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City of Hope researchers successfully prevent graft-versus-host disease

Journal of Clinical Investigation reports regimen may stop common side effect of stem cell transplants for hematologic cancer patients

DUARTE, Calif. -- Through experimental work, an international team of researchers led by City of Hope's Defu Zeng, professor of diabetes immunology and hematopoietic cell transplantation, believe they may have found a way to prevent graft-versus-host disease after stem cell transplants while retaining the transplants' positive effects on fighting leukemia and lymphoma. The preclinical study results were published today in the Journal of Clinical Investigation.

Allogeneic (meaning from a donor) hematopoietic cell transplantation (HCT) is a curative therapy for cancers of the blood and lymph system, including leukemia and lymphoma. It works by introducing healthy immune cells, or T cells, that eliminate tumor cells and prevent the cancer from relapsing. Unfortunately, the same donor T cells can also attack the healthy tissue of the recipient's body such as gut, liver, lung, and skin, leading to induction of graft- (T cell) versus-host (recipient's body) disease, or GVHD. Symptoms can be mild to severe and often include mouth ulcers, gastrointestinal distress, and rashes.

"Currently, immunosuppressive drugs have been used to prevent GVHD, but immune-suppressants also subdue the anti-cancer effects of the donor T cells, potentially resulting in cancer relapse, in addition to other side effects such as an increased risk of infection," explains Zeng. "Therefore, prevention of GVHD while preserving anti-cancer effects remains the 'holy grail' of allogeneic HCT."

According to the paper, titled "PD-L1 interacts with CD80 to regulate graft-versus-leukemia activity of donor CD8+ T cells," the research team, which included graduate students (first authors Qingxiao Song and Xiong Ni) and scientists from City of Hope, Mayo Clinic, Fred Hutchinson Cancer Research Center and three Chinese medical schools, observed that temporary in vivo depletion of a specific type of donor T cells (CD4+) soon after infusion of donor stem cell transplants prevented GVHD while preserving strong graft-versus-leukemia (GVL) effects.

The depletion of CD4+ cells essentially caused another type of T cell (CD8+) to become exhausted in their quest to destroy normal tissue, but strengthened in their fight against cancer, meaning that the donor CD8+ T cells eliminated tumor cells without causing GVHD.

"If successfully translated into clinical application, this regimen may represent one of the novel approaches that allow strong GVL effects without causing GVHD," says Zeng. "This kind of regimen has the potential to promote wide-spread application of allogeneic HCT as a curative therapy for hematological malignancies."

Going forward, Zeng plans to translate this novel regimen into clinical application at City of Hope by carrying out a clinical trial in collaboration with Ryotaro Nakamura, M.D., associate professor of hematology and hematopoietic cell transplantation, and Stephen J. Forman, M.D., F.A.C.P, the Francis & Kathleen McNamara Distinguished Chair in Hematology and Hematopoietic Cell Transplantation and leader of City of Hope's Hematologic Malignancies and Stem Cell Transplantation Institute, which is one of the world's largest and most successful bone marrow and blood stem cell transplant centers.

"If we see promising results, we will extend this trial by working with our collaborators from this current study," says Zeng.

At the same time, Zeng is also working with Arthur D. Riggs, Ph.D., the Samuel Rahbar Chair in Diabetes & Drug Discovery, John Williams, Ph.D., professor in the Department of Molecular Medicine, and, David Horne, Ph.D., vice provost and associate director of the Beckman Research Institute of City of Hope, and chair of the Department of Molecular Medicine, to develop a CD4+ deleting antibody, using the unique Meditope technology invented at City of Hope by Williams and colleagues.

The work described in the Journal of Clinical Investigation paper was supported in part by the National Institutes of Health, the National Cancer Institute, the Nesvig Lymphoma Foundation, the National Natural Science Foundation of China, and the National and Fujian Provincial Key Clinical Specialty Discipline Construction Program of China under grant numbers: R01AI066008, 2R56AI095239 and P30CA033572. The content is solely the

responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

http://bit.ly/2pQvbjk

The impossibility of immorality

Study suggests the brain views immoral acts as if they are impossible

Imagine you're getting hungry at work and you see a candy bar on a co-worker's desk. Why not just eat it while she's out of the room?

Some people might not do it because they know it's wrong. Other people might not do it because it's risky. But a new study suggests that--for most people--their immediate response might actually be to think that it isn't even possible.

The study, co-authored by Assistant Professor of Psychology Fiery Cushman and Jonathan Phillips, a post-doctoral fellow working in Cushman's lab, showed that people, by default, tend to view immoral actions as though they were simply impossible. The study is described in an April 17 paper published in the Proceedings of the National Academy of Sciences.

"When people do something immoral, people tend to say things like, 'No, that can't be right,' or 'I can't believe it,'" Phillips said. "There's a sense that the brain treats these kind of things similarly to how it would react if someone told you it is possible to turn your hat into a candy bar, or something equally impossible."

There may be good reason for the brain to react that way, Cushman said.

"We think this might actually help people act morally in the real world," he said. ""Maybe it's easier to do the right thing if your brain is designed to treat the wrong thing...as if it were impossible. Because if you admitted something was possible, it might start to feel pretty tempting."

In some sense, he said, it's as though every person has two voices in their heads that propose possibilities - a more intuitive one that respects the laws of morality, and a more deliberative one that sticks to the laws of physics.

"Part of what we're learning is why people call things possible or impossible," Cushman said. "It turns out we don't do this like a scientist or philosopher, with the goal of being perfectly accurate about the world. Ordinary people want to be practical about the world, and practically speaking, you shouldn't be doing immoral or irrational things. So a practical approach to decision-making is to simply call all those things impossible, and only focus on the set of things that are worth investing your time in."

To test how people reacted to both immoral and impossible events, Cushman and Phillips created an experiment using the online labor market Amazon Mechanical Turk.

Participants were presented with scenarios in which a person faced a problem, like getting to the airport after their car breaks down. They saw a series of potential solutions that were either immoral, such as seeing someone being mugged, or physically impossible, like turning your hat into a candy bar, and asked to rate whether each one was a "possible" solution.

The trick, Phillips said, is that half the participants had to respond quickly - in just 1.5 seconds - while the other half were told to wait 1.5 seconds before responding.

The results were dramatic - when participants were given more time for reflection, Phillips said, they called one-quarter of immoral actions impossible. When participants were given less time, however, as many as half were called impossible.

"If people have time to reflect on this, they're going to use their well-formed, reasoned understanding of which things are possible and impossible," Phillips said. "But when they have to answer quickly, they don't have time to do that, so they have to rely on this default idea of which things could even happen in the first place."

The study raises a host of additional questions - and could open the door to a new understanding of why some people repeatedly commit immoral actions.

"One of the things we are excited about looking into is people with psychopathic tendencies," Phillips said. "Do they just not care about something like stealing? Or do they care, but the problem is they can't get it out of their head and eventually they break down. It could be that they wouldn't show this effect."

The study also suggests one possible reason why turning to religion is often a successful strategy for those hoping to stop using alcohol or drugs.

"Maybe by making those things immoral, they're saying we know you want it, but you're going to treat it as if it's something you can't do," he said.

"But another question we want to follow up on is: Isn't this a horrible blind spot?" Cushman added. "If you went around assuming that it was impossible for people to do immoral things, wouldn't you be taken for a sucker immediately?"

The truth, Cushman and Phillips said, may be that people actually switch between two systems of evaluating the world around them - one constrained by morality and another that allows us to contemplate immoral behavior in others.

"The first, you use to govern your own actions and to think about the actions of those close to you," Phillips said. "But the other system isn't constructed in that way...because it would be a terrible idea to never consider the possibility that anything bad could happen to you."

http://bit.ly/2oAi1p6

What makes pancreatic cancer so aggressive?

FAU researchers discover key factor for the aggressiveness of pancreatic cancer

Pancreatic cancer is one of the most aggressive tumour types because it starts forming metastases early. The cancer itself, however, is usually only discovered late. This leads to a high patient mortality rate. Researchers at Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) have now discovered why pancreatic cancer and other malignant types of tumours can disseminate so rapidly. The results have now been published in the renowned journal Nature Cell Biology. The FAU researchers led by Prof. Dr Thomas Brabletz and Dr. Marc Stemmler of the Chair of Experimental Medicine I, with the cooperation of the Department of Medicine 5 - Haematology and Oncology, the Department of Surgery at Universitätsklinikum Erlangen, and the Chair of Genetics at the Faculty of Sciences, have discovered that this aggressive type of tumour activates the key factor of an embryonic programme. This factor, called Zeb1, controls how cells migrate and survive in early embryonic development. Zeb1 is blocked in normal, fully developed cells. But when the factor is re-activated in cancer cells, it has fatal consequences: The tumour cells disseminate throughout the body and quickly adapt to the changing conditions in their new environment. They can then develop into metastases and form secondary tumours. The cancer assumes an aggressive progression.

