INSIDE STANFORD MEDICINE

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In a seminar in China, students studied the country's fast-growing problem of chronic disease.

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Brain areas altered during hypnotic trance

By Sarah C.P. Williams

IMAGE POINT FR / SHUTTERSTOCK.COM

Researchers found changes in three areas of the brain that occur when people are hypnotized.

Your eyelids are getting heavy, your arms are going limp and you feel like you're floating through space. The power of hypnosis to alter your mind and body like this is all thanks to changes in a few specific areas of the brain, researchers at the School of Medicine have discovered.

The scientists scanned the brains of 57 people during guided hypnosis sessions similar to those that might be used clinically to treat anxiety, pain or trauma. Distinct sections of the brain have altered activity and connectivity while someone is hypnotized, they report in a study published online July 28 in *Cerebral Cortex*.

"Now that we know which brain regions are involved, we may be able to use this knowledge to alter someone's capacity to be hypnotized or the effectiveness of hypnosis for problems like pain control," said the study's senior author, David Spiegel, MD, professor and associate chair of psychiatry and behavioral sciences.

A serious science

For some people, hypnosis is associated with loss of control or stage tricks. But doctors like Spiegel know it to be a serious science, revealing the brain's ability to heal medical and psychiatric conditions.

"Hypnosis is the oldest Western form of psychotherapy, but it's been tarred with the brush of dangling watches and purple capes," said Spiegel, who holds the Jack, Samuel and Lulu Willson Professorship in Medicine. "In fact, it's a very powerful means of changing the way we use our minds to control perception and our bodies."

Despite a growing appreciation of the clinical potential of hypnosis, though, little is known about how it works at a physiological level. While researchers have previously scanned the brains of people undergoing hypnosis, those studies have been designed to pinpoint the effects of hypnosis on pain, vision and other forms of perception, and not the state of hypnosis itself.

"There had not been any studies in which the goal was to simply ask what's going on in the brain when you're hypnotized," said Spiegel.

Finding the most susceptible

To study hypnosis itself, researchers first had to find people who could or couldn't be hypnotized. Only about 10 percent of the population is generally categorized as "highly hypnotizable," while others are less able to enter the trancelike state of hypnosis. Spiegel and his colleagues screened 545 healthy participants and found 36 people who consistently scored high on tests of hypnotizability, as well as 21 control subjects who scored on the extreme low end of the scales.

Then, they observed the brains of those 57 participants using functional magnetic resonance imaging, which measures brain activity by detecting changes in blood flow. Each person was scanned under four different conditions — while resting, while recalling a memory and during two different hypnosis sessions.

"It was important to have the people who aren't able to be hypnotized as controls," said Spiegel. "Otherwise, you might see things happening in the brains of those being hypnotized, but you wouldn't be sure whether it was associated with hypnosis or not."

Brain activity and connectivity

Spiegel and his colleagues discovered three hallmarks of the brain under hypnosis. Each change was seen only in the highly hypnotizable group and only while they were undergoing hypnosis.

First, they saw a decrease in activity in an area called the dorsal anterior cingulate, part of the brain's salience network. "In hypnosis, you're so absorbed that you're not worrying about anything else," Spiegel explained.

Secondly, they saw an increase in connections See HYPNOSIS, page 6

Study challenges view that sickle cell trait increases the risk of mortality

By Jennie Dusheck

Health experts have long believed that sickle cell gene variants, which occur in about 1 in 13 African-Americans, increase the risk of premature death, even when people carry only a single copy of the variant. But health records of nearly 50,000 active-duty U.S. Army soldiers between 2011 and 2014 shows that's not the case, according to a study led by researchers at the School of Medicine.

People who carry two copies of the sickle cell gene variant have sickle cell disease, which brings a drastically shortened life span of only 40 to 60 years, as well as lifelong bouts of intense pain.

In contrast, those carrying just one copy of the gene variant have what's called sickle cell trait. Earlier studies have suggested that the health consequences of sickle cell trait might be dire, including higher mortality from a potentially fatal condition called exertional rhabdomyolysis. ER, which occurs when molecules from the breakdown of muscles end up in the kidneys, has been known to fell football players, often when they are practicing too hard in the hot sun without drinking enough water. (ER is distinct from heat exhaustion, however.) Likewise, ER is a risk for soldiers on active duty.

STAFF SGT. JASON BAILEY / U.S. AIR FORCE

Researchers tracked the health records of nearly 50,000 African-American soldiers and determined that their mortality risk was not increased if they had sickle cell trait.

Yet, in the first-ever longitudinal cohort study of sickle cell trait in African-American soldiers of all ages, researchers have found they suffered no increase in mortality. Lianne Kurina, PhD, an associate professor of medicine at Stanford, and a team of medical researchers found that having sickle cell trait does not increase the risk of death. A paper describing their findings was published Aug. 3 in *The New England Journal of Medicine*. Kurina is senior author. D. Alan Nelson, PhD, PA-C, a postdoctoral scholar at Stanford and former Army medical officer, is See SICKLE, page 7

Hormone therapy for brain performance: No effect, whether started early, late

AFRICA STUDIO / SHUTTERSTOCK.COM

By Bruce Goldman

A study led by a scientist at the School of Medicine shows that hormone therapy has a negligible effect on verbal memory and other mental skills regardless of how soon after menopause a woman begins therapy.

The study is the first large, long-term clinical trial to compare the effects of estradiol, a type of estrogen, on the mental capabilities of women who commence treatment soon after menopause versus those who begin after a long delay.

"Our results suggest that healthy women at all stages after menopause should not take estrogen to improve memory," said the study's senior and lead author, Victor Henderson, MD, See ESTROGEN, page 6

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

David Entwistle discusses taking the helm of SHC

David Entwistle joined Stanford Health Care as president and CEO on July 5. He succeeded Mariann Byerwalter, who served as interim president and CEO from January through June.

Entwistle's extensive experience in leadership positions at academic medical centers includes most recently having served as CEO of the University of Utah Hospital & Clinics for nine years.

UUHC is the only academic medical center in the Intermountain West, and has about 1,100 board-certified physicians who staff four university hospitals, 10 community clinics and several specialty centers. It is consistently ranked among U.S. News & World Report's Best Hospitals *and in 2010 was No. 1 on the prestigious University HealthSystem Consortium's Quality and Accountability scorecard.*

He earned a master's degree in health services administration at Arizona State University and a bachelor's degree from Brigham Young University.

Entwistle is an avid cyclist who enjoys both road and mountain biking, often accompanied by his teenage son. He also competes in Ironman Triathlons.

He recently shared his thoughts about his new job and Stanford Medicine with Shelley Hebert, a writer with Stanford Health Care.

