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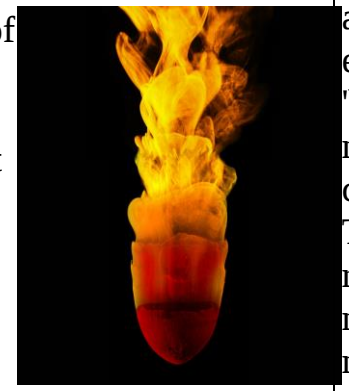
What gives meteorites their shape? New research uncovers a 'Goldilocks' answer

Meteoroids coming from outer space are randomly shaped, but many of these, which land on earth as meteorites, are found to be carved into cones.

Scientists have now figured out how the physics of flight in the atmosphere leads to this transformation.

The progression, discovered through a series of replication experiments in New York University's Applied Mathematics Lab, involves melting and erosion during flight that ultimately results in an ideal shape as meteoroids hurl through the atmosphere. The findings are reported in the journal Proceedings of the National Academy of Sciences (PNAS).



Meteoroids coming from outer space are randomly shaped, but many of these, which land on earth as meteorites, are found to be carved into cones. To explore the forces that produce cone-shaped meteorites, researchers replicated meteoroids traveling through outer space: clay objects, attached to a rod, served as 'mock meteorites' that erode while moving through water.

Credit: NYU's Applied Mathematics Laboratory

"Slender or narrow cones flip over and tumble, while broad cones flutter and rock back and forth, but we discovered between these are cones that fly perfectly straight with their point or apex leading," explains Leif Ristroph, an assistant professor in NYU's Courant Institute of Mathematical Sciences, who led the study. "Amazingly, these 'Goldilocks' cones of the 'just right' angles exactly match the shapes of eroded clay resulting from our experiments and of actual conical meteorites."

"By showing how the shape of an object affects its ability to fly straight, our study sheds some light on this long-standing mystery about why so many meteorites that arrive on Earth are cone shaped," he adds.

The forces behind the peculiar shapes of meteorites, which are meteors or "shooting stars" that survive the fiery flight through the atmosphere and land on Earth, have long been a mystery.

"The shapes of meteorites are not as they are in space, since they are actually melted, eroded, and reshaped by atmospheric flight," explains Ristroph. "While most meteorites are randomly shaped 'blobs,' surprisingly many--some say about 25 percent--are 'oriented meteorites,' and complete samples of these look almost like perfect cones."

To explore the forces that produce cone-shaped meteorites, the researchers, who included Jun Zhang, a professor of physics and mathematics at the Courant Institute and NYU Shanghai, replicated meteoroids traveling through outer space: clay objects, attached to a rod, served as "mock meteorites" that erode while moving through water.

The clay objects held in the water current were eventually carved into cones of the same angularity as conical meteorites--not too slender and not too broad.

However, the researchers recognized the limitations of this experimental design: unlike the clay objects, actual flying meteoroids are not held in a fixed position and can freely rotate, tumble, and spin. This distinction raised the following question: what allows meteorites to keep a fixed orientation and successfully reach Earth?

The team, which also included Khunsa Amin and Kevin Hu, both NYU undergraduates, and Jinzi Huang, an NYU doctoral student at the time of the work, then conducted additional experiments in which they examined how different shaped cones fell through water.

Here they discovered that narrow cones flip over while broad cones flutter. However, in between these two are "just right" cone shapes that fly straight.

"These experiments tell an origin story for oriented meteorites: the very aerodynamic forces that melt and reshape meteoroids in flight also stabilize its posture so that a cone shape can be carved and ultimately arrive on Earth," observes Ristroph. "This is another interesting message we're learning from meteorites, which are scientifically important as 'alien visitors' to Earth whose composition and structure tell us about the universe."

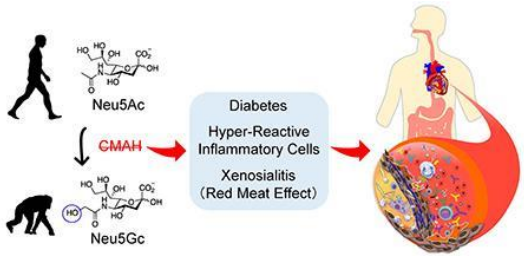
The research was supported by a grant from the National Science Foundation (CBET-1805506).

http://bit.ly/2OlkHZB

Evolutionary gene loss may help explain why only humans are prone to heart attacks

Loss of a gene 2 to 3 million years ago could be linked to why coronary events are so common in humans and so rare in other animals

Researchers at University of California San Diego School of Medicine say the loss of a single gene two to three million years ago in our ancestors may have resulted in a heightened risk of cardiovascular disease in all humans as a species, while also setting up a further risk for red meat-eating humans. The findings are published July 22, 2019 in *PNAS*.



The loss of NeuG5c in humans (retained in other primates) increases atherosclerosis risk by multiple mechanisms, including intrinsic factors such as heightened inflammatory response and hyperglycemia and extrinsic factors such as red meat-derived Neu5Gc-induced xenosialitis. **Kunio Kawanishi**

Atherosclerosis -- the clogging of arteries with fatty deposits -- is the cause of one-third of deaths worldwide due to cardiovascular disease. There are many known risk factors, including blood cholesterol, physical inactivity, age, hypertension, obesity and smoking, but in roughly 15 percent of first-time cardiovascular disease events (CVD) due to atherosclerosis, none of these factors apply.

A decade ago, Nissi Varki, MD, professor of pathology at UC San Diego School of Medicine, with co-author Ajit Varki, MD, Distinguished Professor Of Medicine and Cellular And Molecular Medicine, and colleagues noted that naturally occurring coronary heart attacks due to atherosclerosis are virtually non-existent in other mammals, including closely related chimpanzees in captivity which share human-like risk factors, such as high blood lipids, hypertension and physical inactivity. Instead, chimp "heart attacks" were due to an as-yet unexplained scarring of the heart muscle.

In the new study, the Varkis, and Philip Gordts, PhD, assistant professor of medicine, and others report that mice modified to be deficient (like humans) in a sialic acid sugar molecule called Neu5Gc showed a significant increase in atherogenesis compared to control mice, who retain the CMAH gene that produces Neu5Gc.

The researchers -- members of the Glycobiology Research and Training Center and/or the Center for Academic Research and Training in Anthropogeny at UC San Diego -- believe a mutation that inactivated the CMAH gene occurred a few million years ago in hominin ancestors, an event possibly linked to a malarial parasite that recognized Neu5Gc.

In their findings, the research team said human-like elimination of CMAH and Neu5Gc in mice caused an almost 2-fold increase in severity of atherosclerosis compared to unmodified mice.

"The increased risk appears to be driven by multiple factors, including hyperactive white cells and a tendency to diabetes in the

human-like mice," said Ajit Varki. "This may help explain why even vegetarian humans without any other obvious cardiovascular risk factors are still very prone to heart attacks and strokes, while other evolutionary relatives are not."

But in consuming red meat, humans are also repeatedly exposed to Neu5Gc, which researchers said prompts an immune response and chronic inflammation they call "xenosialitis." In their tests, human-like mice modified to lack the CMAH gene were fed a Neu5Gc-rich, high-fat diet and subsequently suffered a further 2.4-fold increase in atherosclerosis, which could not be explained by changes in blood fats or sugars.

"The human evolutionary loss of CMAH likely contributes to a predisposition to atherosclerosis by both intrinsic and extrinsic (dietary) factors," wrote the authors, "and future studies could consider using this more human-like model."

In previous work, the Varkis and colleagues have shown that dietary Neu5Gc also promotes inflammation and cancer progression in Neu5Gc-deficient mice, suggesting that the non-human sugar molecule, which is abundant in red meat, may at least partially explain the link between high consumption of red meat and certain cancers. Interestingly, the evolutionary loss of the CMAH gene appears to have produced other significant changes in human physiology, including reduced human fertility and enhanced ability to run long distances.

Co-authors include: Chirag Dhar and Raymond Do, UC San Diego and first author Kunio Kawanishi, UC San Diego, now at University of Tsukuba, Japan.

http://bit.ly/2MlPOBX

Researchers find widespread aspirin use despite few benefits, high risks

2019 guidelines now explicitly recommend against aspirin use among those over the age of 70 who do not have existing heart disease or stroke

BOSTON - Medical consensus once supported daily use of low dose aspirin to prevent heart attack and stroke in people at increased risk for cardiovascular disease (CVD). But in 2018, three major clinical trials cast doubt on that conventional wisdom, finding few benefits and consistent bleeding risks associated with daily aspirin use. Taken together, the findings led the American Heart Association and American College of Cardiology to change clinical practice guidelines earlier this year, recommending against the routine use of aspirin in people older than 70 years or people with increased bleeding risk who do not have existing cardiovascular disease.

Aspirin use is widespread among groups at risk for harm including older adults and adults with peptic ulcers - painful sores in the lining of the stomach that are prone to bleeding that affect about one in ten people. In a research report published today in Annals of Internal Medicine, researchers from Beth Israel Deaconess Medical Center (BIDMC) report on the extent to which Americans 40 years old and above use aspirin for primary prevention of cardiovascular disease.

"Although prior American Heart Association and American College of Cardiology guidelines recommended aspirin only in persons without elevated bleeding risk, the 2019 guidelines now explicitly recommend against aspirin use among those over the age of 70 who do not have existing heart disease or stroke," said senior author Christina C. Wee, MD, MPH, a general internist and researcher at BIDMC and Associate Professor of Medicine at Harvard Medical School. "Our findings suggest that a substantial portion of adults may be taking aspirin without their physician's advice and potentially without their knowledge."

Using data from the 2017 National Health Interview Survey (NHIS), a nationally representative survey of U.S. households conducted before the release of the new guidelines, Wee and colleagues characterized aspirin use for primary prevention of CVD. The team

found that about a quarter of adults aged 40 years or older without cardiovascular disease - approximately 29 million people - reported taking daily aspirin for prevention of heart disease. Of these, some 6.6 million people did so without a physician's recommendation.

Concerningly, nearly half of adults 70 years and older without a history of heart disease or stroke reported taking aspirin daily. The authors noted that a history of peptic ulcer disease - another contraindication for the routine use of aspirin - was not significantly associated with lower aspirin use as one would have expected.

"Our findings show a tremendous need for health care practitioners to ask their patients about ongoing aspirin use and to advise them about the importance of balancing the benefits and harms, especially among older adults and those with prior peptic ulcer disease," said lead author Colin O'Brien, MD, a senior internal medicine resident at BIDMC and fellow at Harvard Medical School. Coauthor, Stephen Juraschek, MD, PhD, a primary care physician at BIDMC, cautions that "these findings are applicable to adults who do not have a history of cardiovascular disease or stroke. If you are currently taking aspirin, discuss it with your doctor to see if it is still needed for you."

Juraschek, who is also an Assistant Professor at Harvard Medical School, is supported by grant K23HL135273 from the National Heart, Lung and Blood Institute of the National Institutes of Health. Disclosures can be viewed online at http://www.acponline.org.

http://bit.ly/32Vfivt

New study explains the molecular mechanism for the therapeutic effects of cilantro

Herbs, including cilantro, have long been used as folk remedies

Herbs, including cilantro, have a long history of use as folk medicine anticonvulsants. Until now, many of the underlying mechanisms of how the herbs worked remained unknown. In a new study, researchers uncovered the molecular action that enables cilantro to effectively delay certain seizures common in epilepsy and other diseases.

The study, published in FASEB Journal, explains the molecular action of cilantro (Coriandrum sativum) as a highly potent KCNQ channel activator. This new understanding may lead to improvements in therapeutics and the development of more efficacious drugs.