If, however, Zeb1 is not activated, cancer cells can no longer adapt to their new environment so easily. This in turn leads to the development of a variant of pancreatic cancer which presents significantly lower metastatic capacity. This mechanism is also observed in other tumours, such as aggressive forms of breast cancer. The researchers now hope these findings will help them to develop new treatment strategies for combating metastases of pancreatic cancer and other aggressive tumour types.

Original publication:

Angela M. Krebs, Julia Mitschke, Maria Lasierra Losada, Otto Schmalhofer, Melanie Boerries, Hauke Busch, Martin Boettcher, Dimitrios Mougiakakos, Winfried Reichardt, Peter Bronsert, Valerie G. Brunton, Thomas H. Winkler, Simone Brabletz, Marc P. Stemmler and Thomas Brabletz. The EMT activator ZEB1 is a key factor for cellular plasticity and promotes metastasis in pancreatic cancer. Nat Cell Biol, DOI 10.1038/ncb3513 (2017).

Comment:

M. A. Nieto. News and Views: Context-specific roles of EMT programmes in cancer cell dissemination. Nat Cell Biol, Vol 19 (May 2017).

http://bit.ly/2poNaAy

A potential cure for metastatic prostate cancer? Treatment combination shows early promise

Pilot study suggests that a new paradigm including drug therapy, surgery, and radiation may cure previously incurable cancer, according to a new study in Urology®

Philadelphia, PA - In the past, all forms of metastatic prostate cancer have been considered incurable. In recent years, the FDA has approved six drugs for men with metastatic disease, all of which can increase survival. In a study published in Urology®, researchers demonstrate for the first time that an aggressive combination of systemic therapy (drug treatment) with local therapy (surgery and radiation) directed at both the primary tumor and metastasis can eliminate all detectable disease in selected patients with metastatic prostate cancer.

While the study is only a first step, one-fifth of the patients treated had no detectable disease, with an undetectable prostate-specific-androgen (PSA) and normal blood testosterone, after 20 months. The results suggest that some men who have previously been considered incurable can possibly be cured; investigators also establish a new paradigm for testing various drug combinations in conjunction with local treatment of the prostate to determine which is the best approach (ie, has the highest undetectable disease rate). Such results could not have been achieved with any single therapy alone.

According to lead investigator Howard I. Scher, MD, Chief of the Genitourinary Oncology Service at Memorial Sloan Kettering Cancer Center in New York City, "The sequential use of the three different modalities helped illustrate the role and importance of each in achieving the undetectable PSA with normal testosterone level end point, which represents a 'no-evidence of disease' status." Longer follow-up is needed to determine whether these patients were in fact cured.

Twenty men with metastatic prostate cancer, five with extra-pelvic lymph nodal disease and 15 with bone with or without nodal disease, were treated with androgen deprivation therapy (ADT), radical surgery that included a retroperitoneal lymph node dissection as needed, and radiation therapy to visible metastatic lesions in bone. ADT was stopped after a minimum of six months if an undetectable PSA was achieved after combined modality therapy. Other patients were treated continuously.

The combined treatment regimen including surgery was well tolerated. Matthew J. O'Shaughnessy, MD, PhD, Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, commented "While the role of local therapy in metastatic prostate cancer is still under investigation, aggressive resection of visible disease performed by experienced surgeons was critical to the outcome."

Of the five patients with extra-pelvic lymph node involvement, four achieved an undetectable PSA after ADT and surgery, while the fifth needed radiation to reach this milestone. However, none achieved the primary end point of undetectable PSA with testosterone recovery at 20 months after initiation of therapy with ADT alone, although one patient had a PSA of <.05 ng/mL with a testosterone level of 47 ng/dL at 39 months.

Of the 15 patients with bone metastases, 14 (93%) reached an undetectable PSA when ADT, surgery, and radiation were used. Ultimately, four (27%) achieved the proposed end point, a PSA of <.05 ng/mL and serum testosterone of >150 ng/dL at 20 months after the start of ADT, which remained undetectable in two patients for 27 and 46 months, respectively.

Commenting on the study, Oliver Sartor, MD, Cancer Research, Department of Medicine and Urology, Tulane University School of Medicine, New Orleans, LA, stated, "The end point deserves special mention, as the end point of undetectable PSA after testosterone recovery has been previously discussed but rarely studied. The authors proposed that this end point may serve as a first step toward establishing a curative paradigm. Many in the field agree, but note that the longevity of effect is essential to prove the point of curability.

Regardless, the movement toward a curative paradigm is much needed and the investigators are to be congratulated for setting forth a paradigm that can be used to assess the possibility of cure in a reasonable period of time."

"A multimodal treatment strategy for patients who present with disease that is beyond the limits of curability by any single modality enables the evaluation of new approaches in order to prioritize large-scale testing in early stages of advanced disease. The end point also shifts the paradigm from palliation to cure," remarked Dr. Scher. It is expected that an upcoming Phase 2 trial will further test this endpoint and combined modality approach.

http://bit.ly/2pp311W

Homing pigeons share our human ability to build knowledge across generations

Homing pigeons may share the human capacity to build on the knowledge of others, improving their navigational efficiency over time, a new Oxford University study has found.

The ability to gather, pass on and improve on knowledge over generations is known as cumulative culture. Until now humans and, arguably some other primates, were the only species thought to be capable of it.

Takao Sasaki and Dora Biro, Research Associates in the Department of Zoology at Oxford University, conducted a study testing whether homing pigeons can gradually improve their flight paths, over time. They removed and replaced individuals in pairs of birds that were given a specific navigational task. Ten chains of birds were released from the same site and generational succession was simulated with the continuous replacement of birds familiar with the route with inexperienced birds who had never flown the course before. The idea was that these individuals could then pass their experience of the route down to the next pair generation, and also enable the collective intelligence of the group to continuously improve the route's efficiency.

The findings, published in Nature Communications, suggest that over time, the student does indeed become the teacher. The pairs' homing performance improved consistently over generations - they streamlined their route to be more direct. Later generation groups eventually outperformed individuals that flew solo or in groups that never changed membership. Homing routes were also found to be more similar in consecutive generations of the same chain of pigeon pairs than across them, showing cross-generational knowledge transfer, or a "culture" of homing routes.

Takao Sasaki, co-author and Research Fellow in the Department of Zoology said: 'At one stage scientists thought that only humans had the cognitive capacity to accumulate knowledge as a society. Our study shows that pigeons share these abilities with humans, at least to the extent that they are capable of improving on a behavioural solution progressively over time. Nonetheless, we do not claim that they achieve this through the same processes.'

When people share and pass knowledge down through generations, our culture tends to become more complex over time, There are many good examples of this from manufacturing and engineering. By contrast, when the process occurs between homing pigeons, the end result is an increase in the efficiency, (in this case navigational), but not necessarily the complexity, of the behaviour.

Takao Sasaki added: 'Although they have different processes, our findings demonstrate that pigeons can accumulate knowledge and progressively improve their performance, satisfying the criteria for cumulative culture. Our results further suggest that cumulative culture does not require sophisticated cognitive abilities as previously thought.'

This study shows that collective intelligence, which typically focuses on one-time performance, can emerge from accumulation of knowledge over time.

Dora Biro, co-author and Associate Professor of Animal Behaviour concludes: 'One key novelty, we think, is that the gradual

improvement we see is not due to new 'ideas' about how to improve the route being introduced by individual birds. Instead, the necessary innovations in each generation come from a form of collective intelligence that arises through pairs of birds having to solve the problem together - in other words through 'two heads being better than one'.'

Moving forward, the team intend to build on the study by investigating if a similar style of knowledge sharing and accumulation occurs in other multi-generational species' social groups. Many animal groups have to solve the same problems repeatedly in the natural world, and if they use feedback from past outcomes of these tasks or events, this has the potential to influence, and potentially improve, the decisions the groups make in the future.

The full paper 'Cumulative culture can emerge from collective intelligence in animal groups' written by Takao Sasaki and Dora Bird, features in the 18th April 2017 edition of Nature Communications. (PDF attached)

http://bbc.in/2q2Ogyb

Vaginal mesh implants: Hundreds sue NHS over 'barbaric' treatment

More than 800 UK women are taking legal action against the NHS and the makers of vaginal mesh implants, the Victoria Derbyshire programme has learned.

By Victoria Derbyshire Presenter

The implants are used to treat pelvic organ prolapse and incontinence after childbirth, but some can cut into the vagina - causing severe discomfort. Some women have been left in permanent pain, unable to walk, work or have sex. One called the implants "barbaric". The UK's medicines regulator said it "sympathises" with the women affected.

Kate Langley had to give up her business as a childminder because the pain was so intense she could not look after the children.

The surgeon who first examined her, she explained, "could see the [mesh] tape had come through my vagina - protruding through.

"The mesh had cut its way through - like a cheese-wire," she told the Victoria Derbyshire programme.

Other women, reporting similar symptoms, have said the perforation was so severe their partners had been injured by the mesh during sex.