1 What attracted you to Stanford Health Care?

ENTWISTLE: Here at Stanford, we have the very best. We have the best in terms of individuals who are at the top of their games. They have trained for many, many years and are bringing the benefits of this academic component to providing the best care for our patients. They are also creating an exceptional collaborative environment, which is what I enjoy. We're always pushing the bar.

David Entwistle

2 Where do you see the greatest potential for Stanford Medicine?

ENTWISTLE: One of the things that I'm very passionate about is what can we do to prevent disease. How can we prevent people from getting sick? So when we talk about precision health at Stanford Medicine, that really is saying, "Can we find out what's wrong before it happens and before individuals have to go through sometimes difficult or arduous treatment and related experiences, whether diagnostic or therapeutic? Can we prevent that?" I really feel that we at Stanford will be the leaders in the country in actually doing this.

One of the things that we have the opportunity to do here with the incredible assets of technology and Silicon Valley is advance health care through better application of technology for individuals. From wearable devices that track activity, to monitoring of blood glucose or other aspects of personal health, valuable data is being generated. Stanford is extremely well-situated to be able to apply innovative technology to improve health. The challenge is that while we have increasing availability of data and extensive resources, how can we take these and turn them into better knowledge about predicting, preventing and treating disease? This will be our challenge, but I'm confident we can accomplish this.

3 The landscape of health care is continuing to change. How do you see Stanford Health Care evolving?

ENTWISTLE: As we look at where health care is going — whether you call it population health or accountable care (and there are many different terms in use) — it's really about taking care of groups of individuals and caring for them over periods of time. So we've got to be able to have the locations to be able to do that, with the right facilities and excellent clinicians. As we advance the potential for precision health, it's really about keeping people well, and it's even better if we can also keep them out of the hospital. We have to make sure that we have the facilities and infrastructure to be able to serve patients where they are located. I think creating a network that really will be state-of-the-art nationally is one of the exciting opportunities that Stanford is well-positioned to take advantage of here in the Bay Area.

4 What do you think differentiates Stanford Health Care?

ENTWISTLE: Research is really what differentiates us. It is the fact that we can actually bring the new and innovative technologies, the new treatments and the new diagnoses to the table as we are continuing to push the bar. That's why patients come here.

Huge changes are underway in health care right now, from the Affordable Care Act to delivery reform to the shift toward population health, and how the relationships that we're going to have in the future with our patients will be different from what we have now. The combination of Stanford Health Care with our partners at the School of Medicine and Stanford Children's Health creates tremendous potential impact for our patients as we integrate to bring them solutions.

5 How has your involvement in athletics influenced your perspective on leadership?

ENTWISTLE: Even though many of the events in which I participate are an individual effort, a lot of what I've learned in cycling or in a triathlon is seeing the difference that you can make in your own performance by working together with others in preparing. There is a real power in teams. If you're acting as a team, building on each other's strengths and helping to support each other, then you really can accomplish anything. **ISM**

One special needle saves baby after physician's trip to Madagascar

By Ruthann Richter

S.V. Mahadevan, MD, had no idea when he visited Madagascar two months ago that he would help save the life of an ailing newborn.

Associate professor and chair of emergency medicine at the School of Medicine, Mahadevan traveled to the island country in April to teach some medical procedures to health-care workers there, using simple equipment he had brought. Those same health-care workers put that training into practice in July to rescue a 2-month-old with a life-threatening infection.

"The best part is that while I was thousands of miles away, in some small way I had a chance to impact a baby's life, which is fantastic," Mahadevan said. "That is why we do global health. It's a way of sharing the expertise we've gained over the years with our partners in other countries."

Mahadevan visited Madagascar, one of the poorest countries in the world, at the invitation of economist and disease ecologist Matthew Bonds, PhD, a visiting professor of Earth systems science at Stanford who co-founded the nonprofit group PIVOT, which provides health care to the country's rural poor. The two had met through Michele Barry, MD, director of Stanford's Center for Innovation in Global Health.

Teaching life-saving techniques

Mahadevan spent a week in a remote area of southeastern Madagascar, teaching basic principles and demonstrating simple, life-saving procedures to health professionals at the government-run Ifanadiana District Hospital, which is supported by PIVOT. One technique involved the insertion of a needle into bone to gain access to the circulatory system. These needles are typically used to deliver fluids, antibiotics and other medications when a patient's veins are inaccessible because of dehydration or other factors.

Mahadevan had brought a needle with him, as well as the instrument to insert the needle and a fake bone, for the health workers to practice on. He left the equipment behind when he returned to Stanford.

PIVOT MADAGASCAR

S.V. Mahadevan (center, right) teaches health-care workers in Madagascar how to use a type of needle that penetrates bone to gain access to the circulatory system.

On July 8, he received an exuberant email from a physician there describing the rescue of a child using the intraosseous device. A chubby baby had been suffering from advanced meningitis and was so dehydrated that there was no way to access her veins. Relying on Mahadevan's training, a Malagasy clinician, Tahiry Raveloson, MD, successfully inserted the intraosseous needle into the baby's shin and was able to give the ailing newborn fluids and antibiotics. The caregivers were also able to feed her breast milk via a tube threaded through her nose to her stomach.

After a week, the baby began to recover, becoming conscious and alert, reported Charles Mead, MD, a PIVOT physician who mentors the Malagasy clinicians.

"This is a case where they didn't have an alternative. Without the IV, she wouldn't have had the fluids to survive," Bonds said. In a thank-you email to Mahadevan, he said, "I am always dazzled by the ripple effects of that kind of generosity. It saves lives. It empowers our staff."

These kinds of experiences give health-care providers in the developing world the confidence and ability to carry on in the face of many challenges, said Mahadevan, who founded Stanford Emergency Medicine International and has provided training and care in India, Cambodia, Mongolia and Myanmar, among other countries.

'That sense of hope'

"When you are a health-care provider in a setting like that, there's a lot of helplessness," Mahadevan said. "You see someone come in, and there is nothing you can do, so the next time you just give up. So having something where you can intervene is not only incredible for the patient but

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STANFORD MEDICINE

Scientists coax stem cells to rapidly become bone, heart muscle

By Krista Conger

Researchers at the School of Medicine have mapped out the sets of biological and chemical signals necessary to quickly and efficiently direct human embryonic stem cells to become pure populations of any of 12 cell types, including bone, heart muscle and cartilage.

The ability to make pure populations of these cells within days rather than the weeks or months previously required is a key step toward clinically useful regenerative medicine — potentially allowing researchers to generate new beating heart cells to repair damage after a heart attack or to create cartilage or bone to reinvigorate creaky joints or heal from trauma.

The study also highlights key, but short-lived, patterns of gene expression that occur during human embryo segmentation and confirms that human development appears to rely on processes that are evolutionarily conserved among many animals. These insights may also lead to a better understanding of how congenital defects occur.