"We discovered that cilantro, which has been used as a traditional anticonvulsant medicine, activates a class of potassium channels in the brain to reduce seizure activity," said Geoff Abbott, PhD, professor of physiology and biophysics at the UCI School of Medicine and principal investigator on the study. "Specifically, we found one component of cilantro, called dodecenal, binds to a specific part of the potassium channels to open them, reducing cellular excitability. This specific discovery is important as it may lead to more effective use of cilantro as an anticonvulsant, or to modifications of dodecenal to develop safer and more effective anticonvulsant drugs."

Researchers screened cilantro leaf metabolites, revealing that one - the long-chain fatty aldehyde (E)-2-dodecenal - activates multiple potassium channels including the predominant neuronal isoform and the predominant cardiac isoform, which are responsible for regulating electrical activity in the brain and heart. This metabolite was also found to recapitulate the anticonvulsant action of cilantro, delaying certain chemically-induced seizures. The results provide a molecular basis for the therapeutic actions of cilantro and indicate that this ubiquitous culinary herb is surprisingly influential upon clinically important potassium channels.

Documented use of botanical folk medicines stretches back as far as recorded human history. There is DNA evidence, dating back 48,000 years, that suggests the consumption of plants for medicinal use by Homo neanderthalensis. Archaeological evidence, dating

back 800,000 years, suggests a non-food use of plants by Homo erectus or similar species. Today, evidence of the efficacy of botanical folk medicines ranges from anecdotal to clinical trials. In many cases, these "medicines" are currently consumed, often on a large scale, as foodstuffs or food flavoring. Cilantro, known as coriander in the UK, is one example. Cilantro has been consumed by human beings for at least 8,000 years. It was found in the tomb of Tutankhamen and is thought to have been cultivated by the ancient Egyptians.

"In addition to the anticonvulsant properties, cilantro also has reported anti-cancer, anti-inflammatory, anti-fungal, antibacterial, cardioprotective, gastric health and analgesic effects," said Abbott. "And, the best part is it tastes good!"

This study was supported by the National Institutes of Health, National Institute of General Medicine Sciences and National Institute of Neurological Disorders and Stroke.

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How fat prawns can save lives

Small-scale farming of freshwater crustaceans could be a win-win for communities where schistosomiasis is common

Berkeley -- Before bite-sized crustaceans like crayfish, shrimp and prawns land on our dinner plates, they first have to get fat themselves -- and it turns out they relish the freshwater snails that transmit the parasite that causes schistosomiasis, the second most devastating parasitic disease worldwide, after malaria.

New research led by University of California, Berkeley, scientists provides a roadmap for how entrepreneurs can harness freshwater prawns' voracious appetite for snails to reduce the transmission of these parasites, also known as "blood flukes," while still making a profit selling the tasty animals as food.

The study, which appears in the journal *Nature Sustainability*, shows how small-scale farming of freshwater prawns -- also known as aquaculture -- could be a win-win for communities in emerging and developing economies where schistosomiasis is common.

"River prawns are common aquaculture products in settings around the world, and we know these organisms are voracious predators of the snails that transmit schistosomiasis," said UC Berkeley's Christopher Hoover, a doctoral student in the School of Public Health's Division of Environmental Health Sciences who led the study. "What has not been clear is if we could marry the economic benefits of prawn aquaculture with the disease-control activity of the prawns."

Aquaculture is growing rapidly in settings around the world and has the potential to alleviate mounting pressures on wild fisheries. Freshwater prawns are already being produced in aquaculture systems around the world, from Louisiana to Thailand to Senegal and beyond.

River prawns, like this Macrobrachium prawn raised in a local hatchery in the Senegal River basin, can consume a dozen or more snails per day. A team led by University of California, Berkeley, scientists, has shown how communities can harness freshwater prawn's voracious appetite for snails to battle the parasite that causes schistosomiasis, while still making money selling the prawns for food. **Photo courtesy of Hilary Duff of the Planetary Health Alliance**

In these aquaculture systems, juvenile prawns are first raised in hatchery facilities, then stocked in waterways where schistosomiasis is transmitted, and finally harvested once they reach a marketable size. As the prawns grow, they feed on the snails that carry the schistosome parasite.

The parasite is incapable of infecting the prawns themselves, and schistosomiasis is not transmitted via ingestion, so raising, harvesting and consuming prawns cannot pass along the disease.

The researchers used economic and epidemiologic modeling to pinpoint the optimal points at which to stock and harvest the prawns, with the joint goals of reducing schistosomiasis transmission and generating revenue from selling harvested prawns.

"Our results show that there are highly beneficial configurations of prawn aquaculture systems that minimize tradeoffs between generating revenue from harvesting prawns and reducing schistosomiasis transmission," Hoover said. "We can design systems to maximize profit while having a substantial impact on disease reduction, potentially helping to lift populations out of poverty in emerging and developing economies."

Schistosomiasis, also known as "snail fever," affects around 250 million people a year and kills as many as 200,000. The disease is primarily spread when people come in contact with contaminated water. While drugs are available to treat the disease, they're not enough in some settings. Because drug treatments only address the human component of the parasite's transmission cycle, people are left vulnerable to reinfection, even soon after treatment.

By acting on the environmental component of the transmission cycle -- the intermediate host snail population -- prawn-based interventions can complement drug treatment, yielding greater population benefits.

The model showed that, to reduce parasite loads, introducing native prawns to infected waterways was comparable to the standard approach of widescale administration of schistosomiasis-fighting drugs, and that it could decrease the parasite burden to nearly zero after 10 years.

Prawns may have environmental benefits, as well, including substituting for chemical pesticides to control snail populations and restoring native biodiversity in areas where native prawn species have been decimated by dams.

"Chris' research contributes a new tool to our global efforts to combat schistosomiasis," said Justin Remais, head of the Division of Environmental Health Sciences and co-senior author of the study. "Poverty and schistosomiasis are intrinsically linked, and transmission of the parasite is known to stunt growth and cognitive development in children and to prevent adults from working, reinforcing poverty. By targeting transmission of the parasite itself, while also supporting a locally-sourced production system where economic benefits accrue to the community, this approach has great potential to supplement ongoing disease control campaigns that generally rely on drug treatment alone."

The research team also included scientists Susanne H. Sokolow, Jonas Kemp, Andrea J. Lund, Isabel J. Jones, Fiorenza Micheli and Giulio A. De Leo of Stanford University; James N. Sanchirico of the University of California, Davis; Tyler Higginson of the Middlebury Institute of International Studies at Monterey; Gilles Riveau of the Biomedical Research Center EPLS in Senegal; Amit Savaya and Amit Sagi of Ben Gurion University of the Negev; Shawn Coyle of Kentucky State University; Chelsea L. Wood of the University of Washington; Renato Casagrandi, Lorenza Mari, and Marino Gatto of the Polytechnic University of Milan; Andrea Rinaldo and Javier Perez-Saez of the Swiss Federal Institute of Technology in Lausanne and Jason R. Rohr of the University of Notre Dame.

The study was supported by grants from the National Institute of Allergy and Infectious Diseases, the National Science Foundation and the National Institute of Health's Fogarty International Center.

http://bit.ly/2yhKZ40

Warning to those wanting to spice up their lives

Think twice before adding that extra kick of chili sauce or chopped jalapeno to your meal.

New research involving the University of South Australia shows a spicy diet could be linked to dementia.

A 15-year study of 4582 Chinese adults aged over 55 found evidence of faster cognitive decline in those who consistently ate more than 50 grams of chili a day. Memory decline was even more significant if the chili lovers were slim.

The study, led by Dr Zumin Shi from Qatar University, showed that those who consumed in excess of 50 grams of chili a day had almost double the risk of memory decline and poor cognition.

"Chili consumption was found to be beneficial for body weight and blood pressure in our previous studies. However, in this study, we found adverse effects on cognition among older adults," Dr Zumin says.

UniSA epidemiologist Dr Ming Li, one of five researchers involved in the study, says chili intake included both fresh and dried chili peppers but not sweet capsicum or black pepper.

"Chili is one of the most commonly used spices in the world and particularly popular in Asia compared to European countries," Dr Li says. "In certain regions of China, such as Sichuan and Hunan, almost one in three adults consume spicy food every day."

Capsaicin is the active component in chili which reportedly speeds up metabolism, fat loss and inhibits vascular disorders but this is the first longitudinal study to investigate the association between chili intake and cognitive function.

Those who ate a lot of chili had a lower income and body mass index (BMI) and were more physically active compared to non-consumers. Researchers say people of normal body weight may be more sensitive to chili intake than overweight people, hence the impact on memory and weight. Education levels may also play a role in cognitive decline and this link requires further research.

Additional information

The China Health and Nutrition Survey (CHNS) is an ongoing household-based cohort study conducted in nine provinces in China between 1989 and 2011. Cognitive screen tests were conducted among those aged 55 and above in regular intervals between 1991 to 2006. The participants were asked to recall a 10-word list, counting backwards from 20 and doing some basic subtractions.

It is estimated that dementia affects about 50 million people globally. In 2017, approximately 9.5 million Chinese adults aged 60 years and above had dementia.

The paper, "High chili intake and cognitive function among 4582 adults" is published in Nutrients.

http://bit.ly/2JTcBDp

The Quietly Changing Consensus on Neutering Dogs

A growing body of research has documented the health risks of getting certain breeds fixed early—so why aren't shelters changing their policies?

Sarah Zhang

In the 1970s, a time when tens of millions of unwanted dogs were being euthanized in the United States annually, an orthodoxy began to take hold: Spay and neuter early. Spay and neuter everything. It's what vets were taught. It's what responsible pet owners were told to do.

A growing body of research, however, suggests that spaying and neutering—especially in some large breeds when very young—are linked to certain disorders later in life. "As time has gone on, vets are starting to question the wisdom," says Missy Simpson, a veterinary epidemiologist with the Morris Animal Foundation, which recently published a study that found higher rates of obesity and orthopedic injury in golden retrievers that had been fixed. Other studies have linked early spaying and neutering to certain cancers, joint disorders, and urinary incontinence—though the risks tend to vary by sex, breed, and living circumstances. As such, the American Veterinary Medical Association (AVMA) now says in a guide for veterinarians, "There is no single recommendation that would be appropriate for all dogs."

And yet anyone adopting from a shelter is unlikely to be told of these risks—or even to be given a choice. Today, according to the AVMA, 31 states and the District of Columbia require sterilization or a promise of such before pets can be adopted out of shelters. The American Society for the Prevention of Cruelty to Animals (ASPCA) also advocates early spaying or neutering of all companion animals at two months or two pounds in weight. Its information page for pet owners touts the very real benefits of the

procedures—behavioral changes, fewer uterine infections, a decreased risk of certain cancers—but with nary a mention of possible downsides.

For animal-welfare groups trying to manage unwanted populations, this strategy makes a kind of sense. "We're trying to look at the big picture," says Lori Bierbrier, the medical director of the ASPCA. "One of the ways to manage that population is not to have animals going out and having puppies and kittens all the time." For dogs that already have an owner, she says, whether to spay or neuter is that owner's individual decision. But that also makes talking about the research reevaluating the risks of spaying and neutering tricky. How do you balance raising concerns about risks for individual dogs with the welfare of dogs as a whole?

"Oh my gosh, we got pushback," says Benjamin Hart, a professor emeritus at the University of California at Davis School of Veterinary Medicine. In 2013, a team led by Hart and his wife and collaborator, Lynette Hart, published a study that found higher rates of joint disorders in golden retrievers spayed or neutered before one year of age and of certain cancers in female golden retrievers that were spayed early. It immediately caused an uproar. "This is irresponsible," Hart recalls critics saying. "You're looking at just one breed. You can't generalize."