Ms Langley, who described the meshes as "barbaric", said she has had 53 hospital admissions to try to end the pain, but - like many women - the mesh was so near the nerve it could not be fully removed. She has been left in permanent pain by the implants and has nerve damage.

The plastic meshes are made of polypropylene - the same material used to make certain drinks bottles - and manufactured by many different companies. They are used to ease incontinence and to support organs such as the vagina, uterus, bowel, bladder or urethra which have prolapsed after childbirth.

Claire Cooper began to experience pain three years after her operation. Doctors wrongly believed the source of discomfort was her womb, which she had had removed at the age of 39.

When the pain continued, she said a GP told her she was imagining it.

The news made her want to take her own life. She said she "mapped out" her suicide, but wanted to live on for her children.

She still lives in pain and said her husband has "turned into my carer".

"We haven't had sex for four-and-a-half years. This stuff breaks up marriages. "I wouldn't at all be surprised if there are mesh-injured women that have taken their own lives and didn't know what the problem was," she said.

Ms Cooper is one of a number of women calling for the NHS to stop fitting the implants. "I want the procedure banned, I want the material banned," she said.

Labour MP Owen Smith, who is planning to hold a Parliamentary debate on the issue, called for an investigation into the use of vaginal mesh. He told the BBC: "I think there is a really good case for saying 'suspend its usage' until there is clarity about the scale of the problems we're facing."

Unaware of risks

Between April 2007 and March 2015, more than 92,000 women had vaginal mesh implants in England, according to NHS data from the

Hospital Episodes Statistics, obtained by the Victoria Derbyshire programme. That figure includes a number of different types of implant, including TVT (trans-vaginal tape), TOT (transobturator tape), and SS tape, which is a suprapubic sling.

About one in 11 women has experienced problems, the data suggests.

Now, more than 800 women in the UK are taking legal action against the NHS and manufacturers, including US pharmaceutical giant Johnson & Johnson - the biggest makers of mesh implants.

Its subsidiary, Ethicon, said it was "vigorously defending litigation".

Many of the women the BBC met said they had never been told by their surgeons about the potential risks associated with the implants.

The Medicines and Healthcare products Regulatory Agency (MHRA) says for the majority of women, the use of vaginal mesh implants is safe and effective. The meshes are still prescribed on the NHS across the UK, although a recent review in Scotland said they should not be routinely used for pelvic organ prolapse.

Experts believe if the women are successful in their legal case, the NHS payout for compensation could be tens of millions of pounds.

In the US, thousands of women have sued manufacturers, receiving payouts that total several billion dollars.

Consultant urogynaecologist Dr Sohier Elneil said she sees patients in the UK who have been left facing severe pain and unable to walk. "The typical type of patient I see is a patient who is incapacitated by severe pain of a chronic nature. Often they are on high-dose medication, including opiates.

"They become so incapacitated that many of them are either walking by crutches or sitting in wheelchairs and perhaps more dramatically so, they become unable to look after their families."

Currently in the UK, there are around 100 types of vaginal mesh implants. So far, not one model has been recalled in the UK.

According to one expert, Prof Carl Heneghan, manufacturers have to provide little evidence before their product is clinically approved and made available on the NHS.

"The regulatory body... doesn't even look at the device," he said.

Prof Heneghan also said manufacturers just have to provide documents that show their vaginal mesh implant is similar to one already on the market and it is highly likely to be approved.

One leaked email from Johnson & Johnson suggested it had known problems existed with one of its products since 2004.

The email said the company needed to start a "major damage control offensive" because "the competition will have a field day".

The manufacturers said highlighting this email in isolation was "extremely misleading".

An MHRA spokesman said it was "committed to help address the serious concerns raised by some patients".

It added: "The greater proportion of the clinical community and patients support the use of these devices in the UK."

Ethicon said "these devices have helped millions of women".

It said it had "acted appropriately and responsibly in the research, development and marketing of its pelvic mesh products".

21 April 2017: This article was updated with data from NHS Digital about the number of women who have had implants fitted.

http://bit.ly/2oAmBDO

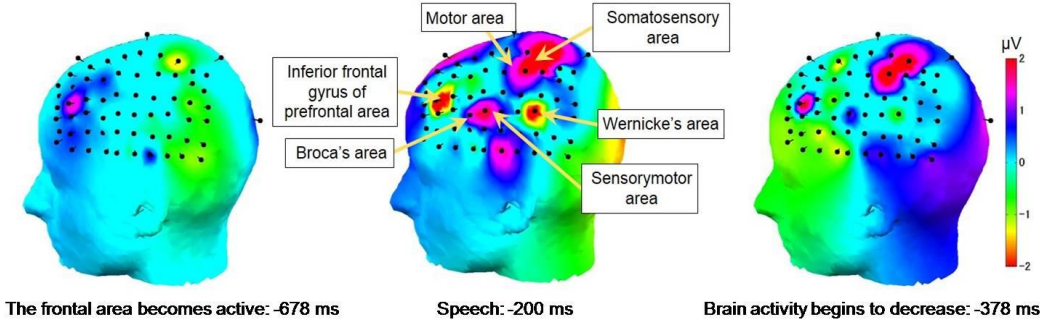
Success in recognizing digits and monosyllables with high accuracy from brain activity measurement

Recognizes numbers 0 to 9 with 90% accuracy using EEG readings

A Japanese research collaborative has developed a technology that can recognize the numbers zero to nine with 90 percent accuracy using electroencephalogram (EEG) readings while the subject utters the numbers. Furthermore, the technology can also recognize 18 types of Japanese monosyllables from EEG signals with 60 percent accuracy, demonstrating the possibility of an EEG-activated typewriter in the near future. The details of this research will be presented at Interspeech 2017 held in Stockholm in August.

The research group collected EEG data of subjects speaking Japanese digits and monosyllables. Using this data, the group conducted digit

and monosyllable recognition experiments. Up until now, speech decoding via EEG signals has been inhibited by a lack of data to allow the use of powerful algorithms based on deep learning or other types of machine learning. The research group has developed a different research framework that can achieve high performance with a small training dataset. The new framework is based on holistic pattern recognition using category theory, or composite mapping, in which a dual space and a tensor space including exterior algebra are introduced. In the experiment of spoken-digit recognition from EEG signals, 90 percent recognition accuracy was achieved. At the same time, 61 percent accuracy in 18 Japanese monosyllable recognition was achieved, outperforming previous research efforts. Humans have sufficient intelligibility of sentences with an 80 percent monosyllable recognition rate.



Shift in brain activity (10 syllable average for 8 subjects). **Toyohashi University of Technology**

Emeritus Professor Nitta and his group aim to develop a brain computer interface that recognizes unvoiced speech, or speech imagery. This technology may enable handicapped people who have lost the ability of voice communication to speak once again. It is also expected that the technology would give a healthy person the most natural interface without any limitations.

Furthermore, the research group plans to develop a device that can be easily operated with fewer electrodes and connected to smartphones within the next five years.

http://bit.ly/2q3CJPc

Medieval medical books could hold the recipe for new antibiotics

Some medievalists and scientists are now looking back to history for clues to inform the search for new antibiotics

Erin Connelly

For a long time, medieval medicine has been dismissed as irrelevant. This time period is popularly referred to as the "Dark Ages," which erroneously suggests that it was unenlightened by science or reason. However, some medievalists and scientists are now looking back to history for clues to inform the search for new antibiotics.

The evolution of antibiotic-resistant microbes means that it is always necessary to find new drugs to battle microbes that are no longer treatable with current antibiotics. But progress in finding new antibiotics is slow. The drug discovery pipeline is currently stalled. An estimated 700,000 people around the world die annually from drug-resistant infections. If the situation does not change, it is estimated that such infections will kill 10 million people per year by 2050.

I am part of the Ancientbiotics team, a group of medievalists, microbiologists, medicinal chemists, parasitologists, pharmacists and data scientists from multiple universities and countries. We believe that answers to the antibiotic crisis could be found in medical history. With the aid of modern technologies, we hope to unravel how premodern physicians treated infection and whether their cures really worked.

To that end, we are compiling a database of medieval medical recipes. By revealing patterns in medieval medical practice, our database could inform future laboratory research into the materials used to treat infection in the past. To our knowledge, this is the first attempt to create a medieval medicines database in this manner and for this purpose.

Bald's eyesalve

In 2015, our team published a pilot study on a 1,000-year old recipe called Bald's eyesalve from "Bald's Leechbook," an Old English medical text. The eyesalve was to be used against a "wen," which may be translated as a sty, or an infection of the eyelash follicle.

A common cause of modern styes is the bacterium *Staphylococcus aureus*. Methicillin-resistant *Staphylococcus aureus* (or MRSA) is resistant to many current antibiotics. Staph and MRSA infections are responsible for a variety of severe and chronic infections, including wound infections, sepsis and pneumonia.

Bald's eyesalve contains wine, garlic, an *Allium* species (such as leek or onion) and oxgall. The recipe states that, after the ingredients have been mixed together, they must stand in a brass vessel for nine nights before use.