"Regenerative medicine relies on the ability to turn pluripotent human stem cells into specialized tissue stem cells that can engraft and function in patients," said Irving Weissman, MD, the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, and also of its Ludwig Cancer Center. "It took us years to be able to isolate blood-forming and brain-forming stem cells. Here we used our knowledge of the developmental biology of many other animal models to provide the positive and negative signaling factors to guide the developmental choices of these tissue and organ stem cells. Within five to nine days we can generate virtually all the pure cell populations that we need."

Weissman and Lay Teng Ang, of the Genome Institute of Singapore, are the senior authors of the study, which was published July 14 in *Cell*. Graduate student Kyle Loh and research assistant Angela Chen, both at Stanford, share lead authorship of the study.

Unraveling the mysteries

Embryonic stem cells are pluripotent, meaning they can become any type of cell in the body. They do so by responding to a variety of time- and location-specific cues within the developing embryo that direct them to become specific cell types. Researchers have learned a lot about how this process is controlled in animals, including fish, mice and frogs.

In contrast to many other animals, human embryonic development is a mysterious process, particularly in the first weeks after conception. This is because cultivating a human embryo for longer than 14 days is banned by many countries and scientific societies. But we do know that, like other animals, the human embryo in its earliest stages consists of three main components known as germ layers: the ectoderm, the endoderm and the mesoderm.

Each of these germ layers is responsible for generating certain cell types as the embryo develops. The mesoderm, for example, gives rise to key cell types, including cardiac and skeletal muscle, connective tissue, bone, blood vessels, blood cells, cartilage and portions of the kidneys and skin.

"The ability to generate pure populations of these cell types is very important for any kind of clinically important regenerative medicine," said Loh, "as well as to develop a basic road map of human embryonic development. Previously, making these cell types took weeks to months, primarily because it wasn't possible to accurately control cell fate. As a result, researchers would end up with a hodgepodge of cell types."

Loh and Chen wanted to know what signals drive the formation of each of the mesodermally derived cell types. To do so, they started with a human embryonic stem cell line, which they chemically nudged to become cells that form what's known as the primitive streak on the hollow ball of cells of the early embryo. They then experimented with varying combinations of well-known signaling molecules, including WNT, BMP and Hedgehog, as a way to coax these cells to become ever-more-specialized precursor cells.

NORBERT VON DER GROEBEN

Irving Weissman is co-senior author of a study describing how biological and chemical signals can be used to efficiently steer stem cells down complex developmental pathways to become specialized tissues that could be used in the clinic.

A yes-and-no strategy

They learned that often the cells progressed down the developmental path through a series of consecutive choices between two possible options. Think about the carnival game in which a disc is dropped down a slanted, peg-studded board to land in one of several cups at the bottom. The eventual destination is determined by whether the disc goes to the left or right of each consecutive peg.

The quickest, most efficient way to micromanage the cells' developmental decisions was to apply a simultaneous combination of factors that both encouraged the differentiation into one lineage while also actively blocking the cells from a different fate — a kind of "yes" and "no" strategy.

For example, cells in the primitive streak can become either endoderm or one of two types of mesoderm. Inhibiting the activity of a signaling molecule called TGF beta drives the cells to a mesodermal fate. Adding a signaling molecule called WNT, while also blocking the activity of another molecule known as BMP, promotes differentiation into one kind of mesoderm; conversely, adding BMP while blocking WNT drives the cells to instead become the other type of mesoderm.

"We learned during this process that it is equally important to understand how unwanted cell types develop and find a way to block that process while encouraging the developmental path we do want," said Loh.

By carefully guiding the cells' choices at each fork in the road, Loh and Chen were able to generate bone cell precursors that formed human bone when transplanted into laboratory mice and beating heart muscle cells, as well as 10 other mesodermal-derived cell lineages.

At each developmental stage, the researchers conducted single-cell RNA sequencing to identify unique gene expression patterns and assess the purity of individual cell populations. By looking at the gene expression profile in single cells, the researchers were able to identify previously unknown transient states that typified the progression from precursor to more-specialized cells.

Segmentation in embryo development

In particular they observed for the first time a transient pulse of gene expression that precedes the segmentation of the human embryo into discrete parts that will become the head, trunk and limbs of the body. The process mirrors what is known to occur in other animals, and confirms that the segmentation process in human development has been evolutionarily conserved.

"The segmentation of the embryo is a fundamental step in human development," said Loh. "Now we can see that, evolutionarily, it's a very conserved process." Understanding when and how segmentation and other key developmental steps occur could provide important clues as to how congenital birth defects arise when these steps go awry.

The ability to quickly generate purified populations of specialized precursor cells has opened new doors to further study.

"Next, we'd like to show that these different human progenitor cells can regenerate their respective tissues and perhaps even ameliorate disease in animal models," said Loh.

Stanford co-authors of the study are data analyst Pang Wei Koh; former undergraduate student Tianda Deng; instructor Rahul Sinha, PhD; graduate students Jonathan Tsai, Amira Barkal, Kimberle Shen and Benson George; research assistant Rachel Morganti; postdoctoral scholar Nathaniel Fernhoff, PhD; assistant professor of pathology Gerlinde Wernig, MD; former graduate student Zhenghao Chen; professor of pathology and of pediatrics Hannes Vogel, MD; assistant professor of genetics and of computer science Anshul Kundaje, PhD; professor of developmental biology William Talbot, PhD; and professor of developmental biology Philip Beachy, PhD.

The study was supported by the California Institute for Regenerative Medicine, the National Institutes of Health, the Howard Hughes Medical Institute, anonymous donors, the Agency for Science, Technology and Research in Singapore, the Siebel Stem Cell Institute, the Fannie and John Hertz Foundation, the National Science Foundation, the Davidson Institute for Talent Development, the Paul and Daisy Soros Fellowship for New Americans and the Alfred Sloan Foundation.

Stanford's departments of Pathology and of Developmental Biology also supported the work. **ISM**

Needle

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also for the health-care provider. It gives them that sense of hope that they can make a difference and a desire to learn more of these interventions that are simple and easy to deploy and inexpensive and can really save a life. That stays with an institution long after someone has done a training."

Bonds said the visit was a "big morale boost" for the staff, who receive training on standard protocols but don't have a lot of access to high-quality training from experts like Mahadevan. Moreover, they operate in a country where per capita spending on health care is just $14 and child mortality is high. The area of island where Mahadevan taught health care workers has a population of 30,000 children younger than 5. He said 5,000 would likely die in the next five years from preventable illnesses, such as diarrheal disease, malaria and respiratory infections. But with PIVOT's help, he hopes to see that number reduced by half.