So they started looking at other breeds. The Harts have since published two follow-up papers, on Labrador retrievers and German shepherds, also finding an elevated risk of joint disorders but not of cancers after early spaying and neutering. And they have just finished another study, on 35 different dog breeds as well as mixed breeds. The risks of cancers and joint disorders appear to vary significantly by breed and sex, Hart says, with small dogs generally less affected by early neutering.

Read: Your dog feels no shame

The takeaway, Hart says, is that when to spay or neuter should be a case-by-case decision, even for dogs adopted out of shelters. Simpson, of the Morris Animal Foundation, says that vets have already, based on recent research, started recommending delaying spaying and neutering for owners of large breeds. Puppies in shelters, though, might not get the same individual attention.

The risk of obesity, Simpson adds, is often the major concern for vets making spaying or neutering recommendations. Somewhere between a quarter to a third of pets in the United States are now obese. The link between obesity and spaying or neutering has to do with hormones. Removing a dog's testicles or ovaries disrupts its hormonal balance, and this makes it both hungrier and slows its metabolism to require fewer calories. Yet animal-welfare groups that promote spaying and neutering are often quick to "debunk" the idea that fixing a dog could make it gain weight. The ASPCA's website says, "Lack of exercise and overfeeding will cause your pet to pack on the extra pounds—not neutering." This is technically true, but it elides a very real biological connection that owners might find useful to know.

When I brought this up with Bierbrier, she said the ASPCA staff would have to look into updating the website. She added that the ASPCA's spay-and-neuter clinic does tell owners taking dogs home after the surgeries that their pets will require less food.

Elsewhere in the world, spaying and neutering is not necessarily seen as the "responsible" thing to do. It is heavily discouraged in parts of Europe, such as Norway. Those countries also have very few stray dogs and a far less casual relationship with dog ownership. Dogs that have not been fixed are, to put it one way, less convenient pets. Intact male dogs will want to roam in search of a mate; female dogs will go into heat and have bloody discharge. The campaign to spay and neuter dogs has also changed their very relationship to us as pets.

http://bit.ly/30VWbjh

Survey finds patients want more guidance from physicians on self-care

National poll finds barriers and disconnects in perceptions about health and well-being

WASHINGTON - Physicians and consumers agree that self-care is important to health and well-being, yet 75 percent of patients say they haven't discussed self-care with their physician within the last two years, according to a new survey released today, conducted by The Harris Poll on behalf of Samueli Integrative Health Programs. Nearly half of doctors (46%) say patients do not seem very interested in the topic, while a majority of patients (72%) say they are interested in discussing self-care with their healthcare provider, which includes lifestyle changes, healthy diet, regular exercise, stress management, and other alternatives to conventional medical treatment.

"Encouraging patients to incorporate self-care practices into their daily lives is not only important for their health, it's a critical component in reducing our country's chronic disease burden," said Wayne Jonas, MD, executive director of Samueli Integrative Health Programs. "In order to truly make a difference in the health of our patients, the future of primary care - indeed all healthcare - must address the patient as a whole person and take an integrative health approach to guide and support healthy behaviors outside the clinic."

The survey - involving more than 1,000 U.S. adults ages 18 and older and more than 300 family medicine and internal medicine physicians - found that while more than nine in 10 physicians (96%) say self-care should be considered an essential part of a patient's overall health, only 39 percent of consumers say they practice it often. The survey was conducted online by The Harris Poll on behalf of Samueli Integrative Health Programs in May and June 2019.

What is Self-Care?

The survey found that despite common depictions of self-care as indulgences such as shopping and pampering, consumers understand that self-care is a broad concept that encompasses physical, mental, emotional, social, and spiritual needs. They report their top self-care practices as getting enough sleep (66%), eating healthy foods (62%), taking care of their mental health (60%), and exercising (59%).

Patients Want More Guidance

Although physicians think patients have limited interest in such topics, a majority of patients would be interested in talking to their doctors about what's important in their lives (57%), and about their life goals (55%). About two-thirds of patients wish their physician shared more resources on self-care (66%), were involved in all aspects of their health management (65%), and incorporated complementary and alternative therapies into their care (64%).

"What these results show us is that patients have a strong desire for their physicians to be involved in more aspects of their health - beyond pills and procedures," said Jonas. "They want a fuller partnership and a relationship where they can discuss their health and well-being in other, deeper ways that impact them. As physicians, it's important that we listen to these desires and adjust how we treat our patients. We need to organize our practices to support behavior change."

Barriers and Disconnects

Doctor-patient disconnects emerged on several points:

Despite knowing the importance of self-care, 43 percent of consumers say they have more pressing issues to focus on, and more than one in four (28%) say they feel guilty when practicing self-care. Women are more likely than men to cite any barriers to self-care (77% vs. 68%). Specifically, women are more likely to be

too tired (31% vs. 20%) or to feel guilty for taking time for themselves (16% vs. 7%).

The top reason that physicians cite for not discussing topics related to self-care more often is a lack of time during appointments (78%). More than nine in 10 (93%) would like to be able to provide their patients more information on self-care, but only one in four (26%) feel very confident in doing so.

Other highlights of the study findings include:

- ***Forty-four percent of consumers believe self-care is only possible for people with enough time, and 35 percent believe self-care is only possible for those with enough money.***
- ***80 percent of physicians say it's very important for them personally to practice self-care, but only 57 percent report doing so often.***
- ***A majority of physicians (59%) say the demands of their job prevent them from practicing self-care as much as they would like.***
- ***One in four physicians (25%) report that feeling burnt out prevents them from practicing self-care.***
- ***Nearly the same proportion of physicians and consumers say they are prevented from practicing self-care because they are unable to get out of bad habits (20% and 19%, respectively).***

Samueli Integrative Health Programs is dedicated to the promotion of personal health and well-being with the support of health teams dedicated to all proven approaches, including conventional, complementary and self-care. Dr. Wayne Jonas, the former director of the NIH Office of Alternative Medicine and the former director of a World Health Organization Center for Traditional Medicine, is clinical professor of Family Medicine at the Uniformed Services University and at Georgetown University School of Medicine.

Survey Method:

About This Study: The Self-Care Survey was conducted online by The Harris Poll on behalf of Samueli Integrative Health Programs among 1,006 U.S. adults ages 18+ (surveyed from May 23 to June 4, 2019) and 304 physicians who specialize in internal medicine or family practice (surveyed from May 23 to June 19, 2019). For complete research method, including weighting variables and subgroup sample sizes, please contact Kathleen Petty at KPetty@TheReisGroup.com.

https://go.nature.com/2K4UhGl

The aberrant global synchrony of present-day warming

Were extended warm or cold periods in the past worldwide, or only regional? Efforts to reconstruct Earth's climate history suggest that the near-global extent of ongoing warming is unparalleled over the past 2,000 years.

Scott St. George

PDF version

The history of Earth's climate is punctuated by a succession of named intervals associated with prolonged shifts to warmer, colder, wetter or drier conditions. During the Common Era (the past 2,000 years), the two best-known such climate epochs are the Little Ice Age[1] and the Medieval Climate Anomaly[2] (also called the Medieval Warm Period; Fig. 1).

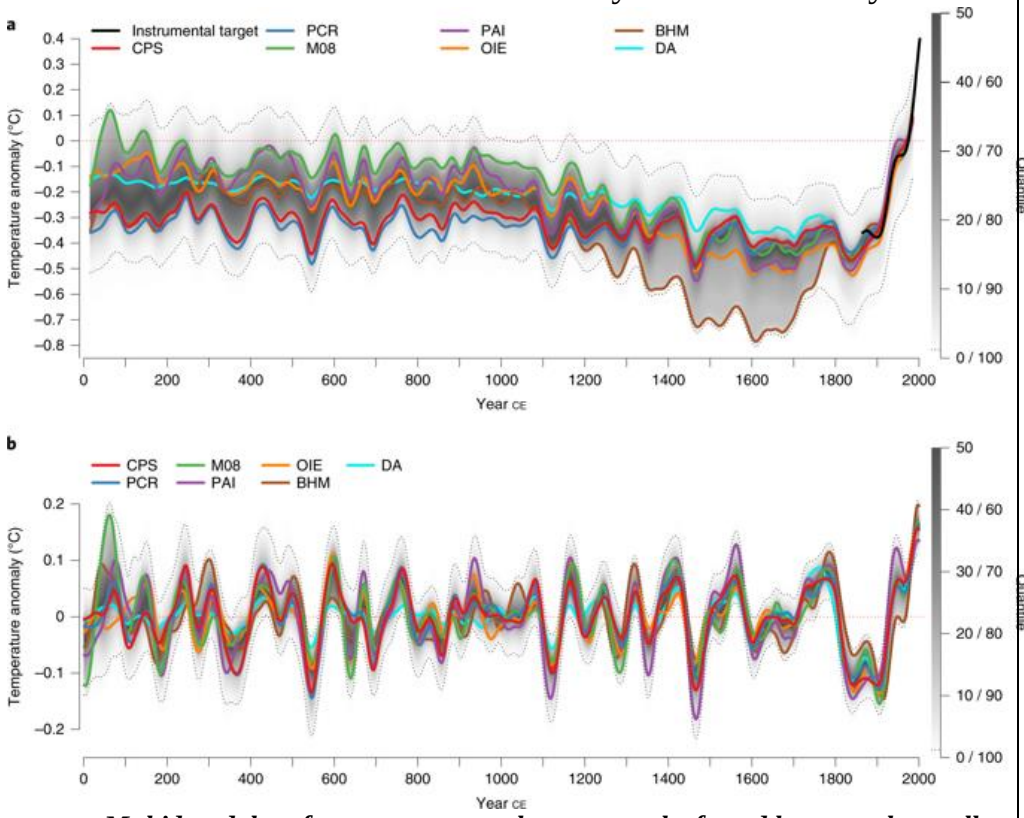
Neukom et al.[3,4] have constructed a set of pre-industrial temperature estimates, and find that past warm and cold periods were much less geographically widespread than is the current warming caused by humans.

All Canada Photos/Alamy

The former was a cool period that extended from the sixteenth to the late nineteenth centuries; the latter was a warm, dry period between ad 950 and 1250. Many assume that these intervals had a global impact. But in a paper in *Nature*[3] and in a companion paper in *Nature Geoscience*[4], Neukom *et al.* demonstrate that these and earlier climate epochs in the Common Era were much smaller in scope than the near-global reach of current human-induced warming.

Figure 1 | Evidence of medieval warmth. Unusually warm weather between the tenth and thirteenth centuries is often cited as one factor that enabled the short-lived Norse colonization of the Americas. Shown here are reconstructed buildings at a site called

L'Anse aux Meadows in Newfoundland, Canada — a Norse settlement that was established in the early eleventh century.



Multidecadal surface temperature changes may be forced by natural as well as anthropogenic factors, or arise unforced from the climate system. Distinguishing these factors is essential for estimating sensitivity to multiple climatic forcings and the amplitude of the unforced variability. Here we present 2,000-year-long global mean temperature reconstructions using seven different statistical methods that draw from a global collection of temperature-sensitive palaeoclimate records. Our reconstructions display synchronous multidecadal temperature fluctuations that are coherent with one another and with fully forced millennial model simulations from the Coupled Model Intercomparison Project Phase 5 across the Common Era. A substantial portion of pre-industrial (1300–1800 ce) variability at multidecadal timescales is attributed to volcanic aerosol forcing. Reconstructions and simulations qualitatively agree on the amplitude of the unforced global mean multidecadal temperature variability, thereby increasing confidence in future projections of climate change on these timescales. The largest warming trends at timescales of 20 years and longer occur during the second half of the twentieth century, highlighting the unusual character of the warming in recent decades.