In our study, this recipe turned out to be a potent antistaphylococcal agent, which repeatedly killed established *S. aureus* biofilms – a sticky matrix of bacteria adhered to a surface – in an in vitro infection model. It also killed MRSA in mouse chronic wound models.

Medieval methods

Premodern European medicine has been poorly studied for its clinical potential, compared with traditional pharmacopeias of other parts of the world. Our research also raises questions about medieval medical practitioners. Today, the word "medieval" is used as a derogatory term, indicating cruel behavior, ignorance or backwards thinking. This perpetuates the myth that the period is unworthy of study.

During our eyesalve study, chemist Tu Youyou was awarded the Nobel Prize in Physiology or Medicine for her discovery of a new therapy for malaria after searching over 2,000 recipes from ancient Chinese literature on herbal medicine. Is another "silver bullet" for microbial infection hidden within medieval European medical literature?

Certainly, there are medieval superstitions and treatments that we would not replicate today, such as purging a patient's body of pathogenic humors. However, our work suggests that there could be a methodology behind the medicines of medieval practitioners, informed by a long tradition of observation and experimentation.

One key finding was that following the steps exactly as specified by the Bald's eyesalve recipe – including waiting nine days before use – was crucial for its efficacy. Are the results of this medieval recipe representative of others that treat infection? Were practitioners selecting and combining materials following some "scientific" methodology for producing biologically active cocktails?

Further research may show that some medieval medicines were more than placebos or palliative aids, but actual "ancientbiotics" used long before the modern science of infection control. This idea underlies our current study on the medieval medical text, "Lylye of Medicynes."

A medieval medicines database

The "Lylye of Medicynes" is a 15th-century Middle English translation of the Latin "Lilium medicinae," first completed in 1305. It is a translation of the major work of a significant medieval physician, Bernard of Gordon. His "Lilium medicinae" was translated and printed continuously over many centuries, until at least the late 17th century.

The text contains a wealth of medical recipes. In the Middle English translation, there are 360 recipes – clearly indicated with Rx in the text – and many thousands more ingredient names.

As a doctoral student, I prepared the first-ever edition of the "Lylye of Medicynes" and compared the recipes against four extant Latin copies of the "Lilium medicinae." This involved faithfully copying the Middle English text from the medieval manuscript, then editing that text for a modern reader, such as adding modern punctuation and correcting scribal errors. The "Lylye of Medicynes" is 245 folios, which equates to 600 pages of word-processed text.

I loaded the Middle English names of ingredients into a database, along with translations into modern equivalents, juxtaposed with relationships to recipe and disease. It is very time-consuming to format medieval data for processing with modern technologies. It also

takes time to translate medieval medical ingredients into modern equivalents, due in part to multiple synonyms as well as variations in modern scientific nomenclature for plants. This information has to be verified across many sources.

With our database, we aim to find combinations of ingredients that occur repeatedly and are specifically used to treat infectious diseases. To achieve this, we are employing some common tools of data science, such as network analysis, a mathematical method to examine the relationships between entries. Our team will then examine how these patterns may help us to use medieval texts as inspiration for lab tests of candidate "ancientbiotic" recipes.

In March, we tested a small portion of the database to ensure that the method we developed was appropriate for this data set. At present, the database contains only the 360 recipes indicated with Rx. Now that the proof-of-concept stage is complete, I will expand the database to contain other ingredients which are clearly in recipe format, but may not be marked with Rx.

We are specifically interested in recipes associated with recognizable signs of infection. With Bald's eyesalve, the combination of ingredients proved to be crucial. By examining the strength of ingredient relationships, we hope to find out whether medieval medical recipes are driven by certain combinations of antimicrobial ingredients.

The database could direct us to new recipes to test in the lab in our search for novel antibiotics, as well as inform new research into the antimicrobial agents contained in these ingredients on the molecular level. It could also deepen our understanding of how medieval practitioners "designed" recipes. Our research is in the beginning stages, but it holds exciting potential for the future.

Disclosure statement

Erin Connelly does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond the academic appointment above.

http://bit.ly/2oVBrIf

Amino acids in diet could be key to starving cancer

Cutting out certain amino acids -- the building blocks of proteins -- from the diet of mice slows tumour growth and prolongs survival, according to new research* published in Nature.

Researchers at the Cancer Research UK Beatson Institute and the University of Glasgow found that removing two non-essential amino acids -- serine and glycine -- from the diet of mice slowed the development of lymphoma and intestinal cancer.

The researchers also found that the special diet made some cancer cells more susceptible to chemicals in cells called reactive oxygen species.

Chemotherapy and radiotherapy boost levels of these chemicals in the cells, so this research suggests a specially formulated diet could make conventional cancer treatments more effective.

The next stage would be to set up clinical trials with cancer patients to assess the feasibility and safety of such a treatment.

Dr Oliver Maddocks, a Cancer Research UK scientist at the University of Glasgow, said: "Our findings suggest that restricting specific amino acids through a controlled diet plan could be an additional part of treatment for some cancer patients in future, helping to make other treatments more effective.

Professor Karen Vousden, Cancer Research UK's chief scientist and study co-author said: "This kind of restricted diet would be a short term measure and must be carefully controlled and monitored by doctors for safety. Our diet is complex and protein -- the main source of all amino acids - is vital for our health and well-being. This means that patients cannot safely cut out these specific amino acids simply by following some form of home-made diet."

Amino acids are the building blocks that cells need to make proteins. While healthy cells are able to make sufficient serine and glycine, cancer cells are much more dependent on getting these vital amino acids from the diet.

However, the study also found that the diet was less effective in tumours with an activated Kras gene, such as most pancreatic cancer, because the faulty gene boosted the ability of the cancer cells to make their own serine and glycine. This could help to select which tumours could be best targeted by diet therapy.

Dr Emma Smith, science communication manager at Cancer Research UK, said: "This is a really interesting look at how cutting off the supply of nutrients essential to cancer cell growth and division could help restrain tumours.

"The next steps are clinical trials in people to see if giving a specialised diet that lacks these amino acids is safe and helps slow tumour growth as seen in mice. We'd also need to work out which patients are most likely to benefit, depending on the characteristics of their cancer."

Maddocks et al. Modulating the therapeutic response of tumours to serine and glycine starvation. Nature

This research was funded by Cancer Research UK and the European Research Council.

http://bit.ly/2oVx1RN

How Bright Lights May Help Wake Patients from a Coma

Could shining bright lights on comatose patients to encourage their natural circadian rhythms help them awaken? A small study from Austria says yes.

By Christopher Wanjek | April 19, 2017 06:35pm ET

The body's ability to awaken from a coma after severe brain injury is tied to its maintenance of its natural circadian rhythms, according to the study, which included 18 patients in various unconscious states.

The scientists found that the chances of regaining consciousness may improve once the body falls back into its natural, healthy cycle of rising and falling body temperatures throughout the day.

The scientists also found that, in a subset of eight patients, two showed increased levels of consciousness after a treatment with carefully timed bright lights that were intended to trigger circadian rhythm activity and natural daily body-temperature fluctuations.

"[T]he closer the body-temperature patterns of a severely brain-injured person are to those of a healthy person's circadian rhythm, the better they scored on tests of recovery from coma," said study leader Christine Blume, a postdoctoral researcher at the Laboratory for Sleep & Consciousness Research at the University of Salzburg in Austria.

The new findings are very preliminary, but they suggest that monitoring circadian rhythms may one day serve as a diagnostic tool to monitor a comatose patient's chance for recovery, the researchers said. In addition, therapies aimed at tweaking those rhythms may ease patients into a more aware state, the research team wrote, in their study, published today (April 19) in the journal Neurology.

Circadian rhythms are daily cycles that tell the body when to eat, sleep or wake. They are set by environmental cues, such as daylight and nightfall. In healthy people, these rhythms include small changes in body temperature. Generally, body temperature increases during the day, with a peak at about 4 p.m., and decreases during the night, with the low point occurring at about 4 a.m., Blume said.

For the new study, the researchers monitored 18 people with severe brain injuries. Some were diagnosed with unresponsive wakefulness syndrome, also called a vegetative state. People in this state have awakened from a coma (which is a state of complete unconsciousness), and may open their eyes and have periods of sleep but otherwise remain unresponsive. Other patients in the study were in a minimally conscious state, meaning that they showed some signs of awareness.

For one week, the researchers continually monitored the body temperatures of these study participants with external skin sensors. They also evaluated the level of consciousness for each person with the Coma Recovery Scale, measuring things such as their responses to sound and their ability to open their eyes with or without stimulation. They found that the patients who scored better on that scale also had body temperature patterns that more closely aligned with a healthy 24-hour rhythm.

Then, the researchers tried to nudge eight of the patients back into a more natural temperature cycle. The researchers exposed these patients to cyclical periods of bright light stimulation over the course of a week. Two participants responded positively to this therapy, expressing increased signs of consciousness.