He said the nonprofit could benefit from additional equipment and is looking for funding to help purchase more intraosseous needles, which cost about $200 apiece. He estimated that six patients every month — both adults and children — could be saved through use of the simple device. **ISM**

Video on terminally ill surgeon nominated for Emmy

The School of Medicine's video about neurosurgeon Paul Kalanithi's reflections on life while facing death from metastatic cancer has been nominated for a News and Documentary Emmy Award presented by the National Academy of Television Arts and Sciences.

The video, "A strange relativity: Altered time for surgeon-turned-patient," was nominated in the New Approaches: Arts, Lifestyle, Culture category, along with pieces by *The New York Times*, The Center for Investigative Reporting, *National Geographic Magazine* and PBS. The video was produced by Mark Hanlon, video director of the medical school's Office of Communication & Public Affairs.

The video was an online companion to an essay by Kalanithi published in the spring 2015 issue of *Stanford Medicine* magazine. In the essay and the video, Kalanithi described how his perception of time changed as a first-time father and doctor-turned-patient facing a terminal diagnosis. Kalanithi, who never smoked, was diagnosed with stage-4 lung cancer at age 36 in May 2013. The essay and video were published just a few weeks before he died on March 9, 2015.

Hanlon produced, photographed and edited the video and wrote and performed the film score.

MARK HANLON

Paul Kalanithi holds his daughter in a screen shot from Mark Hanlon's video "A strange relativity: Altered time for surgeon-turned-patient," which has been nominated for an Emmy.

The full list of nominees is available at http://emmyonline.com/news_37th_nominations. The award presentation is Sept. 21 at Frederick P. Rose Hall in New York City. **ISM**

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Randall Stafford advocates for a plant-based diet

Eating meat is bad for our health and bad for our planet, according to Randall Stafford, MD, PhD, professor of medicine at the Stanford Prevention Research Center.

Studies show that vegetarians and vegans have lower rates of heart disease and cancer, and that nearly 15 percent of all planet-warming greenhouse gases comes from raising cattle, pigs, poultry and other animals. The upshot is that the estimated greenhouse gas emissions of a vegetarian diet are half those of a meat-based diet. To improve public health and combat climate change, China recently released national dietary guidelines whose goal is to cut national meat consumption in half by 2030.

Yet, here in the United States, where we eat 80 percent more meat than do people in China, guidelines recently released by the federal Department of Agriculture don't recommend that we eat less meat. For good sources of protein, the new guidelines list meat, eggs and dairy first, with no suggestion that nuts, seeds and legumes could be a better choice.

Disappointed by this aspect of the USDA Dietary Guidelines for Americans 2015-2020, Stafford wrote a letter to the editor of JAMA that was published July 12. "The health benefits of specific components of plants have been documented, as have the harms associated with constituents largely unique to meat," he wrote. "Vegetarian diets have been associated with a reduction in cardiovascular disease mortality by as much as 29 percent and cancer incidence by 18 percent."

In a recent interview, writer Jennie Dusheck discussed the letter with Stafford, director of the SPRC's Program on Prevention Outcomes and Practices.

ANASTASIA GRANKINA / SHUTTERSTOCK.COM

1 What initially prompted you to write your letter?

Stafford: These guidelines have been long-awaited and there are many aspects that are improvements, but I was very disappointed by the way the guidelines dealt with recommendations about the consumption of meat.

People who consume meat generally have worse health outcomes, particularly in terms of heart disease, stroke and cancer. On the flip side, clinical trials show that people who eat mostly plants have better health outcomes. And the evidence goes further than just suggesting an association — it shows that plant-based diets directly cause better health.

The USDA guidelines clearly state that saturated fats should be reduced. We know most of the saturated fat in our diets comes from animal sources, and yet the guidelines don't take that next logical step and tell consumers to eat less meat. I am bothered by the lack of an explicit message around meat.

2 What would you say to people who think that eating meat is essential to health and a more natural part of a "paleo" diet?

Stafford: The first way to answer that is to think about protein requirements. The average amount of protein people consume in the United States is far more than we need. A plant-based diet can provide all the protein anyone needs — 40 or 50 grams. Two cups of lentils, two cups of yogurt or a single 4-ounce steak would cover a whole day's protein requirement. People are generally misinformed about the amount of protein they need, some believing they need four or five times as much protein as they actually do.

Second, the only real deficit in a vegetarian or a vegan diet is a lack of vitamin B12. That's something that all people who are eating a predominantly plant-based diet should be aware of. The recommended daily requirement for B12 is 2.4 micrograms and even that tiny amount is higher than most people need because it accounts for those people who absorb B12 poorly. On a vegan diet, you could get that much B12 from a vitamin supplement or a tablespoon of nutritional yeast or a serving of fortified tofu. Even if you eat meat, you would need only about 1.5 ounces of beef per day or two forkfuls of fish.

Randall Stafford

The idea of eating unprocessed or minimally processed foods has value — which the paleo diet emphasizes — particularly when it comes to plants. But some anthropologists think the actual meat consumption of our ancestors was quite low, which would undermine the story that justifies lots of meat in the paleo diet. But regardless of what our ancestors ate, we now live in a very different food environment and we need to be very careful about how we interact with that environment.

3 From a global environmental perspective, would it be better if people ate mostly plants?

Stafford: Yes, for a couple of reasons. One is that the process of producing meat generates more greenhouse gases per calorie than does growing plants of the same nutritional value. In essence, we can eat the corn and soy we grow or we can feed these plants to livestock and then eat the livestock. For a lot of reasons, it's energetically much more efficient to eat the plants ourselves.

Food production also relies on other scarce environmental resources. Water is the big one, as is arable land. Both the water and land required for a calorie from meat is far greater than the amount required for plant-based foods.

4 Do you think there's support for your point of view generally?

Stafford: I think there is general agreement among scientists interested in nutrition that a plant-based diet provides better outcomes and that this evidence should be more explicitly reflected in the guidelines. What's so striking about the new guidelines is that they are based on that same information, the same data. Clearly, the recommendation that we reduce our intake of saturated fat comes from that same pool of evidence. But the guidelines don't say which foods contribute to our consumption of saturated fats. Instead, they leave it up to the consumer to figure out that saturated fats mostly come from animals. Essentially, they're only telling part of the story, and leaving out the most practical advice.

5 What do you think it would take for the USDA to change their guidelines?

Stafford: I think it requires a reframing of how we think about dietary guidelines. Dietary guidelines are often focused on the idea that we break foods down into particular components — micronutrients and macronutrients — and that we can define a healthy diet in terms of the proportions of these different categories of nutrients.

But the fact is people eat food; they don't eat protein or saturated fats or carbohydrates alone. So in some sense the very process of creating guidelines that are based on these categories of nutrients misses the fact that people eat foods, not these categories.

It's not enough to just tell people what nutrients they should be consuming. I think it really has to come down to telling people what types of foods they should eat less of and what types of food they should be eating more of.