Because thermometer measurements of air near Earth's surface before ad 1850 are not widely available, we rely on archives of proxy data to extend our perspective on climate further back in time. Trees in cold Arctic or alpine forests have annual rings with widths and wood densities that reflect year-to-year variations in summer temperature[5]. And because the chemical make-up of seawater depends on its temperature, massive corals build endoskeletons that contain a permanent geochemical record of past warming and cooling[6].

Other geological and biological archives that encode temperature information into their physical structure, substance or geochemical composition include lake sediments, glacier ice and bivalve molluscs (such as clams, oysters and mussels). Such archives likewise serve as 'palaeothermometers' that record temperatures stretching hundreds or thousands of years into the past.

Neukom *et al.* weave all of this evidence into a detailed global portrait of surface temperatures that spans the past two millennia. The foundation for their work is provided by the PAGES 2k proxy temperature database[7]. This community-sourced compilation includes nearly 700 records from trees, ice, sediment, corals, cave deposits, documentary evidence and other archives. Partly because the database incorporates so much information, the authors can chart the geographical extent of unusually warm or cold conditions across the entire planet by year.

The team reports in *Nature* that, although the Little Ice Age was the coldest epoch of the past millennium, the timing of the lowest temperatures varied from place to place. Two-fifths of the planet were subjected to the coldest weather during the mid-nineteenth century, but the deepest chill occurred several centuries earlier in other regions. And even at the height of the Medieval Climate Anomaly, only 40% of Earth's surface reached peak temperatures at the same time. Using the same metrics, global warming today is

unparalleled: for 98% of the planet's surface, the warmest period of the Common Era occurred in the late twentieth century — the authors' analysis does not encompass the continued warming in the early twenty-first century, because many of their proxy records were collected more than two decades ago.

In 2005, palaeoclimatologists John Matthews and Keith Briffa[1] cautioned against deeming the Little Ice Age an "uninterrupted, globally synchronous, cold period". These new results certainly bolster their point of view. And we can be confident in that conclusion because Neukom *et al.* carried out an exhaustive set of experiments to confirm that their findings were unaffected by their choice of statistical tools to relate the proxy network to thermometer measurements.

Unfortunately, limitations inherent in the proxies themselves probably still hamper our ability to compare warm or cool intervals with each other throughout the entire Common Era. Tree-ring records, the most frequently used proxy archive in the PAGES 2k database, are sometimes unreliable in registering slow climate changes over several centuries or longer[8]. Moreover, some other proxies — particularly records from marine and lake sediments — exaggerate variations at multidecadal or centennial timescales[9,10]. It is still an open question how well we can compare global temperatures across this entire 2,000-year span.

Read the paper: Consistent multidecadal variability in global temperature reconstructions and simulations over the Common Era

We can be more certain of how and why Earth warms or cools over decadal and multidecadal timescales. In their companion paper in *Nature Geoscience*, Neukom *et al.* show that, in the pre-industrial period (ad 1300–1800), major volcanic eruptions (or the lack of such eruptions) were the main factor behind cold (or warm) swings that persisted for several decades. Shifts in greenhouse-gas concentrations had a smaller, but still detectable, imprint. The team found no indication that variations in the Sun's radiation output affected mean global temperature over the same time frames.

In general, physics-based climate models accurately reproduce proxy estimates of our climate's history over the past millennium. However, these models exaggerate the degree of cooling caused by the two largest volcanic eruptions of the Common Era: the ad 1257 Samalas and the ad 1815 Tambora eruptions in Indonesia[11]. This discrepancy implies that we cannot be sure how bitter a chill would follow a similar eruption in the future.

The familiar maxim that the climate is always changing is certainly true. But even when we push our perspective back to the earliest days of the Roman Empire, we cannot discern any event that is remotely equivalent — either in degree or extent — to the warming over the past few decades. Today's climate stands apart in its torrid global synchrony.

Nature ***571***, *483-484 (2019)* *doi: 10.1038/d41586-019-02179-2*

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Cancer-cell death ironed out

Ferroptosis is a form of cell death. The finding that cells that have certain mutations in the Hippo signalling pathway are susceptible to ferroptosis might offer a way to treat a cancer called mesothelioma.

Dean Fennell

century, there was a rise in a type of cancer called mesothelioma, which is caused by exposure to asbestos used in building materials. Mesothelioma often arises decades after exposure, accounting for tens of thousands of deaths annually worldwide[1]. Even with the treatments currently available, it is inevitably fatal. There is therefore an urgent need to develop more effective therapies for this type of cancer. Writing in *Nature*, Wu *et al.*[2] report that mutations in a cell-signalling pathway that commonly occur in mesothelioma create a tumour vulnerability that might be targeted to treat this disease.

Read the paper: Intercellular interaction dictates cancer cell ferroptosis via NF2–YAP signalling

Mesothelioma most often originates in the lining of the lungs, in cells that form the pleural membrane. Mutations frequently found in mesothelioma cells often inactivate proteins, called tumour suppressors, that function in anticancer pathways. One of the most common such inactivated proteins is called merlin (encoded by the *NF2* gene), which functions in the highly evolutionarily conserved Hippo signalling pathway. This pathway was originally identified in the fruit fly *Drosophila melanogaster*[3,4], and it comprises a signalling cascade that controls cell proliferation and organ size. If merlin or another protein in this pathway, such as LATS2, is inactivated, downstream proteins called YAP and TAZ can boost the expression of genes that promote tumour formation. Certain cancers can even become ‘addicted’ to YAP-mediated transcription for their survival[5].

However, if merlin, LATS2 and another protein called LATS1 are functional, YAP and TAZ undergo phosphorylation (a phosphate group is attached to them), which modifies the proteins and blocks their function by preventing them from entering the nucleus to drive gene expression[6]. Mutations in the genes encoding merlin and LATS2 are positively selected during tumour development[7], consistent with their normal roles as tumour-suppressor proteins in mesothelioma.

Wu and colleagues studied the gene-expression profiles of human cancer cells grown *in vitro*, and report that YAP and TAZ drive the expression of proteins, such as ACSL4, that are needed for a type of cell death called ferroptosis. The authors also uncovered a connection between the ability of cells to suppress ferroptosis and the cell–cell contact that depends on the protein E-cadherin. The authors report that high expression of E-cadherin in human mesothelioma cells grown *in vitro* is associated with resistance to ferroptosis. E-cadherin activates the Hippo pathway, and the authors went on to explore the relationship between this pathway and ferroptosis.

Cell death that occurs through ferroptosis depends on a reaction between cellular iron and hydrogen peroxide[8]. During ferroptosis, a polyunsaturated fatty acid — a type of lipid found in the cell membrane — undergoes a modification called peroxidation, which causes an increase in the level of molecules termed reactive oxygen species. Ferroptosis is often linked to depletion of the amino acid cysteine, which is imported into cells by the protein SLC7A11. Cysteine provides a building block for the production of glutathione, a molecule involved in a pathway that can combat ferroptosis.

The drug sorafenib is approved for clinical use. It can induce ferroptosis by inhibiting SLC7A11. The authors demonstrate that sorafenib treatment of cultured human mesothelioma cells that have mutations in the gene encoding merlin causes the cells to undergo ferroptosis. They report that this sensitivity to ferroptosis depends on YAP- and TAZ-mediated gene expression (Fig. 1).

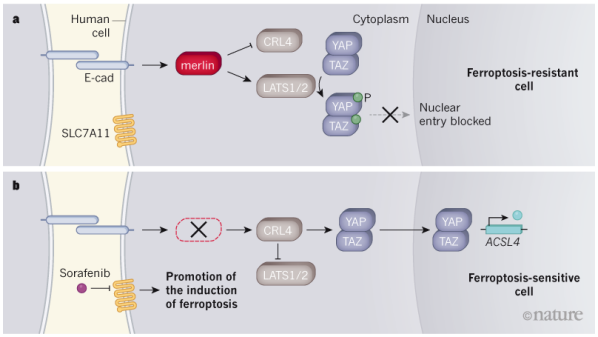

Figure 1 | Regulation of ferroptosis in human cells. Ferroptosis is a type of cell death whose induction is affected by a pathway that depends on the protein SLC7A11. Wu et al.[2] investigated how an anticancer signalling pathway called the Hippo pathway, in which mutations commonly occur in cancer cells, affects ferroptosis. a, Interactions between receptor proteins called E-cadherin (E-cad) on adjacent cells can trigger the Hippo pathway. A protein called merlin in this pathway prevents cancer-promoting gene expression by inhibiting a protein called CRL4. CRL4 inhibition enables the proteins LATS1 and LATS2 to add a phosphate group (P) to the proteins YAP and TAZ, and this phosphorylation prevents the proteins from entering the nucleus and driving gene expression. The authors report that YAP and TAZ drive the expression of genes that promote ferroptosis, revealing that Hippo pathway signalling makes cells resistant to ferroptosis. b, If merlin is not expressed because of a mutation, CRL4 is not inhibited and LATS1 and LATS2 cannot function. YAP and TAZ can enter the nucleus and drive the expression of genes, such as ACSL4, that promote ferroptosis. The authors report that tumour cells that lack merlin can undergo ferroptosis if treated with an inhibitor of SLC7A11, called sorafenib.

Two independent clinical trials[9,10] found that sorafenib caused tumour shrinkage or stabilization in people with mesothelioma. However, neither trial evaluated the mutations present in the patients' tumours, and it is tempting to speculate that the tumours of people who responded particularly well had mutations that inhibited the Hippo signalling pathway and that thereby boosted YAP- and TAZ-mediated gene expression.

Might other mutations beyond those in the Hippo pathway also regulate ferroptosis in mesothelioma? The most commonly mutated gene in this cancer[11] encodes the tumour-suppressor protein BAP1. This enzyme affects gene expression, and can cause a reduction in the expression of SLC7A11, which, in turn, leads to ferroptosis[12]. If the gene that encodes BAP1 is mutated, ferroptosis does not occur[12]. Therefore, the presence of wild-type BAP1 might help to enhance ferroptosis, along with any boost to ferroptosis provided by the use of SLC7A11 inhibitors. It is not known whether drugs that induce ferroptosis, such as sorafenib, would be effective in cells in which mutations inactivate BAP1.

Other approaches to targeting mesothelioma in which the Hippo pathway is inactivated are being explored. For example, in animal studies, loss of merlin expression is associated with cancer-cell vulnerability to inhibition of a protein called focal adhesion kinase[13]. However, no clinical benefit was found with this approach in a clinical trial[14]. Direct targeting of the interaction between YAP and TEAD, a protein to which YAP binds when it drives gene expression, is another strategy being pursued to block cancer-promoting gene expression[15]. Finally, YAP and TAZ recruit the protein BRD4 to drive the expression of specific genes, and use of a small-molecule inhibitor to target BRD4 can disrupt YAP- and TAZ-mediated gene expression[16]. This class of small-molecule inhibitor is entering early clinical trials. All of these approaches aim to block YAP- and TAZ-mediated gene expression. However, if the anticancer strategy being used aimed to trigger ferroptosis in mesothelioma cells, then YAP- and TAZ-mediated gene expression would be required.