Blume cautioned, however, that her team's study sample, comprising only eight patients, was too small to show whether the light stimulation is a beneficial therapeutic tool to help patients with brain injuries regain alertness and awareness. "This is promising, but preliminary, and should be investigated in a larger cohort," Blume told Live Science.

"We indeed hope we can encourage the cycle to return," Blume added. "We therefore encourage doctors to create an environment in the hospital that mimics the natural cycle of light during the day and darkness during the night - especially, daylight lamps may be helpful."

http://bit.ly/2oVEDU7

Climate 420 Million Years Ago Poised for Comeback

Starting in the next century, atmospheric carbon levels could begin to approach those of hundreds of millions of years ago, and have their warming effect augmented by a brighter sun.

- **By Julia Rosen on April 19, 2017**

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"We're hearing a lot of the arguments against action on reducing CO2 being based on, 'well CO2 was higher in the past, so we don't have to worry about it.' Gavin Foster, a geochemist at the University of Southampton. But Foster says that's a flawed argument. For starters, just how far back in time do you have to look to find CO2 concentrations like what we expect to see in the future, and does it even make sense to compare the levels now and then?

To answer these questions, Foster and his colleagues reconstructed the history of atmospheric carbon dioxide for the last 420 million years. They compiled roughly 1,500 estimates of CO2 concentrations from 112 previous studies. When the researchers combined these data, they found that atmospheric carbon dioxide went up and down over time, but that, in general, it gradually declined from almost 3,000 parts per million down to less than 300 parts per million before humans started burning fossil fuels.

However, we have already started to reverse that trend. If we continue on a business-as-usual scenario, by the middle of this century, CO2 could reach levels not seen in 50 million years, according to Foster's reconstruction. That's long before humans evolved, back when the climate was much warmer and there were no large ice sheets at the poles. If we continue on that trajectory, by the year 2250, concentrations could approach what they were in the Triassic, 200 million years ago, when dinosaurs roamed the Earth.

But greenhouse gases aren't the only factor impacting Earth's climate. The sun also plays a major role. It's grown brighter over time, offsetting most of the cooling related to dropping CO2 levels, Foster's team found. And that fact has important implications for modern climate change. Because while we're headed toward a world with CO2 levels similar to what they were in the distant geologic past, it won't just be like rewinding the clock.

"So, because the sun is now brighter than it was 200 million years ago, or 400 million years ago, that radiative forcing from CO2 in the future is going to be that much more potent. And that, we thought, was quite a strong message that hadn't been noted before."

The findings are published in the journal *Nature Communications*. [Gavin L. Foster, Dana L. Royer and Daniel J. Lunt, Future climate forcing potentially without precedent in the last 420 million years]

Foster stresses that this isn't a vision of what will be, but what could be. "It's more of cautionary note that, in the absence of any action, we will be entering a world quite rapidly—in the next 150 years—where the climate is receiving a magnitude of forcing that, as far as we know, it hasn't received for 420 million years…it's outside the bounds at which the Earth is normally functioning. Doesn't sound like a good place to be to me."

http://bit.ly/2oVJXqV

Ancient enzyme protects lungs from common irritant produced by bugs and mold

Chitin-destroying enzymes reduce mortality from inflammatory lung disease in mice, study shows

The beetle's tough shell and the crab's sturdy armor both owe their strength to a compound called chitin (pronounced "KAI-tin"), one of the toughest known natural materials and also one of most common biological compounds on Earth. New research in mice by UC San Francisco scientists shows that the lungs secrete a specialized enzyme capable of destroying chitin, without which chitin particles inhaled from the environment can accumulate in the airways and trigger inflammatory lung disease.

Insects, molds and parasitic worms -- all common sources of allergies or inflammation -- produce billions of tons of chitin a year. Enzymes specialized for breaking down and disposing of chitin, called chitinases, evolved very early in the history of life, and are shared by most living things, from single-celled bacteria and fungi to humans. However, the function of these enzymes in mammals (which don't produce chitin of their own) has long been a mystery to science.

In a new study -- published online April 20, 2017, in Cell -- researchers in the lab of Richard M. Locksley, MD, the Marion and Herbert Sandler Distinguished Professor in Asthma Research at UCSF, have shown that mice that lack chitin-destroying enzymes soon accumulate chitin in their lungs even in sanitized laboratory environments.

These mice go on to develop severe inflammatory lung disease with age, but the team also found that they could dramatically restore lung function in these ailing mice by replacing the missing chitinase enzymes, either genetically or with drugs, a finding that may have implications for understanding and treating age-related lung disease in humans.

"We were very excited to see that improving chitinase activity quickly cleared up the signs of chronic inflammatory lung disease in these mice," said Locksley, who is the senior author of the new study. "To our knowledge this is the first demonstration that chitinases play a key role in preserving lung function in vertebrates."

Study strengthens link between chitin and age-related fibrotic lung disease

Many tissues develop fibrous scar tissue as part of their normal response to injury. These scars typically fade with time, but chronic irritation and inflammation can lead to extensive scarring of organs, known as fibrosis, which our bodies have increasing trouble repairing as we age.

Fibrosis is now seen by many researchers as a central underlying risk factor for many diseases of aging, and can eventually lead organs to fail completely.

In the case of fibrotic lung disease -- which is currently estimated to affect tens of thousands of Americans and appears to be on the rise as the population ages -- researchers suspect that a lifetime of environmental exposures trigger chronic inflammation and fibrosis of lung tissue. The resulting tissue damage frequently leads to death within five to 10 years after diagnosis.

Previous research by the Locksley lab had shown that chitin can trigger lung inflammation in mice, and the researchers had suspected that chronic inhalation of chitin particles over a lifetime (through exposure to dust mites or mold, for example) could play an important role in age-related fibrotic lung disease in humans.

In the new study, which was spearheaded by postdoctoral researcher Steven Van Dyken, PhD, researchers showed that specialized cells lining the airways of mice produce a chitinase enzyme called AMCase, which appears to play a key role in preventing chitin buildup in the mouse lung.

In mice genetically modified to lack this enzyme, chitin spontaneously built up in the airways and triggered a chronic inflammatory immune

response, as well as setting off cellular stress pathways that have previously been linked to lung disease in humans.

Because chitin is so ubiquitous in the environment, the researchers did not have to take any special steps to expose the mice to the compound -- even in highly sanitized laboratory settings, Van Dyken said:

"Chitin is a very common, very tough environmental particle found in our homes and workplaces. Our results clearly show that this stuff naturally gets into the lungs, and in the absence of chitinase enzymes that are capable of breaking it down, it accumulates. With time, chitin buildup can make animals pretty sick in ways that look remarkably like human fibrotic lung disease."

Chitin-clearing enzyme could help patients with fibrotic lung disease

The researchers found that young mice were able to tolerate chitin-triggered inflammation without exhibiting signs of lung dysfunction, but as adults these mice experienced rapidly declining health, including many signs of advancing fibrotic lung disease.

As a result, mice lacking AMCase died at a dramatically younger age than control mice. However, the researchers also found that the symptoms of lung disease in these mice could be rapidly cleared up by restoring chitinase activity genetically or with drugs.

The team also studied humans with inflammatory lung disease and found elevated levels of chitin in their lungs.

They found that humans also produce AMCase, though at considerably lower levels than laboratory mice. The researchers did not find evidence that chitinase activity was any lower than normal in patients with inflammatory lung disease, but they hypothesize a vicious cycle whereby aging-associated lung fibrosis damages the lung's natural ability to use AMCase and possibly other chitinases to clear chitin, allowing increasing chitin buildup to further exacerbate lung inflammation and fibrosis.

The new findings suggest that that enhancing chitinase activity with drugs could be a useful treatment for patients with inflammatory lung disease, the authors said.

"We're excited about potential for using these new insights to help find new treatments for flare-ups or worsening lung disease where people get very sick very quickly," Van Dyken said. "At the moment, there are really no good treatments, so if added doses of chitinase could help or lessen symptoms of fibrotic lung disease, we're really anxious to work towards making such a treatment available."

The study was supported by the National Institutes of Health (AI30663, AI26918, HL128903, HL107202), the Howard Hughes Medical Institute, the Nina Ireland Program for Lung Health, and the Sandler Asthma Basic Research Center at UCSF.

Additional authors on the paper were Hong-Erh Liang, PhD, Ram P. Naikawadi, PhD, Prescott G. Woodruff, MD, Paul J. Wolters, MD, and David J. Erle, MD.

http://bit.ly/2pq1Qzs

Risk of psychosis from cannabis use lower than originally thought, say scientists

Latest research shows that banning cannabis would have low impact on mental health

The research, published in the journal, Addiction, also showed for the first time that there is sufficient evidence to demonstrate that for patients who already have schizophrenia, cannabis makes their symptoms worse.

More than two million people in England and Wales used cannabis in the past 12 months, but the latest research shows that banning the drug would have low impact on mental health.

In order to prevent just one case of psychosis, more than 20,000 people would have to stop using cannabis, as shown by a previous study led by the University of Bristol.