I think the guidelines have moved in the right direction. For instance, the guidelines have moved away from a recommendation to reduce total fat intake and are now focused solely on saturated fat, for which there's more evidence of harm. And the guidelines' emphasis on fibrous vegetables and whole grains are more forthright.

But the whole regulatory and guideline process really needs to become more practical and actionable by consumers. It would be much more direct to simply tell consumers to eat less meat. And that would be the most effective way to reduce the consumption of saturated fats.

Despite the tendency of consumers to be attracted to fad diets, I think Americans are more ready than ever to hear a simple recommendation to eat less meat. The dietary evidence is stronger today than it's ever been. And I think consumers are also uncomfortable with both the environmental impact of their diets and the issues surrounding the ethical treatment of animals. The time is right for the USDA to be more direct in their recommendations, even if it means making a recommendation that is contrary to the interests of some entrenched food manufacturers.

I certainly think more pressure from scientists to have the USDA state the obvious consequences of the data would help. I also think it's important that consumers complain to the USDA that the guidance is not nearly as clear as it could have been. **ISM**

Antibodies could counter atherosclerosis, study finds

By Bruce Goldman

Investigators at the School of Medicine have learned the signal that tumor cells display on their surfaces to protect themselves from being devoured by the immune system also plays a role in enabling atherosclerosis, the process underlying heart attacks and strokes.

A biological drug capable of blocking this so-called "don't eat me" signal is now being tested in clinical trials in cancer patients. The same antibody, the investigators found, was able to prevent the buildup of atherosclerotic plaque in several mouse models of cardiovascular disease. If this success is borne out in human studies, the antibodies could be used to combat cardiovascular disease — the world's No. 1 killer — and do so by targeting not mere risk factors such as high cholesterol or high blood pressure, but the actual lesions bearing direct responsibility for cardiovascular disease: atherosclerotic plaques.

"It seems that heart disease may be driven by our immune system's inability to 'take out the trash,'" said Nicholas Leeper, MD, associate professor of vascular surgery and of cardiovascular medicine.

A study describing the researchers' findings was published July 20 in *Nature.* Leeper is the senior author.

Atherosclerosis is caused by the deposition of fatty substances along arterial walls. Over years, these substances form plaques. It's now known that numerous dead and dying cells accumulate in atherosclerotic plaques, which inflammation renders brittle and vulnerable to rupture, the ultimate cause of heart attack and stroke.

Immune cell malfeasance

Contributing to the pathology is malfeasance on the part of a class of immune cells that first arrive at the site with presumably benign intentions, said Leeper.

"Even a perfectly healthy body turns over more than 100 billion cells a day, every day," he said. "One of the several jobs performed by immune cells called macrophages — from the Greek words for 'big eater'— is to come and gobble up those dead and dying cells, which might otherwise begin releasing substances that can foster inflammation."

Many cells in the human body feature a "don't eat me" signal on their surface: a protein called CD47. The protein tells the immune system that a cell is alive, still going strong and part of a person's healthy tissue.

Normally, as a cell approaches death, its CD47 surface proteins start disappearing, exposing the cell to macrophages' garbage-disposal service. But atherosclerotic plaques are filled with dead and dying cells that should have been cleared by macrophages, yet weren't. In fact, many of the cells piling up in these lesions are dead macrophages and other vascular cells that should have been cleared long ago.

"The fact **See ANTIBODIES, page 5**

Students study fast-growing problem of chronic disease in China

By Ruthann Richter

In March of 2015, Stanford researcher Randall Stafford, MD, PhD, seized on a unique opportunity to partner with colleagues in China, where traditional medicine is based on a concept of wellness. Within the setting of the historic Peking University, he organized a graduate-level seminar on disease prevention, hoping to explore what it means to be well and to collaborate on research in a country where chronic disease has become epidemic.

"Culturally there is a foundation for thinking about quality of life that is most evident within traditional Chinese medicine — the whole person, balance and the need to pay attention to the quality of life as something that precedes disease," said Stafford, a professor of medicine at the Stanford Prevention Research Center. "It's a big contrast with Western medicine, which focuses on acute disease and doesn't really value prevention. That concept of wellness resonates with people in China, perhaps more so than in the United States."

In June of this year, Stafford returned to the 4-year-old Stanford Center at Peking University, recruiting colleagues Judith Prochaska, PhD, MPH, and Michael Baiocchi, PhD, to lead a group of 15 students from both Stanford and China in a seminar on prevention research. During the three-week seminar, the faculty members conducted lectures and small-group discussions on how to promote changes in behavior that can help prevent cancer and heart disease, as well as on China's changing health-care system, research practices and how to design studies.

KENNY FU

JONATHAN KOS-READ

Top: Students from China and Stanford attended a seminar led by Michael Baiocchi (front, far left), Randall Stafford (front, second from right) and Judith Prochaska (front, far right). Right: A man smokes atop a building in Beijing. Half of all men in China smoke cigarettes, Prochaska says.

China has by far the largest number of deaths in the world due to cancer, heart disease and stroke, in part because of lifestyle and behavior factors, such as increased cigarette smoking, obesity, alcohol consumption and sedentary lifestyles. Stafford said the burden of chronic disease in the country, especially in large cities like Beijing, is rapidly catching up to levels in the United States and other Western nations.

He said China is dealing with many of the same issues as other emerging economies: how to balance economic growth with globalized lifestyles and environmental degradation, which can contribute to poor health.

"There's been much investment in developing a skilled workforce, particularly through a large university system. But the population's ability to be productive is compromised by the fact that many people are getting sick and developing chronic diseases in their middle years, just when that investment in training should be paying off," Stafford said. "There definitely is a huge interest and urgency in chronic disease prevention."

A health-care system in transition

Prochaska, an associate professor of medicine, said a minority of people in China access primary care and instead go directly to hospital clinics if they need medical attention. Together, the faculty and students visited a primary care clinic that is serving as a model of change in a national move to shift more of the care burden to such clinics.

That transition to a different model of care offers the country a number of important opportunities, including possible improvements in how it stores and uses health information, Baiocchi said. Currently, China has no established system of electronic medical records, he said.

"Now that China is changing how they are delivering care, they will have an opportunity to structure their data and record it in their health-care system," said Baiocchi, an assistant professor of medicine. "They could become the dominant place for health research."

Prochaska, who is an expert on smoking behavior, said tobacco use is a major health issue for the country, which is the world's largest maker of cigarettes, producing over 2 trillion a year with over 900 different brands. She said half of all men in China smoke cigarettes, which can cost as little as 75 cents a pack.

While in Beijing, she and her colleagues were able to connect with researchers at the city's main cancer hospital, **See CHINA, page 6**

Antibodies

continued from page 4

that there are so many dying cells in an atherosclerotic plaque, although those sick cells are supposed to be cleared promptly by macrophages, got us thinking," said Yoko Kojima, MD, PhD, a basic life science research associate who is the study's lead author.