Identifying a tumour that has an inactivated Hippo signalling pathway as a means of a developing personalized cancer therapy —

the ultimate goal — poses some challenges for mesothelioma. Focusing only on tumours that have lost merlin function would probably miss mesotheliomas in which Hippo signalling is inhibited by inactivation of other proteins, such as LATS1 and LATS2. A previous study[17] of the Hippo pathway in various cancers has revealed that 22 genes are commonly transcribed by YAP and TAZ, and this transcriptional profile might offer a way to identify ferroptosis-sensitive tumours. Furthermore, because this profile was found[17] in several types of tumour, triggering ferroptosis might be worth exploring for cancers other than mesothelioma.

Wu and colleagues' report highlights a strategy that could offer a way of developing a personally tailored anticancer therapy. However, therapies targeted to mutations in an individual's mesothelioma are still in their infancy. Clinical trials that take this approach, for example the mesothelioma stratified therapy trial in which I am involved (see go.nature.com/2o19lah), might help to make progress in such endeavours, and provide improved treatments at a time of unmet clinical need.

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Competing Financial Interests

http://bit.ly/2KdFt8u

Animal adaptations 'not keeping pace with climate change'

International study highlights impact on phenology.

Nick Carne reports.

The world's climate is changing at a pace that is leaving some animal species unable to adapt quickly enough, according to an international team of 64 researchers.

Their meta-analysis focussing on birds, published in the journal *Nature Communications*, shows that the historical phenology of these species – the timing of life cycle events such as breeding and migration – is mismatched to current climate.

The great tit (Parus major) is known to cope relatively well with climate change. **Bernard Castelein**

Species can potentially respond by altering their phenology, they say, but only if there is sufficient genetic variation or plasticity in their behaviour and development.

Changes in body size, body mass or other morphological traits that also have been associated with climate change show no systematic pattern, they add.

The research was led by Viktoriia Radchuk, Alexandre Courtiol and Stephanie Kramer-Schadt from the Leibniz Institute for Zoo and Wildlife Research (Leibniz-IZW) in Germany.

With colleagues from 19 countries, they reviewed 10,090 scientific abstracts and extracted data from 71 published studies (covering 17 species in 13 countries), seeking information relating changes in climate to possible changes in phenological and morphological traits.

Next, they evaluated whether observed trait changes were associated with higher survival or an increased number of offspring.

"We demonstrate that in temperate regions, the rising temperatures are associated with the shift of the timing of biological events to earlier dates," Radchuk says.

Co-author Thomas Reed, from University College Cork, Ireland, notes that the results were obtained by comparing the observed response to climate change "with the one expected if a population would be able to adjust their traits so to track the climate change perfectly".

It is particularly worrisome, the researchers say, that the data covered predominantly common and abundant species such as the great tit (*Parus major*), the European pied flycatcher (*Ficedula hypoleuca*) or the common magpie (*Pica pica*), which are known to cope with climate change relatively well.

"Adaptive responses among rare or endangered species remain to be analysed. We fear that the forecasts of population persistence for such species of conservation concern will be even more pessimistic," says Kramer-Schadt.

The researchers say that to date most global multi-species studies assessing animal responses to climate change have focused primarily on changes in distribution ranges, and models commonly used to predict distributions and population viability under climate change usually do not incorporate the potential for species to adapt.

"Our results are an important first demonstration that, at least in a range of bird species, adaptive phenological responses may partially alleviate negative fitness effects of changing climate," they write in their paper.

"Further work is needed to quantify the extent of such buffering and to broaden the taxonomic scope to determine if this conclusion also applies to species already encountering higher extinction risk for reasons unrelated to climate."

https://wb.md/2Ze38vL

Guiding Patients to and Through Second Opinions

Advice From Medical Oncologists

Debra A. Patt, MD, MPH, MBA; Bradford R. Hirsch, MD, MBA

This transcript has been edited for clarity.

Debra A. Patt, MD, MPH, MBA: I'm Debra Patt, a medical oncologist and executive vice president of Texas Oncology in Austin, Texas. Welcome to Medscape Oncology Insights. Joining me today is Dr Brad Hirsch, a medical oncologist at Texas Oncology, to talk about second opinions.

Have you ever incurred a second opinion where you disagreed with the medical recommendation of another doctor?

Challenges With Second (and Third) Opinions

Bradford R. Hirsch, MD, MBA: Absolutely. As a matter of fact, a few weeks ago I saw a patient who had had three opinions. He had gone to California, another center in Texas, and then he came to me. He was incredibly confused. I think that the best thing you can do under these circumstances is to just sit down with the patient, work through the logic of it, and try to show where the evidence exists. Help the patient understand how to reconcile all of the different things they have heard. Listen to what they found previously and what they feel to be the right path, and try to support them through that.

Patt: I often see my major role as an educator to our patients, and educating them on reasonable medical decisions is really important in sorting through disparate recommendations. It's important, too, because sometimes they may receive recommendations that you feel are not appropriate for them. We have obligations to patients—of course, first to do no harm, and then help as we can. But it's important to know that we are not obligated to follow someone else's recipe of treatment if we feel like it's not appropriate for the patient.

Hirsch: I agree. It puts the patient in an incredibly difficult circumstance if one of the doctors says they are not going to treat them unless their specific recommendations are followed. So it's about reconciling it all and landing in a good place.

Tips for a Smooth Second Opinion

Patt: Do you have any pearls of wisdom when guiding patients through a second opinion discussion?

Hirsch: Sure. I always try to figure out what their goal is and understand why they want a second opinion. I think that guides where they go. Maybe they are looking for a clinical trial opportunity that is not available in other places or maybe they are looking for more advice about what opportunities are out there. We help to guide them about what we can do as a practice and what I can do as a physician versus making sure they get to the right place. I also try to guide them on places where they are not going to have to go through another 100 tests unless they are important to do, and where I really believe there is expertise and where we can all work together to improve their care.

Patt: I couldn't agree with you more. I talk with patients very openly about seeking a second opinion, and while I think that it's not necessary, it can sometimes be helpful. It's important to have those discussions transparently with your patients because it does build trust, and we have the opportunity to guide our patients around second opinions by giving them some advice.

People seek second opinions for a couple of clear reasons. Sometimes there are deficiencies in health literacy. Sometimes there are questions about medical decision-making or access to clinical trials. And sometimes there may not be an optimal fit with the person who has told them they have cancer for the first time that leads them to seek another opinion to make sure that they are on the right track.

It's useful to understand what patients seek from a second opinion so you as their doctor can help guide them in the right way. I read a study regarding health literacy, showing that patients leave the room with about 20% of what their doctors tell them, and I certainly feel that.[1] When I tell patients they have a new cancer diagnosis, they leave the room like a deer in headlights. We try to do things to make that better by giving patients treatment care plans. I often invite patients to have a spouse or other caregiver in the room with them. I give them something written when they leave the room. I let them record me if they want to so they can hear that again. I also have my nurse call them the next day. I try to improve their health literacy.

But still, sometimes hearing it from another doctor can improve their health literacy and let them make more logic-based treatment decisions, which I find helpful.

Hirsch: I totally agree. There is a misconception that if you are going to get a second opinion, it means you are going to travel to an academic medical center in another part of your state or even a different state. Often, it's just a second opinion where they can go down the road to another doc within community medicine or academic medicine, who can give them a new insight and a new opportunity. It's really about understanding what they are looking for in that process.

Patt: I think that's true. Sometimes people seek a second opinion in distant locations. They might travel to a major cancer center or somewhere else because of a clinical trial we don't happen to have open at our site or because they want to see someone in particular. When we can guide them around that, it's helpful because, to your point, there are some keys that they need to understand. The first is that they don't need to repeat expensive testing. It's completely unnecessary to have a CT scan, labs, or a biopsy repeated. That is an unnecessary spend of money.

It's also important to have transparency with your patients. When they have a treatment plan recommended to them, they can come back. Most patients prefer to have treatment and cancer care close to their home where they can have dinner with their family, where they can sleep in the same bed as their spouse. That way, it gives you an opportunity to address the treatment plan and to look to see if there is any discordance and manage some of that.

Sometimes a Second Opinion Is Necessary

Hirsch: There are times when you actually need a second opinion and when they need to go somewhere else.

I had a patient with a malignant metastatic pheochromocytoma, of which there are 100 or 200 a year in the country, and there was one trial of a new drug that was only at two centers in the country. I tried to get them a second opinion and their insurance company would not let them be seen, so I spent a month battling to get them the second opinion. So there are times when it's actually wrong not to send them to those organizations as well.

Patt: I, too, have seen utility in facilitating second opinions for many of my patients. I'm fortunate to have great clinical trials at my center, but we don't have everything. Frequently, if they have intractable cancers where I don't have a good clinical trial fit for them, and I know nationally that somewhere else they would have a clinical trial fit, getting them to those right places can be really helpful. But I think if doctors approach this transparently with their patients, encourage them to do what is going to make them feel comfortable, and have open and honest discussion with them, they can navigate the environment better.

I often manage that referral, so patients tell me who they would like to see and I make sure they get all of the appropriate information. It makes that second opinion process much better for them.

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http://bit.ly/2SI2LqJ

MERS-CoV vaccine is safe and induces strong immunity in Army-led first-in-human trial

First vaccine candidate to be tested in humans

SILVER SPRING, MD - A Middle East respiratory syndrome coronavirus (MERS CoV) vaccine candidate was shown to be safe, well-tolerated, and induced a robust immune response in a Phase 1 first-in-human clinical trial. Initial findings from the trial were published today in The Lancet Infectious Diseases.

The study, conducted at the Walter Reed Army Institute of Research (WRAIR) Clinical Trials Center, evaluated a candidate DNA vaccine (GLS-5300) co-developed by GeneOne Life Science Inc. and Inovio Pharmaceuticals. Though other vaccine candidates have previously been tested for use in camels, which are the suspected source of the virus that causes MERS, this is the first vaccine candidate to be tested in humans.

Seventy-five healthy adult volunteers received one of three dosages of the candidate vaccine at three time points (initial, one month, three months) and were followed for one year after final vaccination. Vaccinations were given with an electrical impulse to help with vaccine uptake. Vaccine-induced immune responses were compared to those of individuals who had recovered from natural MERS CoV infection.

The GLS-5300 MERS CoV vaccine was well tolerated with no major side effects reported by the volunteers. More than 85 percent of volunteers exhibited a detectable immune response to MERS CoV after just two vaccinations. This immune response persisted throughout the study and was similar in magnitude to the response seen in survivors of natural MERS CoV infection.

MERS is a severe respiratory disease akin to the Severe Acute Respiratory Syndrome (SARS) and was first identified in Saudi Arabia in 2012. MERS CoV has infected more than 2,200 people

and killed nearly 40% of those infected. There are currently no licensed vaccines or specific treatments for MERS. MERS has been identified as a priority disease by the World Health Organization (WHO) and as a top target for vaccine development by the Coalition for Epidemic Preparedness Innovations (CEPI).

"The world witnessed the emergence and devastation of SARS in 2002 and then MERS ten years later. MERS hasn't gone away, and there's every indication that the family of viruses to which SARS and MERS belong, coronaviruses, are here to stay," said Dr. Kayvon Modjarrad, director of WRAIR's Emerging Infectious Diseases Branch, the principal investigator of the study and first author on the publication. He added, "Military personnel are at particular risk for MERS, given the deployments to the Middle East and South Korea where the largest MERS outbreaks have occurred. This study is, therefore, an important advancement for the U.S. Army, the military community as a whole and global stakeholders in the research and development of both MERS and corona virus countermeasures."

