor potential ankyrin 1 (TRPA1). Also known as the wasabi receptor, this ion channel detects a wide range of chemical threats. It

plays a role in the tear-inducing reaction to too much wasabi, and has also been linked to responses – such as coughing and reduced breathing rates – to toxic gases including chlorine, tear gases and some industrial isocyanates. TRPA1 antagonists have previously been shown to reduce inflammation in response to tear gases and isocyanates in mice. 'We have tested one novel TRPA1 inhibitor against methyl isocyanate in rats and are currently evaluating a second,' explains White.

Agonists of the various TRP channels with respiratory roles are being tested by a number of pharmaceutical companies, including GlaxoSmithKline, against indications such as asthma and chronic obstructive pulmonary disease; none has been approved so far. GSK is also testing a novel TRPV4 antagonist against chlorine in animal models. We have tested one novel TRPA1 inhibitor against methyl isocyanate in rats

A challenge of working with antidotes to chemicals threats is that human trials are often not possible or even ethical. To overcome this, the Food and Drug Administration's (FDA) Animal Rule offers a route for these drugs to be approved without testing in humans. 'The animal rule requires that, generally, you test in two species,' explains White. The European Medicines Agency (EMA) does not have a formal equivalent.

White is also working on an antidote for the toxic industrial chemical methyl mercaptan, in collaboration with Gerry Boss at the University of California, San Diego, in the US. In November 2014, four workers were killed at a DuPont plant near La Porte in Texas following a leak of this gas. 'Boss is studying cobinamide, a cobalamin [vitamin B_{12}] analogue that has a high affinity for methyl mercaptan, and he's got some great results so far in the rodent model,' explains White. Some different vitamin B_{12} analogues are already approved by the FDA and EMA for cyanide poisoning. Cyanide acts via a number of pathways, the most significant being by inhibiting cytochrome c oxidase-dependent cellular respiration. The cobalt in the approved vitamin B_{12} analogues binds with cyanide anions in the body to produce a non-poisonous compound that is excreted in urine. It is thought the same happens with methyl mercaptan.

Boss has shown that the methyl mercaptan-neutralising effect of cobinamide is boosted by sodium thiosulfate, an already approved cyanide antidote, in mice. He now plans to test this combination against methyl mercaptan in rabbits and pigs.

Scaling up

CounterACT also funded cardiologist Calum MacRae at the Brigham and Women's Hospital in Boston and Randall Peterson at the University of Utah, both in the US, to explore new cyanide antidotes. Current cyanide antidotes are given intravenously, which would be logistically difficult with large casualty numbers. 'They're not scalable solutions,' explains MacRae. 'One of the goals of our programme is to build out something that is scalable with a focus on intramuscular injections.'

MacRae, Boss and colleagues have screened over 150,000 approved drugs and novel molecules against cyanide in a zebrafish model developed in his lab. 'The fish precisely recapitulates virtually all of the cyanide toxicities [in humans],' he explains. 'We have successfully identified three potential antidotes this way.' The furthest developed is an analogue of the anticancer drug cisplatin.[1] Like many of the existing cyanide antidotes, the metal (platinum) in cisplatin binds to cyanide anions to form a relatively non-toxic compound. This novel chelation agent has a higher affinity for cyanide than existing chelation agents, explains MacRae. Fish, mice and rabbit data support this. 'This compound is now being tested in larger animals. We are hoping to get it into a pre-clinical toxicology programme by the fall of 2019 if funding allows.'

Unusually for a chemical threat antidote, clinical trials may follow. Sodium nitroprusside infusions, used for rapidly reducing blood

pressure, metabolise to form thiocyanate, he explains. ‘Testing the agent in people who have therapeutically induced cyanide toxicity is potentially feasible.’

Organophosphates

Pesticides are another class of chemicals that fall under CounterACT’s remit for having the potential to cause mass casualties. Small scale exposures, both accidental and otherwise, to these are also fairly routine. In the UK, for example, four multiple-casualty exposures to pesticides were reported to the National Poisons Information Service between April 2017 and March 2018. There were a further 4000 accesses to its database concerning pesticides over the same period.

Source: © Sipa/REX/Shutterstock

Sarin – an organophosphate-based nerve gas – was used to deadly affect during a terrorist attack in Japan in 1995

Many pesticides are organophosphates. The World Health Organization has reported that organophosphate pesticides cause 200,000 deaths each year in developing countries. Nerve agents such as VX, sarin, soman and the Novichok agents are also organophosphates and disrupt the nervous system in the same way.