CD47 in atherosclerotic tissue

In the new study, Leeper, Kojima and their colleagues performed genetic analyses of hundreds of human coronary and carotid artery tissue collected at Stanford and at Sweden's Karolinska Institute. They found that CD47 is extremely abundant in atherosclerotic tissue compared with normal vascular tissue, and correlated with risk for adverse clinical outcomes such as stroke.

Much of what's now known about CD47's function stems from pioneering work by Irving Weissman, MD, professor of pathology and of developmental biology and director of Stanford's Institute of Stem Cell Biology and Regenerative Medicine and the Ludwig Cancer Stem Cell Institute. In the late 1990s and early 2000s, Weissman and his colleagues first identified CD47 as being overexpressed on tumor cells, which helps them evade destruction by macrophages. Weissman's group went on to show that blocking CD47 with monoclonal antibodies that bind to and obstruct the protein on tumor cells restores macrophages' ability to devour those cells. Phase-1 clinical safety trials of CD47-blocking antibodies in patients with solid tumors and blood cancers are now underway.

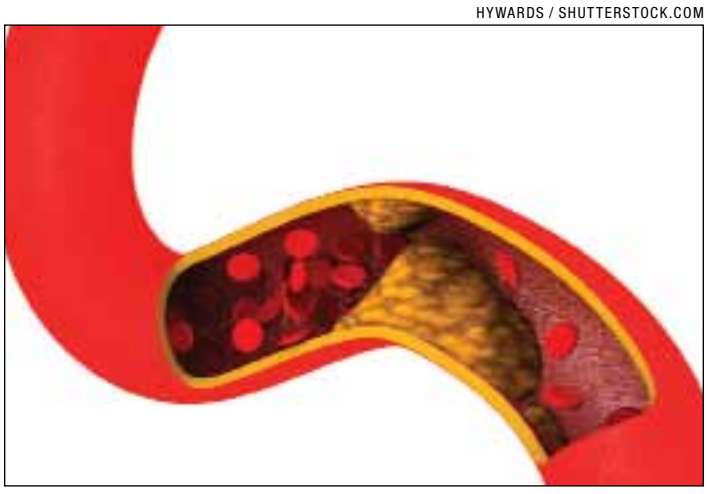
Alerted to the Leeper lab's discovery, Weissman, a co-author of the new study, provided anti-CD47 antibodies so Leeper's group could test their efficacy in battling atherosclerosis.

In a laboratory dish, anti-CD47 antibodies induced the clearance of diseased, dying and dead smooth muscle cells and macrophages incubated in conditions designed to simulate the atherosclerotic environment. And in several different mouse models of atherosclerosis, blocking CD47 with anti-CD47 antibodies dramatically countered the buildup of arterial plaque and made it less vulnerable to rupture. Many mice even experienced regression of their plaques — a phenomenon rarely observed in mouse models of cardiovascular disease.

Nicholas Leeper

Looking at data from other genetic research, the scientists learned that surplus CD47 in atherosclerotic plaques strongly correlates with elevated levels, in these plaques, of a well-known inflammation-promoting substance called TNF-alpha. Further experiments showed that TNF-alpha activity prevents what would otherwise be a progressive decrease of CD47 on dying cells. Hence, those cells are less susceptible to being eaten by macrophages, especially in an atherosclerosis-promoting environment.

HYWARDS / SHUTTERSTOCK.COM



Atherosclerosis is caused by the deposition of fatty substances and dead cells along arterial walls. Over the years, these substances form plaques.

A vicious circle?

"The problem could be an endless loop," said Leeper, "in which TNF-alpha-driven CD47 overexpression prevents macrophages from clearing dying cells in the lesion. Those cells release substances that promote the production of even more TNF-alpha in nearby cells."

Leeper and Weissman said they hope to find out, in clinical trials of human patients, whether CD47-blocking antibodies will prove effective in breaking that vicious circle.

"This opens up the door for these antibodies' use in noncancerous pathological states where cell proliferation is a primary attribute of the diseased cells," said Weissman, who is the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research.

One side effect of anti-CD47 antibodies in the mouse experiments, Leeper said, was transitory anemia. "Young red blood cells have high surface levels of CD47, which tells macrophages to leave them alone. Older red blood cells lose this protection, allowing macrophages to cull them from the herd," he said. Anti-CD47 antibodies render these older cells more prone to macrophage attack. But the anemia appeared to clear up fairly quickly in the mice as their bodies adapted by producing numerous fresh red blood cells with high surface CD47 levels.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Leeper and Weissman have filed a patent describing inhibition of CD47 as a method to prevent atherosclerosis. Both researchers hold equity in Palo Alto-based Forty Seven Inc., a company they cofounded that has licensed related intellectual property from Stanford's Office of Licensing Technology for cancer applications.

The study was carried out in collaboration with investigators at the David Geffen School of Medicine at UCLA and the Icahn School of Medicine in New York City. Other Stanford study co-authors are instructors Jens-Peter Volkmer, MD, and Clint Miller, PhD; postdoctoral scholars Paola Betancur, PhD, Daniel Direnzo, PhD, and Vivek Nanda, PhD; life science research assistant Kelly McKenna; laboratory manager Jianqin Ye, MD, PhD; associate professor of pathology Andrew Connolly, MD, PhD; and professor of cardiovascular medicine Thomas Quertermous, MD.

The study was funded by the National Institutes of Health.

Stanford's departments of Medicine, of Surgery, of Developmental Biology and of Pathology also supported this work. **ISM**

Hypnosis

continued from page 1

between two other areas of the brain — the dorsolateral prefrontal cortex and the insula. He described this as a brain-body connection that helps the brain process and control what's going on in the body.

Finally, Spiegel's team also observed reduced connections between the dorsolateral prefrontal cortex and the default mode network, which includes the medial prefrontal and the posterior cingulate cortex. This decrease in functional connectivity likely represents a disconnect between someone's actions and their awareness of their actions, Spiegel said. "When you're really engaged in something, you don't really think about doing it — you just do it," he said. During hypnosis, this kind of disassociation between action and reflection allows the person to engage in activities either suggested by a clinician or self-suggested without devoting mental resources to being self-conscious about the activity.

David Spiegel

Treating pain and anxiety without pills

In patients who can be easily hypnotized, hypnosis sessions have been shown to be effective in lessening chronic pain, the pain of childbirth and other medical procedures; treating smoking addiction and post-traumatic stress disorder; and easing anxiety or phobias. The new findings about how hypnosis affects the brain might pave the way toward developing treatments for the rest of the population — those who aren't naturally as susceptible to hypnosis.

"We're certainly interested in the idea that you can change people's ability to be hypnotized by stimulating specific areas of the brain," said Spiegel.