The GLS-5300 MERS-CoV product is a DNA vaccine candidate, which allows for rapid design and production in response to emerging infectious diseases. Underscoring the potential for rapid deployment of DNA vaccines, GLS-5300 was advanced into the clinic within nine months of preclinical vaccine candidate selection. The promising results from this study have prompted advancement to a second Phase I/IIa trial in South Korea and a Phase II study in the Middle East.

Emerging infectious diseases such as MERS pose an ongoing threat to military operations and readiness, and WRAIR's Emerging Infectious Diseases Branch (EIDB) develops vaccines, drugs and diagnostics to address these threats. The branch is also studying and developing countermeasures for Ebola, Marburg, Zika and Lassa, among other emerging threats.

This study was funded by the U.S. Department of the Army and GeneOne Life Science, Inc. and conducted at WRAIR. This work was partially supported through a cooperative agreement (W81XWH-07-2-0067) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DoD). The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70- 25.

http://bit.ly/2YxfT7i

Extra weight in 60s may be linked to brain thinning years later

May accelerate brain aging by at least a decade

MINNEAPOLIS - Having a bigger waistline and a high body mass index (BMI) in your 60s may be linked with greater signs of brain aging years later, according to a study published in the July 24, 2019, online issue of Neurology®, the medical journal of the American Academy of Neurology. The study suggests that these factors may accelerate brain aging by at least a decade.

"People with bigger waists and higher BMI were more likely to have thinning in the cortex area of the brain, which implies that obesity is associated with reduced gray matter of the brain," said study author Tatjana Rundek, MD, PhD, of University of Miami Miller School of Medicine and a member of the American Academy of Neurology. "These associations were especially strong in those who were younger than 65, which adds weight to the theory that having poor health indicators in mid-life may increase the risk for brain aging and problems with memory and thinking skills in later life."

The study involved 1,289 people with an average age of 64. Two-thirds of the participants were Latino. Participants' BMI and waist circumference were measured at the beginning of the study. An average of six years later, participants had MRI brain scans to measure the thickness of the cortex area of the brain, overall brain volume and other factors.

A total of 346 of the participants had a BMI of less than 25, which is considered normal weight; 571 people had a BMI of 25 to 30, which is considered overweight; and 372 people had a BMI of 30 or higher, which is considered obese.

For waist circumference, which can be different for men and women, the normal weight group, which was 54 percent women, had an average of 33 inches. The overweight group, which was 56 percent women, had an average of 36 inches, and the obese group, which was 73 percent women, had an average of 41 inches.

Having a higher BMI was associated with having a thinner cortex, even after researchers adjusted for other factors that could affect the cortex, such as high blood pressure, alcohol use and smoking. In overweight people, every unit increase in BMI was associated with a 0.098 millimeter (mm) thinner cortex and in obese people with a 0.207 mm thinner cortex. Having a thinner cortex has been tied to an increased risk of Alzheimer's disease.

Having a bigger waist was also associated with a thinner cortex after adjusting for other factors.

Rundek said, "In normal aging adults, the overall thinning rate of the cortical mantle is between 0.01 and 0.10 mm per decade, and our results would indicate that being overweight or obese may accelerate aging in the brain by at least a decade."

"These results are exciting because they raise the possibility that by losing weight, people may be able to stave off aging of their brains and potentially the memory and thinking problems that can come along with brain aging," Rundek said. "However, with the rising number of people globally who are overweight or obese and the difficulty many experience with losing weight, obviously this is a concern for public health in the future as these people age."

Rundek noted that the study does not prove that extra weight causes the cortex to get thinner; it only shows an association.

A limitation of the study was that, like many studies of older people, it is possible that the healthiest people are more likely to live longer and take part in studies, so that may affect the results.

The study was supported by the National Institute of Neurological Disorders and Stroke and the Evelyn F. McKnight Brain Institute.

http://bit.ly/2OxiOZQ

Lobster organs and reflexes damaged by marine seismic surveys

Seismic air guns damage sensory organs and righting reflexes of rock lobster

A new study of the impact on marine life of seismic air guns, used in geological surveys of the seafloor, has found that the sensory organs and righting reflexes of rock lobster can be damaged by exposure to air gun signals.

Published in the journal Proceedings of the Royal Society B, the research by scientists from IMAS and the Centre for Marine Science and Technology at Curtin University is the latest in a series of studies they have conducted into how seismic surveys affect marine animals.

The study was funded by the Australian Government through the Fisheries Research and Development Corporation (FRDC), Origin Energy, and the Victorian Government's CarbonNet Project.

Lead author Dr Ryan Day said researchers exposed rock lobster to seismic air gun noise during field tests in Tasmania's Storm Bay and examined the effects on a key sensory organ, the statocyst, and the lobsters' reflexes.

"While the impact of air guns on whales and fishes has been relatively well-studied, the effects on marine invertebrates such as lobsters, crabs and squid remain poorly understood," Dr Day said.

"We chose to study the impact on rock lobster because they are a high value fishery and an important part of global marine ecosystems.

"Previous studies have shown that the statocyst, a sensory organ on a lobster's head, is critical in controlling their righting reflex, enabling them to remain coordinated and evade predators.

"After exposing lobsters to the equivalent of a commercial air gun signal at a range of 100-150 metres, our study found that the animals suffered significant and lasting damage to their statocyst and righting reflexes. "The damage was incurred at the time of exposure and persisted for at least one year - surprisingly, even after the exposed lobsters moulted," Dr Day said.

The study's Principal Investigator, Associate Professor Jayson Semmens, said that while the ecological impacts of the damage were not evaluated, the impairment would likely affect a lobster's ability to function in the wild.

"This study adds to a growing body of research that shows marine invertebrates can suffer physiological impacts and changes to their reflexes in response to anthropogenic noise such as seismic surveys," Associate Professor Semmens said.

"In recent years our research team has also looked at the impact of seismic surveys on lobster embryos, scallops and zooplankton

"Such studies are important to enable government, industry and the community to make informed decisions about how such activities can best be conducted while minimising negative outcomes for fisheries and ecosystems globally," he said.

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Fungal compound deodorizes skunk smell

Being sprayed by a skunk is no fun for people or their pets, and the strong, stinky secretions can serve as a nasty reminder of the wildlife encounter for days or weeks.

Available "de-skunking" formulas often either don't work well or can irritate the skin and eyes. Now, researchers reporting in ACS' *Journal of Natural Products* have identified a compound from fungi that safely and effectively neutralizes skunk spray odor.

When skunks feel threatened, they spray fluids from their anal glands that contain several nasty-smelling organosulfur compounds. The human nose can detect extremely low concentrations of these substances, making it difficult to completely rid clothing, hair, fur or skin of the stink. Various home and commercial remedies claim to neutralize skunk odor, but they often don't work well or contain skin and eye irritants. Robert Cichewicz and colleagues wondered if a natural product they had previously identified from fungi, called pericosine A, could react with and neutralize odoriferous compounds in skunk spray.

To find out, the researchers mixed pericosine A with different organosulfur compounds from skunk spray and analyzed the products of the reactions. They discovered that the fungal compound reacted with two types of organosulfur compounds -- thiols and thioesters -- and converted them to stable, odorless products. Then, the team very slightly altered the structure of pericosine A and adjusted other ingredients in the reaction to produce a formula that would be safer and more effective for skin application than the original compound. Finally, the researchers used in vitro eye and skin tests to determine that the fungal compound was non-irritating.

The authors acknowledge funding from the University of Oklahoma.

For more on skunk smells, watch a previously posted Reactions video here.

The abstract that accompanies this study is available here.

http://bit.ly/2Oo2TwX

One dose of HPV vaccine may be enough, Australian research finds

One dose of human papillomavirus (HPV) vaccine has comparable effectiveness to two or three doses for preventing cervical pre-cancer, according to a new study.

In a large national data linkage study published in *Papillomavirus Research*, researchers compared cervical screening outcomes for a

quarter of a million Australian women who were eligible for vaccination under the national program.

Researchers found that in women who were vaccinated at a young age, when most had not yet been exposed to HPV, that receipt of even one dose of HPV vaccine lowered the chance of having a pre-cancerous lesion detected at cervical screening.

Lead author Julia Brotherton from the VCS Foundation and the University of Melbourne said this data adds to other evidence starting to emerge that one dose of HPV vaccine may eventually prove to be sufficient for protection.

"If one dose vaccination proves to be enough, it will really simplify our ability to protect more people against these cancer-causing viruses," Associate Professor Brotherton said.

"That could make a huge difference, especially in less well-resourced countries that currently have high rates of cervical cancer but can't currently afford vaccination or screening."

However, Associate Professor Brotherton emphasised that until the results of formal trials were in and recommendations changed, that young people should make sure that they complete the two-dose vaccination course currently in place for best protection.

"The HPV vaccine has proven itself to be both very safe and remarkably effective," Associate Professor Brotherton said.

"We are proud that Australia is contributing data from our world leading program to add to the evidence on this issue."

Vaccination is a key part of the World Health Organisation's recent call to work towards the elimination of cervical cancer as a public health problem, together with HPV based screening, facilities for early diagnosis and treatment, and palliative care.

In Australia, HPV vaccination is routinely offered free of charge under the National Immunisation Program to both girls and boys in early high school at age 12-13 years, with free catch up available up to the age of 19 through local doctors and clinics.

As in Australia, most countries are only now beginning to be able to assess the vaccine's impact on screening outcomes from the vaccination of girls at the routine target age rather than in young women who were already sexually active prior to vaccination.

Recent data from Denmark and the US also support the possibility that one dose may be sufficient, but results of randomised trials are awaited before official recommendations are changed.

The data was analysed by a team of researchers from the VCS Foundation, the Australian Institute of Health and Welfare and cervical screening program managers from the ACT, NT, Tasmania, Victoria and Western Australia.

Background notes:

- ***Human papillomavirus (HPV) is a group of viruses that are extremely common worldwide.***
- ***There are more than 100 types of HPV, of which at least 14 are cancer-causing.***
- ***HPV is mainly transmitted through sexual contact and most people are infected with HPV shortly after the onset of sexual activity.***
- ***Cervical cancer is caused by sexually acquired infection with certain types of HPV.***
- ***Two HPV types (16 and 18) cause 70 per cent of cervical cancers and pre-cancerous cervical lesions.***
- ***There is also evidence linking HPV with cancers of the anus, vulva, vagina, penis and oropharynx.***
- ***Cervical cancer is the second most common cancer in women living in less developed regions with an estimated 570 000 new cases (1) in 2018 (84 per cent of the new cases worldwide).***
- ***In 2018, approximately 311 000 women died from cervical cancer; more than 85 per cent of these deaths occurring in low- and middle-income countries.***
- ***Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention***

(diagnosis and treatment of invasive cervical cancer) and palliative care.

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Genes underscore five psychiatric disorders

A group of international doctors has uncovered the genes that contribute to the development of ADHD, autism spectrum disorder, bipolar disorder, major depression and schizophrenia.

A group of international doctors has uncovered the genes that contribute to the development of ADHD, autism spectrum disorder, bipolar disorder, major depression and schizophrenia.

A collaborative research project carried out by The University of Queensland and Vrije Universiteit in Amsterdam analysed more than 400,000 individuals to determine the genes behind these five psychiatric disorders.

UQ psychiatrist Professor Christel Middeldorp said several sets of genes marked all five disorders. "Before this analysis, we knew a lot of psychiatric disorders were related to each other due to their hereditary nature," Professor Middeldorp said. "We often see multiple family members with mental illness in one family, but not necessarily with the same disorder.

"We investigated if specific sets of genes were involved in the development of multiple disorders, which genes are not only related to say, ADHD, but also to the other four psychiatric disorders.