This means that at a population level, an increased risk of psychosis from cannabis use is low, and those vulnerable to developing serious mental health problems is relatively rare. The research highlights, however, that more reviews on the impact of high potency cannabis is needed in order to make a full assessment of the risks.

Ian Hamilton, lecturer in mental health at the University of York, said: "The link between cannabis and psychosis has been an ongoing research topic since the drug became popular in the 1960s. Most of the

high profile studies that we have access to, however, are from a time when low potency cannabis was the norm, but today high potency is more common.

"High potency cannabis contains less of a chemical that is believed to protect against negative side-effects, such as psychosis, and a higher level of a chemical that can trigger psychosis. In this new study, we looked at both low and high potency, but it is clear that we need more evidence from high potency-related health cases to further investigate this link in modern-day users."

Despite this, the research was clear that the more high potency cannabis used, the higher the risk of developing mental health problems, even if they are relatively low in number. For those who already had schizophrenia cannabis exacerbated the symptoms.

The greatest risk to health, however, comes from cannabis users who combine the drug with tobacco. This exposes young people in particular to tobacco dependency at an early age, increasing the chances of cancers, infections, and other health-related issues.

Previous research at York showed that regulating cannabis use could result in more effective strategies aimed at helping drug users to access the right support and guidance. The policy report illustrated, however, that there is too much uncertainly around treatment regimes in an unregulated market to target the appropriate level of care.

Mr Hamilton said: "Regulation could help reduce the risks to health that cannabis use poses, as a regulated cannabis market would introduce some quality control.

"This would provide users with information about the strength of cannabis on offer, something they usually only discover after exposure in the current unregulated market.

"The public health message about the link between cannabis and psychosis has been a difficult one to communicate, but the evidence still points to the benefits of regulations that seek to advise on the greatest potential health risks, which currently arise due to tobacco use."

http://bit.ly/2ppUNGW

Is soda bad for your brain? (and is diet soda worse?)

Both sugary and diet drinks correlated with accelerated brain aging

Americans love sugar. Together we consumed nearly 11 million metric tons of it in 2016, according to the US Department of Agriculture, much of it in the form of sugar-sweetened beverages like sports drinks and soda.

Now, new research suggests that excess sugar -- especially the fructose in sugary drinks--might damage your brain. Researchers using data from the Framingham Heart Study (FHS) found that people who drink sugary beverages frequently are more likely to have poorer memory, smaller overall brain volume, and a significantly smaller hippocampus -- an area of the brain important for learning and memory.

But before you chuck your sweet tea and reach for a diet soda, there's more: a follow-up study found that people who drank diet soda daily were almost three times as likely to develop stroke and dementia when compared to those who did not.

Researchers are quick to point out that these findings, which appear separately in the journals Alzheimer's & Dementia and Stroke, demonstrate correlation but not cause-and-effect. While researchers caution against over-consuming either diet soda or sugary drinks, more research is needed to determine how -- or if -- these drinks actually damage the brain, and how much damage may be caused by underlying vascular disease or diabetes.

"These studies are not the be-all and end-all, but it's strong data and a very strong suggestion," says Sudha Seshadri, a professor of neurology at Boston University School of Medicine (MED) and a faculty member at BU's Alzheimer's Disease Center, who is senior author on both papers. "It looks like there is not very much of an upside to having sugary drinks, and substituting the sugar with artificial sweeteners doesn't seem to help."

"Maybe good old-fashioned water is something we need to get used to," she adds.

Matthew Pase, a fellow in the MED neurology department and an investigator at the FHS who is corresponding author on both papers, says that excess sugar has long been associated with cardiovascular and metabolic diseases like obesity, heart disease, and type 2 diabetes, but little is known about its long-term effects on the human brain. He chose to study sugary drinks as a way of examining overall sugar consumption. "It's difficult to measure overall sugar intake in the diet," he says, "so we used sugary beverages as a proxy."

For the first study, published in Alzheimer's & Dementia on March 5, 2017, researchers examined data, including magnetic resonance imaging (MRI) scans and cognitive testing results, from about 4,000 people enrolled in the Framingham Heart Study's Offspring and Third-Generation cohorts. (These are the children and grandchildren of the original FHS volunteers enrolled in 1948.) The researchers looked at people who consumed more than two sugary drinks a day of any type -- soda, fruit juice, and other soft drinks -- or more than three per week of soda alone. Among that "high intake" group, they found multiple signs of accelerated brain aging, including smaller overall brain volume, poorer episodic memory, and a shrunken hippocampus, all risk factors for early-stage Alzheimer's disease. Researchers also found that higher intake of diet soda--at least one per day--was associated with smaller brain volume.

In the second study, published in Stroke on April 20, 2017, the researchers, using data only from the older Offspring cohort, looked specifically at whether participants had suffered a stroke or been diagnosed with dementia due to Alzheimer's disease. After measuring volunteers' beverage intake at three points over seven years, the researchers then monitored the volunteers for 10 years, looking for evidence of stroke in 2,888 people over age 45, and dementia in 1,484 participants over age 60. Here they found, surprisingly, no correlation between sugary beverage intake and stroke or dementia. However, they found that people who drank at least one diet soda per day were almost three times as likely to develop stroke and dementia.

Although the researchers took age, smoking, diet quality, and other factors into account, they could not completely control for preexisting conditions like diabetes, which may have developed over the course of the study and is a known risk factor for dementia. Diabetics, as a group, drink more diet soda on average, as a way to limit their sugar consumption, and some of the correlation between diet soda intake and dementia may be due to diabetes, as well as other vascular risk factors. However, such preexisting conditions cannot wholly explain the new findings.

"It was somewhat surprising that diet soda consumption led to these outcomes," says Pase, noting that while prior studies have linked diet soda intake to stroke risk, the link with dementia was not previously known. He adds that the studies did not differentiate between types of artificial sweeteners and did not account for other possible sources of artificial sweeteners. He says that scientists have put forth various hypotheses about how artificial sweeteners may cause harm, from transforming gut bacteria to altering the brain's perception of "sweet," but "we need more work to figure out the underlying mechanisms."

http://bit.ly/2pSAmzv

New data unearths pesticide peril in beehives

Honeybees create honey in their hive through the topped-out combs, and they keep beebread -- their food -- in the other combs

Emma Mullen

Honeybees - employed to pollinate crops during the blooming season - encounter danger due to lingering and wandering pesticides, according to a new Cornell University study that analyzed the bee's own food.

Researchers used 120 pristine honeybee colonies that were placed near 30 apple orchards around New York state. After allowing the bees to forage for several days during the apple flowering period, the scientists examined each hive's "beebread" - the bees' food stores made from gathered pollen - to search for traces of pesticides.

In 17 percent of colonies, the beebread revealed the presence of acutely high levels of pesticide exposure, while 73 percent were found to have chronic exposure.

"Surprisingly, there is not much known about the magnitude of risk or mechanisms of pesticide exposure when honeybees are brought in to pollinate major agricultural crops," said lead author Scott McArt, assistant professor of entomology at Cornell. "Beekeepers are very concerned about pesticides, but there's very little field data. We're trying to fill that gap in knowledge, so there's less mystery and more fact regarding this controversial topic."

More than 60 percent of the found pesticides were attributed to orchards and surrounding farmland that were not sprayed during the apple bloom season, according to the study. McArt said that persistent insecticides aimed at other crops may be surrounding the orchards. In addition, pre-bloom sprays in orchards may accumulate in nearby flowering weeds.

"We found risk was attributed to many different types of pesticides. Neonicotinoids were not the whole story, but they were part of the story." he said. "Because neonicotinoids are persistent in the environment and accumulate in pollen and nectar, they are of concern. But one of our major findings is that many other pesticides contribute to risk."

The study, "High Pesticide Risk to Honeybees Despite Low Focal Crop Pollen Collection During Pollination of a Mass Blooming Crop was published April 19 in Nature Scientific Reports.

The New York Farm Viability Institute funded this research.

http://bit.ly/2p6da0N

Why Some Creative People Are More Attractive

Showing a bit of creativity on your online dating profile could make you appear more attractive to potential dates, a new study suggests.

By Sara G. Miller, Staff Writer | April 20, 2017 02:17pm ET

In the study, people were asked to rate the attractiveness of individuals in photos who were said to have written a short piece of creative writing to display their creativity.

The findings suggest that "creativity can enhance your attractiveness both as a potential date and as a potential social partner [or] same-sex friend," said study author Christopher Watkins, a lecturer in psychology at Abertay University in Scotland. But the attractiveness-boosting effects of creativity don't work for everybody.

Rather, the findings also suggest the effects of creativity "tend to be stronger for people with average-looking faces than people with very good-looking faces," Watkins told Live Science.

In addition, in some cases, the men got a larger boost in their attractiveness from being creative than women did, according to the study, which was published Wednesday (April 19) in the journal Royal Society Open Science.

This finding — that creativity may be more beneficial for men — makes sense considering previous findings: A man may use "creative displays" to "signal" his desirable qualities, such as intelligence, to a potential female date, Watkins said.