The neurotransmitter acetylcholine naturally binds to acetylcholine receptors at synapses (the junction between nerve cells) to trigger muscle contractions and modulate signalling in the brain. The job of the enzyme acetylcholinesterase is to break it down. Organophosphates inhibit this enzyme by phosphorylation, causing a build-up of acetylcholine and over-stimulation of the receptors. In large enough doses, this can lead to seizures, paralysis, respiratory arrest – and potentially death.

A trio of drugs comprise the current standard of care for treating organophosphate poisonings. Oximes such as pralidoxime (2-PAM) reactivate acetylcholinesterase, atropine blocks the acetylcholine receptor preventing over-stimulation, and a benzodiazepine – diazepam or midazolam – stops seizures, by enhancing the effect of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at the $GABA_A$ receptors.

Autoinjectors containing the above drug combinations – that can be rapidly administered by the poisoned person themselves – are already on the market but need to be used within minutes of exposure for maximum effectiveness. Even then they are not guaranteed to protect the brain against long-term damage. ‘If you think about a civilian casualty scenario, it’s very unlikely that they’re going to be treated within 20 minutes of exposure,’ says Pamela Lein, a neurotoxicologist at the University of California, Davis, in the US.

Lein heads up a handful of efforts looking at improving the seizure-control aspect of organophosphate poisoning treatment. One potential approach, being explored in collaboration with UC Davis colleague Michael Rogawski, is to supplement midazolam with two other approved drugs – the neurosteroid allopregnanolone, which enhances the activity of GABA at the $GABA_A$ receptor, and perampanel, an antagonist of another nervous system receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). ‘The beauty of the combination that we’re working with is that all three drugs are currently approved for use in humans. We’re just repurposing them,’ Lein explains.

’We have really good proof of concept in animal models, and are ready to start pre-clinical testing,’ she adds. ‘If this passes those stages, because these are already approved in humans, we’re hoping for a quicker path forward to get these into clinical applications for chemical-induced seizures.’ She does, however, expect that clinical

trials will be necessary against seizures with causes other than chemical threat agents.[2]

Oxime antidotes

A number of research groups globally are also looking at improving the oxime component of the current organophosphate treatment, with a focus on developing compounds that can enter the brain. Janice Chambers, professor of toxicology at Mississippi State University in the US leads the CounterACT-funded effort. The current drug, pyridinium oxime 2-PAM, doesn't effectively cross the blood–brain barrier, she explains, meaning acetylcholinesterase's function isn't restored in the brain. 'We are trying to tone down the effect of the organophosphate in the brain so that seizures and related brain damage may be reduced or eliminated.'

Chambers' team has looked at over 100 different novel pyridinium oximes, finding four which she describes as 'really promising'. 'The premise that we are using is that if we increase the lipophilicity, we might be able to counterbalance that positive charge that tends to prevent it from going across the blood–brain barrier,' she explains. Rat studies of their four pyridinium oximes against sarin and VX surrogates support her theory.[2] 'Our oximes can shorten the time of seizures compared to 2-PAM and prevent brain damage.'

The team's compounds have been licensed to drug development company Defender Pharmaceuticals, and the potential of using a cocktail of oximes is currently being explored in animal models. '2-PAM and some of the other oximes that we know can't get into the brain are better acetylcholinesterase reactivators than our oximes – they're more effective at keeping the animal alive by restoring cholinesterase in the peripheral nervous system and maintaining respiration. So, a cocktail of our oxime and 2-PAM might be more effective overall to save lives and save brains,' she explains.

Military intervention

CCRP's focus is on protecting civilians from mass exposure to chemicals; the US Department of Defense funds a complementary effort, through the Defense Threat Reduction Agency (DTRA), to protect the military. DTRA funds a similar portfolio of projects to CCRP, working towards novel therapeutics against chemical agents, explains Alison Myska, chemical countermeasures lead at the DTRA. It is particularly interested in approaches that can be self-administered 'For a soldier, airman, marine or coastguard, they need to be treated in a timeframe of seconds to minutes post-exposure because they have an operational mission to finish,' she says.