"These are genes that play a role in the same biological pathway or are active in the same tissue type. "Genes that are highly expressed in the brain were shown to affect the different disorders, and some genes were related to all the illnesses we studied. "It shows that there is a common set of genes that increase your risk for all five disorders."

The study's lead author Dr Anke Hammerschlag said it was due to the biological pathways shared by the genes in the brain. "We found that there are shared biological mechanisms acting across disorders that all point to functions in brain cells," Dr Hammerschlag said.

"The synapse plays a vital role as this is the connection point between brain cells where the cells communicate with each other.

"We also found that genes especially active in the brain are important, while genes active in other tissues do not play a role."

New pharmaceutical drugs could potentially target these shared pathways. "Our findings are an important first step towards the development of new drugs which may be effective for a wide range of patients, regardless of their exact diagnosis," she said. "This knowledge will bring us closer to the development of more effective personalised medicine."

This research is published in Psychological Medicine (DOI:10.1017/S0033291719001776).

http://bit.ly/2yhUlwN

Changes in human diet shed light on human evolution

Change in the human diet reflects a behavioral shift approximately 1.65 million years ago

by Kristen Mitchell, George Washington University

A shift in diet has long been seen as one of the critical adaptations that distinguishes our own genus Homo from earlier human ancestors. The timing and context of this dietary shift, however, has been hotly debated. A recent study by Columbian College of Arts and Sciences researchers finds that this change in the human diet reflects a behavioral shift approximately 1.65 million years ago.

David Patterson, Ph.D. and lead author on the paper, researched the ecological context of the human lineage between 2 and 1.4 million years ago at East Turkana in northern Kenya. As a Ph.D. candidate, he did field research in this region, which provides some of the best evidence of the transition from earlier Homo ancestors to *Homo erectus*, our extinct relative with many modern human like characteristics.

Dr. Patterson and researchers with the GW Center for the Advanced Study of Human Paleobiology studied how vegetation in this region changed during this period. They also looked at dietary changes of other mammals for comparison for patterns in the genus *Homo*.

"Our data supports the idea that once you see *Homo erectus* in the record, then you also see changes in the human body form to something that looks more human than all of the hominins that came before it," Dr. Patterson said.

This research revealed the dietary shift did not occur with the earliest members of the *Homo genus*, but actually occurred later in time, roughly 300,000 later in *Homo erectus*, said Andrew Barr, assistant professor of anthropology.

"Through the study of the diets of contemporary mammals, as well as the ancient soils preserved in the Turkana Basin, this work rules out the possibility that the dietary shift in our ancestors merely reflected a change in environmental conditions," he said.

The research team found that vegetation did not change significantly during this period and most other large mammals stayed dietarily static. The only changes appeared to be within the genus *Homo*, between early *Homo* and *Homo erectus*, Dr. Patterson said.

This is significant because in order for experts to say a certain trait made human ancestors fundamentally more human, such as this dietary changes, they need to understand similar types of data in other animals. If a similar dietary transition can be documented in other animals it is not unique to humans, Dr. Patterson said. One of the characteristics that separates humans from great apes is a varied diet that includes different resources the great apes either cannot eat or eat in very small quantities.

This research found that about 1.65 million years ago, human ancestors began to consume more resources from C4 plants, which include grasses and sedges—or the animals that eat them. This raises the question: What drove this dietary transition?

This research contributes to the broader conversation in the paleoanthropological community and existing hypotheses about the timing and significance of dietary changes in the genus *Homo*, said Dr. Patterson, now an assistant professor at the University of North Georgia.

"Our data suggests and supports this long-standing idea that something really, really interesting happened within the human lineage when *Homo erectus* came about in eastern Africa," Dr. Patterson said.

More information: *David B. Patterson et al. Comparative isotopic evidence from East Turkana supports a dietary shift within the genus Homo, Nature Ecology & Evolution (2019).* *DOI: 10.1038/s41559-019-0916-0*

http://bit.ly/2SIYGT1

How our bodies coddle cancer

Tumors resist chemotherapy with help from a surprising source: nearby normal cells. Researchers are developing workarounds.

By Bob Holmes 07.18.2019

For cancer patients and their doctors, the scenario is all too agonizingly familiar: A course of chemotherapy appears to eradicate the tumor completely, but then it reemerges months later. Somewhere, somehow, a few cancer cells survive the therapy, dashing hopes of a cure.

Those survivors aren't evading chemo on their own — they have accomplices. Cancer researchers have long noticed that doses of chemo drugs that reliably kill cancer cells in laboratory cultures tend to be strikingly less effective in actual patients. They surmised that something about the environment in which a tumor sits — the tumor microenvironment — must be helping to shield it from the drugs' full lethal effect. Today they know that noncancerous tissues

surrounding a tumor play a crucial role in this betrayal, and they are beginning to understand how it is accomplished.

They've learned that noncancerous cells within and around the tumor can physically block delivery of chemo drugs to the cancer, or send chemical signals that encourage tumor cells to survive, or prevent the immune system from launching an effective attack. As they gain a better understanding of the tumor environment and its complex ecology, they hope to develop improved chemotherapies that are both more effective and less toxic. "It's really the forefront of cancer therapy," says Michael Hemann, a cancer researcher at MIT.

When vessels go wayward

Part of the protective effect of the tumor microenvironment is a matter of plumbing. For decades, cancer researchers have wondered whether they could starve tumors into submission by choking off their blood supply and thus preventing their fast-growing cells from getting enough food and oxygen. In the early 2000s, they developed a drug, Avastin (bevacizumab), that blocks a molecular signal triggering blood vessel growth, or angiogenesis. But, mysteriously, Avastin failed to improve survival unless patients received chemotherapy drugs at the same time — implying that Avastin was somehow helping the chemo to be more effective.

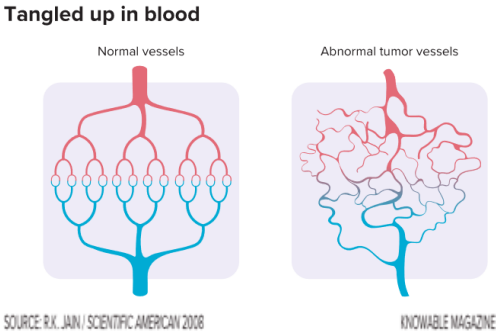
That piqued the interest of Rakesh Jain, a chemical engineer turned cancer researcher at Harvard Medical School and Massachusetts General Hospital in Boston. "I said, 'Aha, that's interesting,' " Jain says. "How can a drug that kills the blood supply help chemotherapy? You need the blood supply to get the drugs into the tumor." He started digging deeper, and what he found turned conventional wisdom on its head.

The blood vessels that deliver food and oxygen — and chemotherapy drugs — to a tumor tend to be highly abnormal. Instead of the usual large, straight, simply branched vessels, the ones in and around a tumor are often unevenly distributed, misshapen and tangled. As a result, some parts of the tumor end up far from any blood vessels and thus have little exposure to chemo. Those same regions become starved of oxygen, and this hypoxia suppresses the immune system and also acts as a signal for the tumor cells to metastasize, or disperse to new sites.

Moderate doses of Avastin or other angiogenesis inhibitors, Jain found, don't outright suppress formation of blood vessels around a tumor but can actually make them look more normal, so that they can deliver chemotherapy more efficiently and evenly.

Indeed, when Jain's clinical collaborators gave angiogenesis inhibitors to patients with glioblastoma, a form of brain cancer, he found — surprisingly — that patients who responded with increased blood flow to the tumor lived longer than patients in whom the blood flow declined.

Angiogenesis inhibitors work, in other words, for exactly the opposite reason than scientists initially thought, as Jain and his colleague describe in the 2019 *Annual Review of Physiology*.



The blood vessels that supply a tumor often become misshapen and tangled, preventing chemo drugs from reaching the tumor. Drugs that restore normal blood flow can help make chemo more effective.

There's a second way in which the tumor microenvironment physically interferes with chemo drug delivery. Some tumors — pancreatic cancer is a good example — attract many connective tissue cells, or fibroblasts, into their vicinity, forming what is essentially scar tissue. As these cells squeeze into the tumor microenvironment, they increase the pressure there, which can collapse blood vessels and further impair delivery of chemo drugs.

Jain is experimenting with ways to reduce the pressure and thereby improve chemo drug delivery. He's had promising early results in a small trial with a common blood-pressure medication, losartan, and clinical trials are underway. "The beauty of that is it is safe and cheap. It costs 14 cents a day. How many cancer drugs cost that little?" says Jain.

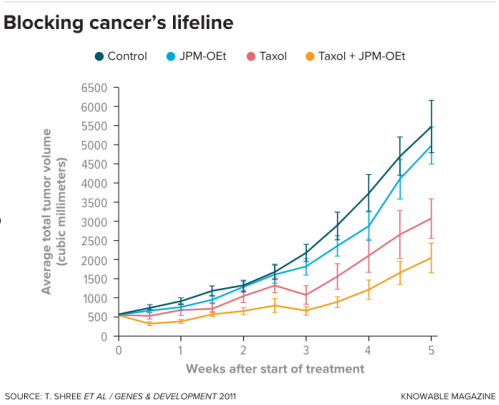
Tumors enjoy more than just physical protection from their microenvironment. As chemotherapy drugs poison the cancer, neighboring normal cells respond to the carnage as though it were a wound, triggering inflammation and releasing chemical signals that encourage the survival of nearby cells. That's helpful in repairing a wound but potentially catastrophic for a cancer patient. "The tumor cells see these signals and read them as a survival signal that allows them to survive chemotherapy," Hemann says.

To identify which of the many ongoing cellular signals are most important in cancer-cell survival, Hemann and his colleagues used viruses to randomly inactivate single genes in tens of thousands of leukemia cell cultures, then injected the resulting cells into live mice. Next, the researchers gave chemotherapy to the mice and watched to see which gene knockouts made cells more sensitive to the drugs. "We essentially let the biology do the work and tell us what is important in this setting," Hemann says.

One key gene turned out to code for a molecule called interleukin-6, which is normally involved in inflammation and wound repair. Another set of genes codes for a class of structural support proteins called integrins. Ordinarily, when integrins contact a cell they provide a signal that the cell is in its proper place and should remain alive. Tumor cells masquerade as normal neighbors, co-opt those signals and use them to survive as well, Hemann and his colleague Eleanor Fiedler explain in the 2019 *Annual Review of Cancer Biology*.

The cells that send these survival signals often do so in only a few particular microenvironments, creating refuges where tumor cells can hide out against chemotherapy. For the leukemias that Hemann studies, the refuge is in the bone marrow. Other cancers tend to find refuge in sites such as bone, liver or brain — not coincidentally, the places where surviving cancer cells eventually emerge as metastatic tumors. Cancer researchers are still working out the details of these survival signals and how they work, but if they can find ways to deprotect these places, they may be able to improve the effectiveness of chemotherapy and, at the same time, reduce the incidence of metastasis.

Some of the most important survival signals come from the white blood cells of the immune system. Ordinarily, cells such as cytotoxic T cells and macrophages serve a defensive function, hunting down and eradicating invaders and tumor cells. But chemotherapy can persuade these defenders to turn traitor and begin supporting the cancer.



Healthy, noncancerous cells near breast tumors send survival signals that help cancer cells resist Taxol, a commonly used chemo drug. In an experiment with mice that have mammary tumors (a model for human breast cancer), adding a second drug (JPM-OEt) that blocks these survival signals makes Taxol more deadly to the tumors.