In the study, Watkins did three experiments, all of which involved asking people to rate the overall attractiveness of people in photos. The specific details of each experiment varied slightly, but in general, photos of people, who varied in their levels of physical attractiveness, were paired with short pieces of creative writing, which the person in the photo was said to have written.

To simplify matters, photos were either considered "attractive" or "less attractive" (in other words, good-looking or average-looking), and the creative writing "creative" or "less creative."

For example, a photo of a man who was considered good-looking was paired with a short story that was considered creative, according to the study. Or, the same photo was paired with a short story that was rated as "less creative."

A group of young adults, both men and women, was asked to rate the overall attractiveness of the individual, according to the study.

When photos of men were paired with a creative piece of writing, the people in the study rated them, on average, as attractive overall — regardless of whether the photo was that of a good-looking man or an average-looking man, Watkins found. In other words, creativity helped boost average-looking men's attractiveness.

But for women, in two of the experiments, it was the physical attractiveness rating that played more a role in their overall attractiveness, according to the study: Women who were deemed good-looking were seen as more attractive overall, regardless of their level of creativity.

Watkins also found, unexpectedly, that creativity made women with average-looking photos even less attractive, and didn't boost the attractiveness of women who were already considered good-looking.

The finding that creativity made certain women less attractive may suggest that creative women who are considered average-looking are subtly put down, Watkins wrote.

He wrote that the finding should be taken lightly, however: In one of the three experiments, creativity appeared to enhance the attractiveness of both men and women who were considered average-looking, while it didn't boost the attractiveness of men and women who were already considered good-looking.

In other words, in this experiment, "creativity enhanced the appeal of both men and women with average-looking faces," Watkins said.

http://bit.ly/2ppYYT8

Kids Under 12 Shouldn't Take Codeine Drugs, FDA Says

Children younger than 12 should not take codeine, a drug found in some cough and pain medicines

By Rachael Rettner, Senior Writer | April 20, 2017 03:45pm ET

Children younger than 12 should not take codeine, a drug found in some cough and pain medicines, according to new rules from the Food and Drug Administration (FDA) that further restrict the use of this drug in kids. Parents should read the ingredient labels on pain and cough medicines to make sure that they don't contain codeine or another medication called tramadol before giving the medication to children, the agency said.

The FDA said today (April 20) that it is making changes to its requirements for the labels of codeine-containing drugs because of reports that some children experience life-threatening breathing problems, and even die, after taking medicines that contain codeine. From 1969 to 2015, the FDA received 64 reports of serious breathing problems tied to the use of codeine-containing medicines in children. Those cases included 24 deaths. Most cases of serious side effects tied to the drug occurred in children under 12 years old, the FDA said.

In addition to the new warnings on codeine for kids, the FDA also warned against the use of another pain-relieving drug called tramadol in children under 12, and against the use of either drug by women who are breastfeeding.

"Our decision today was made based on the latest evidence and with this goal in mind: keeping our kids safe," Dr. Douglas Throckmorton, deputy center director for regulatory programs at the FDA's Center for Drug Evaluation and Research, said in a statement.

Both codeine and tramadol are types of opioid medications. Codeine is found in some over-the-counter cough medicines, as well as in prescription pain and cough medicines. Tramadol is found in some prescription pain medicines and is approved for use only in adults.

In 2013, the FDA warned against one common use among children of medicines that contain codeine: as a pain reliever after surgery done to remove tonsils or adenoids. Today's new warning is broader because it says codeine-containing drugs should not be used to treat pain or cough due to any cause in kids under 12.

The FDA also said today that codeine should not be used in teens ages 12 to 18 if they are obese or have conditions such as obstructive sleep apnea or severe lung disease, which can increase the risk of serious breathing problems.

Parents can speak with their health care providers about alternatives for cough or pain management in children, the agency said.

Mothers who are breastfeeding are also advised not to take codeine or tramadol, because the drugs may lead to serious side effects in some infants, including excessive sleepiness, serious breathing problems and deaths, the FDA said.

These side effects happen because some people are "ultrarapid metabolizers" of codeine or tramadol, Throckmorton said. This means they break down the drugs much faster than is typical, which leads to dangerously high levels of the active drug in their bodies, he said.

http://bit.ly/2p9MmyJ

Potential anti-aging component of cord blood refreshes minds of old mice

The findings are just in mice, and debate swirls around the anti-aging pursuits.

Beth Mole - 4/20/2017, 11:14 PM

A protein found in the plasma of human umbilical cord blood perked up the memories of elderly mice, researchers reported Wednesday in *Nature*.

Researchers at Stanford had first noted that injecting middle-aged mice with plasma from human cord blood could boost activity in their hippocampi, an area of the brain critical for creating and banking memories. The mice also got better at memory tests. After some analysis, the researchers focused in on one plasma protein called TIMP2. With injections of just that protein, the senior rodents again improved on memory and learning tests (though not quite to the extent that mice given whole plasma did). Still, they became faster at navigating a maze and restored nesting skills they lost with age, and they could better remember a chamber where their feet get zapped with a slight electrical shock.

TIMP2 is an intriguing find in the pursuit of anti-aging therapies; TIMP2 levels in the blood of mice and men start high in life but then wane in later years. And the researcher found that blocking TIMP2 in young mice seemed to prematurely age their memories.

But the findings are still only in mice—they may mean nothing for humans, and TIMP2 treatments may be unsafe in older adults. And debate still swirls around how to pursue anti-aging research and what this new finding might mean. For instance, as Irina Conboy, a researcher who studies aging at the University of California, Berkeley noted to *NPR*, TIMP2 levels are elevated in people with Alzheimer's disease. And it's still unclear how TIMP2 might tinker with our brains.

Age-old pursuit

The new finding is just the latest in decades of work trying to find a remedy for the assault of time on the body. Long ago, researchers stitched mice together, connecting their circulatory systems, to show that young blood pumped into old mice could rejuvenate them. And more recent work had tracked the benefits down to mysterious contents of plasma.

Back in 2014, researchers reported data suggesting that another plasma component, called GDF11, seemed to spur the growth of blood vessels and neural stem cells.

The new findings don't negate or conflict with the findings of GDF11, the authors of the new study as well as those of the GDF11 work said. Harvard neuroscientist Lee Rubin, a coauthor of some of the GDF11 work, told *Science* that the new data suggests that "it isn't just one thing. A lot of individual factors in blood can improve function." (Rubin is an advisor to a company called Alkahest, which is studying

using plasma to treat Alzheimer's and was cofounded by one of the authors of the new study, Stanford's Tony Wyss-Coray.)

Stanford neuroscientist Joseph Castellano, lead author of the new study, told *NPR*, "The only thing, of course, is that it's a mouse experiment, and mouse experiments often don't actually translate faithfully into the human setting."

And other researchers, such as Berkeley's Conboy, think that the Castellano team is looking at things the wrong way entirely—it may not be that old blood lacks good components but that it may contain accumulated bad stuff. In her work, she hasn't seen any positive brain effects of swapping old blood for new blood.

"We have hundreds of proteins that change with age," she said. If there are any therapies in the (distant) future that can turn back the clock, they will likely involve fiddling with several of them.

Nature, *2017. DOI: 10.1038/nature22067 (About DOIs).*

http://bit.ly/2pSKV5r

Displaying lab test costs in health records doesn't deter doctors from ordering them

As hospitals work to reduce unnecessary costs, study on price transparency suggests displaying Medicare allowable fees does not affect behavior

PHILADELPHIA - Patients are stuck for a blood draw almost every day they are admitted to a hospital. Lab tests are one of the most common orders placed by doctors, but research indicates that nearly one-third of these tests are not needed. Hospitals nationwide are seeking ways to use price transparency - displaying the price of lab tests at the time when doctors are placing the order - to nudge doctors to consider whether the benefits are worth the cost. But, results of a new study show that simply displaying the Medicare allowable fees did not have an overall impact on how clinicians ordered these tests. The results, from the Perelman School of Medicine at the University of Pennsylvania, are published today in JAMA Internal Medicine and presented at the Society of General Internal Medicine annual meeting in Washington, DC.

"Price transparency is increasingly being considered by hospitals and other health care organizations as a way to nudge doctors and patients toward higher-value care, but the best way to design these types of interventions has not been well-tested," said senior author Mitesh S. Patel, MD, MBA, MS, an assistant professor of Medicine and Health Care Management in Penn's Perelman School of Medicine and the Wharton School, and director of the Penn Medicine Nudge Unit. "Our findings indicate that price transparency alone was not enough to change clinician behavior and that future price transparency interventions may need to be better targeted, framed, or combined with other approaches to be more successful."

In the new study - the largest of its kind - researchers randomly assigned 60 groups of inpatient laboratory tests to either display Medicare allowable fees in the patient's electronic health record (intervention arm), or not (control arm). The randomized clinical trial was conducted at three hospitals within the University of Pennsylvania Health System over a one-year period and compared changes in the number of tests ordered per patient per day, and associated fees, for more than 98,000 patients (totaling over 142,000 admissions).