For a soldier or airman, they need to be treated in a timeframe of seconds

DTRA is also looking at preventatives that can be given ahead of exposure. 'These are small-molecule drugs, proteins or enzymes that we could give somebody beforehand to protect them or at least mitigate the effects to get through until they can get the treatment,' Myska says. Previous attempts to make nerve agents prophylactics only managed a few hours of protection. A significant breakthrough funded by the DTRA was announced in January 2018; a nanoscavenger that gives a week's worth of protection to repeated sarin exposure in guinea pigs. 'The enzymes eat through the organophosphates in the bloodstream, like Pacman does for the little dots in the video game, before they reach the nervous system,' Myska explains.

Contributors to this multi-institution project include scientists at the US Army Medical Research Institute of Chemical Defense in Maryland. The nanoscavenger is an organophosphorus hydrolase enzyme coated with a zwitterionic non-fouling polymer layer.[4] The polymer prevents the enzyme from being recognised and destroyed by the immune system, and therefore dramatically extending the time in remains in the blood.

'We are planning work right now in larger animal models to show that they are safe and efficacious, that they don't cause any adverse reaction even with repeated dosing,' says Myska. 'We will then work with our partners to seek approval under the FDA Animal Rule.'

In the domain of antidote development, it will only ever be possible to treat a fraction of the vast number of drugs and chemicals to which we could potentially be exposed. It helps to remember that for the majority, treating the symptoms is sufficient. And for those that pose the most significant mass casualty threat, antidotes are either already available or under development.

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Physicians Call for Action on Root Causes of Drug Shortages

Physicians increasingly expressing their frustration about inadequate supply of critical hospital medicines

Kerry Dooley Young

Physicians and others in the healthcare industry are increasingly expressing their frustration about an inadequate supply of critical hospital medicines and are calling for action from private enterprise and US officials to resolve the root causes of these chronic drug shortages.

Leah Houston, MD, of New York City, recalled once having to use paddles to perform cardioversion for a patient in rapid atrial fibrillation because of a shortage of diltiazem (multiple brands).

"This is a commonly used generic medicine and is the first line of treatment, and there is no good reason that it shouldn't be readily available at all times," Houston said in a comment to the US Food and Drug Administration (FDA), which was posted online at Regulations.gov in January.

The FDA is at the center of federal efforts to address the persistent shortages of workhorse products of hospital care.

In response to the agency's request for feedback on addressing drug shortages, many physicians told the agency about having to take special measures because of missing products. Tracy Pfeifer, MD, New York City, recalled a situation 4 years ago in which lactated Ringer's solution was unavailable. She also told the FDA about a fellow physician who sent "an email plea" to colleagues to find out where his wife could get drugs she needed to continue treatment for ovarian cancer.

"We cannot get certain antibiotics, multiple medications are always on 'back order,' " Pfeifer also told the FDA. She stressed that the United States is not a poor nation where such shortages might be expected. "Why are medications not available?" she asked.

Federal officials, medical groups, and healthcare companies have been struggling for years to address the fragile US supply of critical hospital products.

"As of October 2018, and as you well know, there are currently 91 medically necessary drugs on the FDAs shortage list," Martin Van Trieste, the chief executive officer of Civica Rx, a new nonprofit venture started by hospitals to address the shortages, told the FDA in a comment. "Approximately 200 drugs have been on and off the FDA's drug shortage list during the past several years."

A 2012 law gave the FDA expanded authority to monitor the supply. Drugmakers, for example, must notify the FDA about disruptions or discontinuations of manufacturing of critical products. The FDA also has been extending the use-by dates for products in critical need, such as injectable sodium bicarbonate and sterile water.

In a mandated annual report to Congress, the FDA said it prevented 145 new shortages in 2017. There were 39 new drug shortages that year, compared to a peak of 251 new shortages in 2011.

Still, shortages of staple products such as saline persist. Many generic hospital drugs are manufactured by a single company. Clinicians scramble to find alternative therapies or engage in compounding, according to the American Society of Health-System Pharmacists.

"We certainly don't have easy solutions, or we would have fixed this problem a long time ago, but it's gone on too long," FDA Commissioner Scott Gottlieb, MD, said at a November 2018 meeting on drug shortages. "The risks have mounted over time, and the frustrations have really reached a tipping point."

Cheaper Than a Gallon of Milk

There are a few specific, easily identifiable contributors to shortages, such as the disruption of Puerto Rico's pharmaceutical industry caused by Hurricane Maria in 2017.