A treatment that combines brain stimulation with hypnosis could improve the known analgesic effects of hypnosis and potentially replace addictive and side-effect-laden painkillers and anti-anxiety drugs, he said. More research, however, is needed before such a therapy could be implemented.

The study's lead author is Heidi Jiang, a former research assistant at Stanford who is currently a graduate student in neuroscience at Northwestern University.

Other Stanford co-authors are clinical assistant professor of psychiatry and behavioral sciences Matthew White, MD; and associate professor of neurology Michael Greicius, MD, MPH.

The study was funded by the National Center for Complementary and Integrative Health, the National Institute of Biomedical Imaging and Bioengineering, the Randolph H. Chase, M.D. Fund II, the Jay and Rose Phillips Family Foundation and the Nissan Research Center.

Stanford's Department of Psychiatry & Behavioral Sciences and Department of Neurology and Neurological Sciences also supported the work. ISM

Estrogen

continued from page 1

professor of health research and policy and of neurology and neurological sciences. "At the same time, they don't need to be overly concerned about negative effects of estrogen on memory."

The study, which was published online July 20 in *Neurology*, addresses one specific aspect of a longstanding controversy concerning the benefits and harms of hormone therapy for postmenopausal women, whose bodies no longer produce estrogens and progesterone as they did during childbearing years.

Doubts about benefits

Hormone therapy was extremely popular in the United States in the latter part of the last century, but its use — while still widespread, with users numbering in the millions — has dropped off considerably since 2002, when findings from the Women's Health Initiative, a large-scale longitudinal study, raised deep doubts about many of what had been believed to be the treatment's broad benefits.

Victor Henderson

The evidence since then has been mixed on many counts, with a number of small studies, typically relatively short in duration, continuing to suggest potential benefits from hormone therapy. One question is whether the retention of mental abilities — such as memory, reasoning, planning and selective attention — is improved by starting hormone therapy soon after menopause rather than many years later.

The new study is part of a recently completed trial, the Early versus Late Intervention Trial with Estradiol, which enrolled large numbers of postmenopausal women to examine hormone therapy's potential for countering atherosclerosis. Among other things, ELITE was designed to determine whether outcomes for women taking estradiol, the dominant natural sex steroid in premenopausal women, and progesterone, a steroid involved in the menstrual cycle, would be different than in women who took Prempro, which was used as part of the Women's Health Initiative in the early 2000s. Prempro is a mixture of modified estrogens derived from mares' urine combined with medroxyprogesterone acetate, a substance whose effects approximate but do not duplicate those of progesterone.

> "Our results suggest that healthy women at all stages after menopause should not take estrogen to improve memory."

The trial also sought to determine when women should begin hormone therapy to ensure maximal benefits. Depending on the hoped-for clinical outcome, some evidence, mostly from animal studies, suggests that for a woman to benefit from hormone replacement, it may be essential to start soon after menopause, before the rapid postmenopausal decline in estrogen and progesterone availability irreversibly damages hormone-starved cells and tissues.

Estradiol or placebo

For the ELITE trial, which took place at the University of Southern California where Henderson's collaborators are based, healthy postmenopausal women were divided into two groups: an "early group," composed of women whose last menstrual period had occurred no more than six years prior to the start of the study, and a "late group," composed of women whose last period had occurred at least 10 years before the start of the study. Women in the two groups were then randomly assigned to daily oral regimens of either estradiol or a placebo. Estradiol-receiving women who hadn't undergone hysterectomies were also given progesterone, which can help protect against estrogens' uterine-cancer-promoting effect. Women receiving placebo instead of estradiol got a progesterone placebo instead of progesterone.

Henderson, collaborating with researchers at USC, received funding to study hormone therapy's effects, over a five-year duration, on these women's cognitive abilities. This adjunct trial, called ELITE-cog, analyzed tests of mental abilities of 567 women between the ages of 41 and 84, representing both the "early" and "late" groups of women. The women's verbal memory; their executive functions, such as judgment, planning, reasoning and focusing attention; and their overall neuropsychological condition were assessed at the beginning of the trial and at 2.5 years and five years later.

The difference between the two groups of women on any of these measures was negligible, Henderson and his colleagues found. In fact, there was no appreciable difference in test performance between women receiving estradiol and those given a placebo, regardless of how soon after menopause the women began treatment, the study indicated.

Even when the scientists, in a separate analysis, excluded data from all women in the "early group" who'd begun hormone therapy any later than three years after menopause, they observed neither positive nor negative effects on these women's mental ability compared to that of women initiating treatment more than 10 years after menopause.

Henderson, who is also the director of the Stanford Alzheimer's Disease Research Center, cautions that because women with cognitive deficits or outright dementia were excluded in this analysis, the study's results apply only to women with good mental skills at the time they begin treatment. Also, the findings cannot be extrapolated to cardiovascular or other health outcomes of hormone therapy, which must be assessed individually, he said. Indeed, Henderson noted that there's now some evidence that hormone therapy, initiated early, may have beneficial cardiovascular effects, while it is clear that late hormone therapy can contribute to heart disease.

Hormone therapy during the first five years after the onset of menopause is still approved for relief of moderate-to-severe hot flashes and night sweats, and also has beneficial effects on bone density. "If you're considering hormone therapy for those reasons, this study indicates that there's no particular reason to fear harmful effects on cognition over a five-year period of use," said Henderson. "But there's no reason to expect that this treatment, by itself, will result in meaningful improvement of mental abilities, either."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The study was supported by the National Institutes of Health.

Stanford's departments of Health Research and Policy and of Neurology and Neurological Sciences also supported the work. ISM

China

continued from page 5

with whom they will collaborate on a study on tobacco prevalence and cancer risk. The hospital manages cancer records for the whole city and has extensive data on each cancer patient, including information on the environment and the characteristics of the community in which they live. This will enable the researchers to look at how these environmental factors contribute to cancer incidence, Stafford said.

"This is an opportunity for us to have access to these great data and to be a partner in the analysis to look at the data in a new way," he said.

The seminar offered many opportunities for cross-cultural interactions, said Stanford medical student Carlie Arbaugh, who was one of the participants. In addition to classroom sessions, she explored the rich history of Beijing, which proved to be a living laboratory of learning.

Lots of smokers

"One thing I found pretty striking was that the topics we discussed in class were things I saw when I was walking through the city or riding the subway," Arbaugh said. "The smoking rate is incredibly high among men in China, while very low for women. I saw a lot of men smoking. As for diet, I noticed a discrepancy between food here and in China in terms of oil and salt content. Salt consumption in the U.S. is high and in China it's even higher. The food was delicious, but I was always very thirsty after I ate."

She said her exposure to an entirely new culture will help inform training at Stanford and future medical practice.