Results of the study showed that in the year prior to the study, when cost information was not displayed, the average number of tests and associated fees ordered per patient per day was 2.31 tests totaling $27.77 in the control group, and 3.93 tests totaling $37.84 in the intervention group. After the intervention, when cost information was displayed for the intervention group, researchers noted the average number of tests and associated fees ordered per patient per day did not change significantly and was 2.34 tests totaling $27.59 in the control group, and 4.01 tests totaling $38.85 in the intervention group.

Though the study found no overall effect, the authors noted important findings in specific patient groups that have implications for how to

improve price transparency in the future. For example, there was a slight decrease test ordering for patients admitted to the Intensive Care Unit - an environment in which doctors are making rapid decisions and may be more exposed to the price transparency intervention. The authors also found that the most expensive tests were ordered less and the cheaper tests were ordered more, suggesting that future interventions might be more successful if they are better designed to framed relative pricing.

"Electronic health records are constantly being changed, from how choices are offered to the way information is framed," said C. William Hanson, MD, chief medical information officer for the University of Pennsylvania Health System, and a member of the steering committee for the Penn Medicine Nudge Unit. "By systematically testing these approaches through real-world experiments, health systems can leverage this new evidence to continue to improve the way care is delivered for our patients."

"Price transparency continues to be an important initiative, but the results of this clinical trial indicate that these approaches need to be better designed to effectively change behavior" said Patel, who is also a staff physician at the Crescenz VA Medical Center, and whose work is supported by the Penn Center for Health Incentives and Behavioral Economics.

Other Penn authors on the study include Jennifer S. Myers, Dylan S. Small, Irving Nachamkin, Dana Murray, Gregory Kurtzman, Jingsan Zhu, Wenli Wang, Deborah Mincarelli, Daniel Danoski, Brian P. Wells, Jeffrey S. Berns, Patrick J. Brennan, C. William Hanson, and C. Jessica Dine. Lead author Mina Sedrak conducted the study during a fellowship in Hematology-Oncology at Penn and is currently at the City of Hope.

http://bbc.in/2pcmHW6

New evidence in France of harm from epilepsy drug valproate

A drug given to pregnant women for epilepsy and bipolar disorder caused "serious malformations" in up to 4,100 children, a French study suggests.

Mothers treated with valproate for epilepsy were up to four times likelier to give birth to a malformed child, the preliminary study found.

Introduced in France in 1967, valproate is prescribed widely worldwide. Doctors in France are now advised not to give it to girls, women of childbearing age and pregnant women.

The drug's manufacturer, Sanofi, responded in a statement that it had been "totally transparent with health authorities". "We are aware of the painful situation confronting the families of children showing difficulties that may have a link with the anti-epileptic treatment of their mother during pregnancy," it said. Some of those affected say France and the company were too slow to warn of side-effects.

The risk of birth defects associated with valproate, marketed as Epilim, Depakine, Depakote and Stavzor among other names, has been known since the 1980s, especially for spina bifida. In the UK, the National Health Service (NHS) issued an alert earlier this month saying valproate should only be given to girls and women of childbearing age under specialist supervision and only when other medications had been found not to work.

Counting the cost: James Reynolds, BBC News, Paris

Valproate - prescribed in France, the UK and many other countries - now carries a clear warning : serious risk of birth defects.

In France, it turns out that it took far too long for this danger to become apparent. The drug was first introduced here in 1967. By the early 1980s, there were fears that the drug might be a factor in birth defects, including spina bifida, but prescription rules were only finally tightened in 2014.

France is now working out the damage caused during this long period. Families of children with birth defects want to know why it took so long for this country's authorities to identify the serious risks associated with taking the drug during pregnancy.

'Very high'

According to the new report (in French) by France's National Agency for the Safety of Medicines (ANSM), between 2,150 and 4,100 children suffered severe malformations linked to the drug.

"The study confirms the highly teratogenic [capable of causing birth defects] nature of valproate," Mahmoud Zureik, ANSM's scientific director and co-author of the report, told AFP news agency.

"The figure of about 3,000 severe malformations is very high."

Types of birth defects attributed to the drug include spina bifida - which occurs when a section of the spinal column does not form properly - and defects of the heart and genital organs.

The risk of autism and developmental problems was also found to be higher, and will be explored in a follow-up report due later this year.

Women treated for bipolar disorder were at a lower risk than those treated for epilepsy, the study found, but were still twice as likely to give birth to children with major birth defects.

According to ANSM, this is because women treated for bipolar disorder were less exposed to the drug. In its alert issued on 6 April, the NHS noted that valproate was an "effective medication used to treat epilepsy and bipolar disorder" but added that it was also aware of its "off-label" use to treat migraine or chronic pain.

Lawsuit

Some families of children with birth defects born to women who took the drug while pregnant - grouped under an umbrella association known as APESAC (in French) - have sued Sanofi, saying that it did not adequately warn about the risks.

"The number of victims is potentially huge," APESAC president Marine Martin told AFP. "We need to take into account children with malformations and autism, as well as families that lost a baby due to treatment during pregnancy." Ms Martin says two of her children, a girl and a boy, suffered physical defects brought on by valproate.

French MP Gerard Bapt welcomed the report. "It now appears fundamental that valproate in all its forms should not be prescribed for women of child-bearing age," he said. Medically necessary exceptions, he added, should be rare and accompanied by "mandatory contraceptive use".

http://bit.ly/2olw5Hv

'Connshing syndrome' named as a new cause of high blood pressure

Research led by scientists at the University of Birmingham has revealed a new cause of high blood pressure which could lead to major changes in managing the disease.

High blood pressure, also known as hypertension, often goes unnoticed but if left untreated can increase the risk of heart attack and stroke. Studies estimate that one in four adults suffer from hypertension, but most patients have no identifiable cause for the condition. However, it is known that in up to 10 per cent of hypertensive patients the overproduction of the adrenal hormone aldosterone - a condition known as primary aldosteronism or Conn syndrome - is the cause of disease.

Now the University of Birmingham-led study has, for the first time, made the important discovery that a large number of patients with Conn syndrome do not only overproduce aldosterone but also the stress hormone cortisol.

Professor Wiebke Arlt, Director of the Institute of Metabolism and Systems Research (IMSR) at the University of Birmingham, said: "Our findings show that the adrenal glands of many patients with Conn syndrome also produce too much cortisol, which finally explains puzzling results of previous studies in Conn patients.

"These previous studies had found increased rates of type 2 diabetes, osteoporosis and depression in Conn patients -- problems typically caused by overproduction of cortisol, also termed Cushing syndrome, and not by too much aldosterone."

The authors of the University of Birmingham-led study, conducted in collaboration with a group of scientists from Germany, decided to name this new cause of hypertension - the combined overproduction of aldosterone and cortisol -- as Connshing syndrome.

At present, many Conn syndrome patients are treated with drugs that are directed against the adverse effects of aldosterone. However, this leaves the cortisol excess untreated.

Second author of the study, published in JCI Insight, Katharina Lang - an academic clinical lecturer at IMSR -- said: "These findings are very likely to change clinical practice.

"Patients will now need to undergo more detailed assessment to clarify whether they suffer from Conn or Connshing syndrome.

"Previously, patients with Conn syndrome were never assessed for the overproduction of other hormones but this will now change thanks to the results of this study.

"Also, researchers now will need to investigate whether treating the Connshing patients with an additional drug, which counteracts the cortisol excess, will improve their health outcomes."

http://bbc.in/2oCoKiQ

Early hip fracture surgery will save hundreds of lives

Hundreds of lives could be saved if patients with hip fractures were operated on in under 24 hours, a new study reveals.

Researchers in Bristol found 8% more patients died after 30 days if they were operated on between 24 and 36 hours after admission to hospital. The delay is thought to have caused 670 excess deaths in four years. Project leader Timothy Chesser said it was the "first time" the benefits of early surgery had been revealed.

Data was collected by a team at Southmead Hospital from the National Hip Fracture Database, the largest such list in the world.

The study focussed on 241,446 patients across England and Wales who were admitted to hospitals with hip fractures between January 2011 and December 2014, and the mortality rate for these patients 30 days after they were admitted.

Improved outcomes

Guidance issued by the National Institute for Health and Clinical Excellence in 2011 called for patients to be operated on either the same day, or the day after, hospital admission.

But the new report says that even earlier surgery can improve outcomes for elderly patients who are often frail, with multiple medical problems.

"We found 8% more patients died if they were operated on between 24 and 36 hours compared to those given surgery within 24 hours, and the risk increased to 20% for those receiving surgery after 48 hours," said Adrian Sayers, the lead author on the paper.

Timothy Chesser, the clinical lead of the research project, said early surgery was not advisable for every patient, but was beneficial in the majority of cases. "We have shown for the first time that early surgery is much better for patients," he said. "The caveat is some of these patients are very sick and would benefit from greater time to get better before surgical procedures."