Much has been written about the manufacturing troubles at companies such as Hospira, a leading maker of injectable drugs that Pfizer Inc acquired in 2015. In a 2018 warning letter, the FDA said a discovery of mold caused a temporary halt in production at the firm's generic-drug plant in McPherson, Kansas. There is also growing concern about the broader market dynamics for generic drugs.

The public debate on the cost of medicines tends to focus on newer products that cause consumer sticker shock. Cancer medicines, for example, can cost $15,000 a month.

The low prices drugmakers get for older injectable medicines are not enough to entice more companies into making these products. "[T]here may be critical drugs that may sometimes be priced too low relative to the full cost of reliably producing a predictable and high-quality pharmaceutical product," wrote Gottlieb and Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, in a blog post.

In its comment to the FDA, Pfizer said it has spent more than $800 million over the past 2 years on its injectable drug business. It intends to spend more than $1.4 billion over the next several years, wrote Robert Jones, Pfizer's senior vice president for government relations. "But when you contrast that investment with the fact that two-thirds of the generic sterile injectable units Pfizer sells annually cost less than the average gallon of milk, it places the challenge of market sustainability into perspective," Jones wrote.

In the comment, Jones also told the FDA about the challenges of having a fickle customer base for critical hospital products. Buyers rarely make serious commitments on price or volume, according to his comment.

Even after entering into multiyear contracts to sell medicines, makers of hospital drugs can see these agreements "undermined at any time during the life of the contract" by a challenge on price from a rival pharmaceutical firm, Jones wrote.

"This lack of contractual commitments impedes manufacturers' ability to deploy capital for new capacity, redundancies or excess inventory, which is predicated on reasonable levels of predictability and expected return on investment," he wrote.

Exception to Kickback Law

In an article published online in October 2018 in the *Journal of the American Medical Association*, Martin Makary, MD, MPH, of Johns Hopkins University, and colleagues questioned whether the structure of group purchasing organizations (GPOs) contributes to the persistent shortages of injectable generic drugs.

Congress in 1972 enacted a federal law to prevent kickbacks that could put patients at risk, Makary and colleagues wrote. In 1987, GPOs were granted an exception to the law, which lobbyists and policy analysts refer to as a safe harbor exemption.

This exception to the kickback law helps GPOs to use "creative strategies" to boost their profit, according to Makary and colleagues. GPOs ask manufacturers to pay undisclosed vendor fees as a condition for having their products placed among the offerings available to hospitals. Manufacturers also can pay premium fees to become the sole supplier of a product, Makary and colleagues wrote. As a result, one or two manufacturers may be responsible for a regional or national supply chain, the authors said.

"Although there is limited evidence to support the direct link between GPOs and drug shortages, the vendor fee model of GPOs has the potential to create barriers to market entry for manufacturers by rewarding fewer larger manufacturers and thus increasing dependence on fewer supply chains," Makary and colleagues wrote.

The group Physicians Against Drug Shortages also criticizes the GPO business model as a contributor to shortages, and it does so with much stronger language than Makary used.

In the *JAMA* article, Makary and colleagues note that GPOs do provide many benefits for hospitals, such as simplifying purchases of many supplies.

In contrast, Robert Campbell, MD, an anesthesiologist and founder of Physicians Against Drug Shortages, describes the GPOs as having a "payola" model. He calls for a change in federal rules that now allow GPOs to collect fees from their suppliers.

"End the pay to play market model and we will have a renaissance of high quality manufacturing for all these drugs," Campbell wrote in his FDA comments. "Prices will fall, supply will be restored, capital investment for quality improvement will be possible, and new entrants with innovative products will emerge."

Physicians Against Drug Shortages had encouraged its supporters to respond to the FDA's comment period, which ended January 11. There were more than 147 comments posted on the Regulations.gov site that used the same language to question an exception in federal anti-kickback law. In its comment to the FDA, the American Society of Anesthesiologists (ASA) appeared to be at odds with Physicians Against Drug Shortages.

Although not naming Physicians Against Drug Shortages, the ASA said it "was aware" of a group that associated GPOs with drug shortages. "Yet, the Society is not aware of any independent and reliable data or information that supports this argument," Linda Mason, MD, president of the ASA, said in a comment to the FDA.