In a mouse version of breast cancer, for example, cell damage caused by the chemotherapy drug Taxol (paclitaxel) draws macrophages to the tumor. The macrophage swarm activates a class of protein-digesting enzymes called cathepsins. These act as pro-survival signals, making the chemo only about half as lethal as it should be, according to research published in *Genes and*

Development by cancer researcher Johanna Joyce, now at the Ludwig Institute for Cancer Research at the University of Lausanne, Switzerland, and her colleagues. When Joyce's team paired chemotherapy with a drug that blocked cathepsins, they restored the chemo's killing power.

Joyce is now testing whether something similar happens in humans — taking tissue samples from patients with breast and brain cancers to see how the chemical signals in the tumor microenvironment change during and after chemotherapy.

Similar approaches may work for other types of cancer. For pancreatic cancer, one of the deadliest types of tumor, surgical oncologist David Linehan of the University of Rochester Medical Center in New York has had promising results from blocking a different signalling molecule, CCR2, which is involved in attracting macrophages to the tumor after chemotherapy. In preliminary tests on a few dozen patients, published in *Lancet Oncology*, those treated with chemotherapy and the CCR2 inhibitor showed much better response to chemotherapy than patients who did not receive the inhibitor, his team found. Further clinical trials are now being planned.

No one knows yet whether doctors will be able to treat multiple types of cancer by blocking a single survival pathway, or whether every tumor type will require a different strategy. It is even possible that therapies may need to be tailored to the genetic background of each individual patient. "Of course, that makes things infinitely more complex," says Joyce.

But no matter how specific the therapies may eventually need to be, clinicians hope that understanding how tumors hide from chemotherapy will someday pay big dividends. Right now, oncologists set chemotherapy doses as high as patients can tolerate, to try to kill every last cancer cell — even those hiding out in protected spaces. If doctors can strip away the protection provided by the microenvironment, Hemann says, "the prediction is that these tumor cells are going to be much more susceptible to the chemotherapy we give. So not only can we make cures more achievable, but we can also lower the dose and make the therapies more tolerable." That's an outcome every cancer patient would welcome.

10.1146/knowable-071819-1 ***Bob Holmes*** *is a science writer based in Edmonton, Canada.*

http://bit.ly/2MmXF1S

T cells trim the fat and protect against obesity

Immune cells protect against obesity by regulating the diverse communities of intestinal bacteria in mice

日本のニュース

Specialized immune cells protect against obesity by regulating the diverse communities of intestinal bacteria in mice, according to a new study, which shows how changes in gut microbiota can influence the development of metabolic disorders. The results suggest the potential for new microbiome-based therapies for obesity and other metabolic diseases.

Obesity, a common metabolic syndrome affecting the health of nearly two billion people worldwide, has been linked to a variety of factors including genetics, diet, behavior and most recently, the host's microbiome. Studies in mice have revealed differences in the gut microbiota composition in lean and obese animals, which can predispose a mouse to obesity. Moreover, transplanted microbiota of obese humans can confer metabolic defects into otherwise healthy animals.

Building on previous research, which identified the immune system as a key factor in regulating the composition of the microbiome, Charisse Petersen and colleagues discovered that specialized immune cells called T follicular helper (TFH) cells shield mice from obesity by promoting the production of immunoglobulin A (IgA) antibodies by B cells in the gut. Genetically altered mice with

defective TFH cell development produced little IgA. This resulted in symptoms of metabolic syndrome, including fat accumulation and insulin resistance, which are characteristics of human metabolic disease.

According to Petersen et al., dysfunctional IgA production impeded the colonization of Clostridia bacterial species, allowing the expansion of Desulfovibro bacteria.

Clostridia and Desulfovibro, respectively, suppress and enhance the expression of genes that direct the absorption of dietary lipids.

In a related perspective, Yuhao Wang and Lora Hopper write that "the Petersen et al.'s findings beautifully illuminate how immune system defects can lead to metabolic disease."

http://bit.ly/2LLcYCi

Strange bacteria hint at ancient origin of photosynthesis

Structures inside rare bacteria are similar to those that power photosynthesis in plants today, suggesting the process is older than assumed.

The finding could mean the evolution of photosynthesis needs a rethink, turning traditional ideas on their head.

Photosynthesis is the ability to use the Sun's energy to produce sugars via chemical reactions. Plants, algae, and some bacteria today perform 'oxygenic' photosynthesis, which splits water into oxygen and hydrogen to power the process, releasing oxygen as a waste product.

Some bacteria instead perform 'anoxygenic' photosynthesis, a version that uses molecules other than water to power the process and does not release oxygen.

Scientists have always assumed that anoxygenic photosynthesis is more 'primitive', and that oxygenic photosynthesis evolved from it. Under this view, anoxygenic photosynthesis emerged about 3.5 billion years ago and oxygenic photosynthesis evolved a billion years later.

However, by analysing structures inside an ancient type of bacteria, Imperial College London researchers have suggested that a key step in oxygenic photosynthesis may have already been possible a billion years before commonly thought.

The new research is published in the journal Trends in Plant Science.

Lead author of the study, Dr Tanai Cardona from the Department of Life Sciences at Imperial, said: "We're beginning to see that much of the established story about the evolution of photosynthesis is not supported by the real data we obtain about the structure and functioning of early bacterial photosynthesis systems."

The bacteria they studied, Heliobacterium modesticaldum, is found around hot springs, soils and waterlogged fields, where it performs anoxygenic photosynthesis. It is very distantly related to cyanobacteria, the main bacteria that performs oxygenic photosynthesis today.

It is so distantly related that it last had a 'common ancestor' with cyanobacteria billions of years ago. This means that any traits the two bacteria share are likely to also have been present in the ancient bacteria that gave rise to them both.

By analysing the structures that both H. modesticaldum and modern cyanobacteria use to perform their different types of photosynthesis, Dr Cardona found striking similarities.

Both structures contain a site that cyanobacteria and plants exclusively use to split water - the first crucial step in oxygenic photosynthesis.

The evolution of cyanobacteria is usually assumed to also be the first appearance of oxygenic photosynthesis, but the fact that H. modesticaldum contains a similar site means that the building blocks for oxygenic photosynthesis are likely much more ancient

than thought, as old as photosynthesis itself, and therefore could have arisen much earlier in Earth's history.

Dr Cardona also suggests that this might mean oxygenic photosynthesis was not the product of a billion years of evolution from anoxygenic photosynthesis, but could have been a trait that evolved much sooner, if not first.

Dr Cardona said: "This result helps explain in fantastic detail why the systems responsible for photosynthesis and oxygen production are the way they are today- but for it to make sense it requires a change of perspective in the way we view the evolution of photosynthesis.

"Under the traditional view - that anoxygenic photosynthesis evolved first and was the only type for about a billion years or more before oxygenic photosynthesis evolved - these structures should not exist at all in this type of bacteria."

The work was funded by the Leverhulme Trust and the Biotechnology and Biological Sciences Research Council.

http://bit.ly/2OoBtaf

What Tick Saliva Does to the Human Body

Ticks use their saliva to create a "lake of blood" inside their hosts.

Sarah Zhang

José Ribeiro was 33 when he got his first tick bite, in the 1980s, and he remembers it as a momentous occasion. He had recently started studying tick saliva, a complex molecular cocktail that ticks inject into their hosts to inhibit pain, prevent blood clotting, and suppress the immune system—all so the tick can feed undetected for days and days and days. Ribeiro had been studying this in a lab, but now he was finally witnessing it in the flesh. In *his* flesh.

Hard ticks inject saliva that suppresses the host immune system **Jana Bulantová / Creative Commons**

He marveled at the bite. It did not hurt. It did not itch. "I was amazed at how they could be so stealthy," recalls Ribeiro, who now studies disease-carrying insects and ticks at the National Institute of Allergy and Infectious Diseases. Ticks use saliva to manipulate the body of their hosts so their bites stay painless, itchless, and as unobtrusive as a bug swelling with blood can be. Scientists have since cataloged more than 3,500 proteins from the saliva of various tick species.

Ticks evolved this molecular cocktail because they, unlike virtually any other blood feeder, feed for days at a time on a single host. Most tick species feed only once during each stage of their life cycle (larva, nymph, adult), so they have to get a "voluminous blood meal" out of each host, says Sarah Bonnet, who studies ticks at the French National Institute for Agricultural Research. A tick might even wait years between feedings. In the meantime, it must subsist entirely on its previous blood meal. Each meal counts for a lot.

When a tick starts to feed, it doesn't suck blood out of blood vessels. Instead, it secretes enzymes in its saliva that destroy a small ring of host tissue. This creates a "feeding cavity," which Ribeiro likens to a "lake of blood." "The tick sucks blood from that lake," he says. For this strategy to work though, ticks also need to make proteins that prevent blood from clotting, as it normally wants to do in an injury site. Over the course of days, a host's body will try to heal the wound by sending cells that make collagen. Normally, this would allow the wound to scar over, but tick saliva has molecules to counteract this, too.

Lastly, the tick has to evade a host's immune system. Mammals, including humans, have complex immune systems with multiple lines of defense, and tick saliva can neutralize pretty much all of them. To start, ticks secrete molecular "mops," which bind to and neutralize histamine. Histamine is best known for causing itching

and redness, but it also plays an important role in opening up blood vessels to allow immune cells to get to a site of injury. Tick saliva prevents this, so tick bites don't itch and immune cells can't get to the bite. Tick saliva also degrades pain-inducing molecular signals in a host. That's why tick bites also do not hurt. Ticks then inject molecules that neutralize or evade a suite of white blood cells that would otherwise be eating or attacking an invader.

The exact cocktail of a tick's saliva proteins changes every few hours, Ribeiro says. The thousands of proteins in its saliva are highly redundant in function, and the tick cycles through them as a way of circumventing a host's immune system. Immune systems take time to recognize and react to a foreign tick protein, and this strategy simply doesn't give a host's cells a chance to do that. Suppose, Ribeiro says, "Monday a tick starts feeding on you and injecting the saliva in you." By Friday, when your body can mount a proper immune response against those first proteins, "the tick has already changed the repertoire."

Ticks, of course, are noteworthy not just because they bite, but because they transmit diseases when they bite—including Lyme disease, babesiosis, Rocky Mountain spotted fever, and many, many others. And pathogens may take advantage of the fact that tick saliva suppresses a host's immune system. Bonnet has found that ticks carrying the bacteria for cat-scratch disease (which, despite the name, is also transmitted by ticks) make more of a saliva protein called IrSPI. In a recent preprint, which has not yet been peer-reviewed, her team isolated IrSPI and found that it suppresses multiple types of white blood cells, weakening a host's defenses at the bite. The upshot is that ticks can feed undetected, and bacteria can spread into a new host undetected. Tick saliva seems to help not just ticks, but the bacteria that live inside them.

But Bonnet thinks IrSPI could also be turned into a weakness. It could be a target for vaccines. If people are inoculated against IrSPI, their bodies might immediately recognize a tick bite and mount an immune response, preventing the tick from working its saliva tricks. (That's why people who are bitten repeatedly will sometimes find the bites starting to itch.) Scientists are also interested in components of tick saliva that could be useful in cases where doctors want to inhibit pain or prevent blood from clotting. Ribeiro notes that this could be challenging because the proteins in tick saliva tend to be large and complicated—in other words, difficult to mass produce. But molecules from tick saliva are already being used to study certain unknown pathways in the human immune system. For example, scientists have used tick saliva to study how HIV infects cells.

Using tick saliva to study the human immune system makes a kind of sense. Over millions of years of evolution, ticks have essentially reverse engineered their hosts' immune systems to evade them.