The ASA recommended that Congress' investigative unit, the Government Accountability Office (GAO), conduct a study of drug shortages and the entire drug supply chain. The GAO issued reports on the topic in 2014, 2015, and 2016. "ASA believes it is time to revisit this issue and see if there are any new circumstances or events exacerbating drug shortages," Mason wrote.

The trade association that represents GPOs also objected to the idea that kickback protection plays a role in shortages. Todd Ebert, MS, chief executive officer of the Healthcare Supply Chain Association, told *Medscape Medical News* that the GPO exception to the kickback law allows GPOs to "deliver billions in annual savings to hospitals and other healthcare providers, Medicare and Medicaid, and taxpayers."

"The GPO Safe Harbor is not unusual — in fact, it is one of 23 such provisions in the 1987 Act," said Ebert, who is a registered pharmacist. He also said GPOs help mitigate shortages, which he attributed to "quality control problems, manufacturing issues, and barriers to getting new suppliers on line."

In its comment to the FDA on drug shortages, the American Medical Association (AMA) noted that past GAO reports had identified low profit margins as a contributing factor to persistent shortages. The AMA urged the FDA's Drug Shortages Task Force to consider "mergers and consolidations, economic factors including federal

reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing."

The AMA also recommended an examination of federal healthcare programs' payment rates for drugs that are susceptible to shortages.

"Carefully targeted policies to address potential underinvestment in vital products subject to intractable shortages should be evaluated," wrote James L. Madara, MD, chief executive officer of the AMA, in the comment.

Civica Rx

Drug shortages have proven taxing on pharmacy staff at hospitals, where personnel have to scramble to cope with the dearth of needed medicines. "We have spent countless hours working as interdisciplinary teams to develop alternate solutions," Jennifer Fulmer Groves, vice president of pharmacy operations for Providence St. Joseph Health, told *Medscape Medical News* in an email.

In some cases, pharmacists may need to track down alternative medications or restrict use of a drug in short supply to treat patients who meet specific criteria, Groves said.

Providence St. Joseph Health is part of a coalition of hospitals that last year launched Civica Rx, a venture intended to stop the shortages. Its goal is to provide drug manufacturers with more stable contracts with hospital customers.

Seven major health systems last year announced the kickoff of Civica Rx, which is meant to be a virtual generic drug company. Other founding members include Intermountain Healthcare and Mayo Clinic. By January, an additional 12 health systems had joined the Utah-based Civica Rx as founding members. The nonprofit Laura and John Arnold Foundation also is a supporter of Civica Rx.

"By working with philanthropic donors and other health systems, Providence St. Joseph Health is in the process of creating a drug manufacturer that will produce medications that have been in short supply in the market," Groves said.

In his comment to the FDA, Civica Rx's Van Trieste said the venture aims to use long-term guaranteed contracts and will refuse to pay fees and rebates "to middlemen in the pharmaceutical supply chain."

In an interview with *Medscape Medical News*, Van Trieste spoke of a broad strategy for enticing manufacturers into making the generic products hospitals need. In some cases, companies already have the needed FDA clearance and the manufacturing capacity to make these products, but they've opted not to, owing to low profits.

Van Trieste, a veteran pharmaceutical executive who earlier worked for Amgen, Bayer, and Abbott Laboratories, observed that the problem with generic hospital drugs extends beyond simple economics. These older products don't capture the attention of investors and the public in the same way that experimental treatments and upstart medical firms do.

"The economic model has broken down, but another piece of it is these are older generic drugs. They're not the sexy new biotech drugs," Van Trieste said. "These drugs are decades old, and some of them even a century old. There's no pizzazz to the products themselves. But they are essential for hospitals to operate. When they're not available, then it creates a crisis."

Although Civica Rx is only in its start-up phase, the approach it has taken is worth looking at, said Rosemary Gibson, a senior advisor at the Hastings Center and coauthor of *China Rx: Exposing the Risks of America's Dependence on China for Medicine*.

"It would assure the manufactures that they will have customers that won't come and go," she told *Medscape Medical News.*

The intense focus on reducing costs has resulted in the shifting of key elements of generic drug production to China and has weakened the domestic supply, she said. The current difficulties in keeping hospital pharmacies well stocked may be "just the tip of the iceberg," she said.

"We're going to see more shortages and more quality problems because we are treating these products like a cheap commodity," she said.