"For me personally, having the opportunity to learn more about Chinese culture is really valuable, regardless of where I end up practicing, as I want to work with underserved communities in the U.S. or abroad," Arbaugh said. "And I can already start applying what I learned. There are many Chinese patients at Stanford Hospital, as well the Cardinal Free Clinics, where I work. Now I feel I'll be able to connect with those patients a little better."

The seminar concluded with a public event at which the faculty discussed their ongoing research interests and students presented their team projects on proposed solutions to prevention problems. For instance, Arbaugh said she and her teammates tackled the problem of weight gain among male college students in China by proposing a phone app to track fruit and vegetable intake and activity levels, as well as a first-year class for university students about exercise, nutrition, stress management and sleep.

Prochaska said the Stanford Center at Peking University presented an opportunity for faculty to teach at a world-renowned campus in a beautiful, historic, cross-cultural setting. Peking University is one of the pre-eminent academic institutions in China.

"It is truly a unique opportunity for Stanford to make a bridge to the East in science and for personal enrichment in terms of seeing another culture," she said. "I highly encourage faculty to take advantage of the opportunity."

Baiocchi also said he was inspired by the unique setting of the seminar and by the challenges of being in a foreign environment.

"I found myself asking different kinds of questions," he said. "You're still very much in an academic environment, but you have a mixture of new challenges and some distance from your day-to-day activities. So it was extremely productive." Stafford said the Beijing campus is a valuable resource that is underutilized by Stanford faculty and students.

"We really do live in a world where health is now a global issue, and Americans remain very isolated and unaware of what's going on in the rest of the world," he said. "I think that needs to change." ISM

OBITUARY

Pediatric pulmonologist Nanci Yuan dies of cancer at 47

By Erin Digitale

Nanci Yuan, MD, clinical associate professor of pediatric pulmonary medicine at the School of Medicine, died July 1 of colon cancer in Santa Clara, California. She was 47.

Yuan, who was known for her devoted work with children with severe forms of inherited muscle dysfunction and sleep disorders, built the Pediatric Sleep Center at Lucile Packard Children's Hospital Stanford into a nationally recognized program that now delivers diagnostic and therapeutic care to almost 2,000 children annually. She helped write the standards for caring for children with severe congenital muscle disease and introduced a home ventilator program that allowed young patients with chronic respiratory failure to receive life-sustaining breathing support at home rather than in the hospital, letting them spend more time with their families.

Nanci Yuan

"Nanci was completely comfortable advocating for her patients, and she did so with great courage and integrity," said David Cornfield, MD, chief of the Division of Pulmonary Medicine and a longtime colleague of Yuan's.

"She provided incredible service to patients and their families," said Richard Moss, MD, professor emeritus of pediatrics, who hired Yuan to help build the division in 2003. "Nanci was fantastic about going from A to Z, everything from the initial evaluation to finding the best treatment for a patient."

Yuan was born in Sao Paulo, Brazil, in December 1968 and immigrated with her family to the Bay Area, growing up in Daly City steeped in Chinese culture and language. She earned an undergraduate degree in biology from the University of California-Berkeley and graduated from Hahnemann University Medical School in Philadelphia in 1996. After medical school, Yuan undertook a pediatrics residency at Kaiser Permanente Hospital in Oakland and a fellowship at Children's Hospital Los Angeles. During her training, she gained board certification in pediatrics as well as pediatric pulmonary, sleep and pediatric sleep medicine.

Caring for patients and their families

After Yuan was hired at Stanford in 2003, she set out to build programs focused on the respiratory aspects of sleep medicine and neuromuscular disease. She was deeply involved in care for children with spinal muscular atrophy type 1, a rare disease that is usually fatal in early childhood, and was senior author of the first-ever consensus statement defining a standard of care for such congenital myopathies.

"Nanci was so dedicated to her patients that, to some families, she was like a second mother," said MyMy Buu, MD, clinical assistant professor of pediatrics, who trained under Yuan and later became a colleague. "She gave families of children with respiratory failure treatment options that were truly family-centric. And she brought her human side to interactions with her patients."

Her work also affected children with many other types of medical problems, including cardiac diagnoses and cancer, and she increased the hospital's ability to diagnose and treat sleep problems in very young children, often working closely with colleagues in otolaryngology and neurology to address structural problems or neurologic issues that interfered with breathing during sleep.

"She was able to provide meaningful added value to a place that already had one of the most vaunted sleep programs in the world," Cornfield said. "It was really a testament to her strength of will, commitment and focus."

Shortly after relocating to northern California, Yuan met and married Ricky Chang. Together they had twins, Neo and Claire, now 9, and created a home where their children would be comfortable and fluent with both their Chinese and American heritage. Yuan is also survived by her parents, George and Bernice Yuan, and sister, Margarida Yuan.

"She was extremely accomplished as an expert clinician and mentor, and also was really a friend to a lot of people," Moss said. "I'm going to miss her tremendously."

In lieu of flowers and gifts, Yuan requested donations to her family trust for her children at http://gofund.me/nanciyuan. ISM

Sickle

continued from page 1

the lead author.

Inconclusive studies

Case reports suggesting a connection between sickle cell trait and deaths of individual patients have dominated the medical literature, according to the new study. A paper published in 1987 reported a 2,800 percent increase in the risk of exertion-induced sudden deaths among African-American military recruits thought to have sickle cell trait. But the actual sickle cell status of every individual was not known.

Despite relatively weak evidence, Kurina said, it's been assumed that sickle cell trait increases the risk of death, of exertional rhabdomyolysis and of heat stroke. This assumption has led to mandated screening by organizations such as the Air Force, the Navy and the NCAA. But the American Society for Hematology and other organizations have argued that screening programs raise questions about job discrimination. The Army typically screens only before combat deployment and high-altitude activities, the study said.

For the study, the researchers reviewed the health records of 47,944 African-American soldiers who served on active duty between 2011 and 2014 and for whom sickle cell status was known. The researchers got the health records from the Stanford Military Data Repository data set, which Nelson and Kurina created. The repository includes all digitally recorded health encounters at military medical facilities or civilian institutions, general health information and official records of physical performance and mortality of all active-duty U.S. Army soldiers. The data in the repository are de-identified to protect privacy.

Kurina and her colleagues found that the risk of exertional rhabdomyolysis was only 54 percent higher among African-American soldiers with sickle cell trait than among those without it. A 54 percent increase might sound like a lot, but it's far less than the 300 percent increase caused by some ordinary prescription drugs. And smoking, obesity and increasing age each incur a heightened risk of ER that is about the same as sickle cell trait, the study showed.

Why the difference?

A major reason for the difference between the current study and previous ones, Kurina said, may be better safety for active-duty soldiers. As of 2003, soldiers who are engaged in strenuous exercise are required to drink plenty of fluids, build up to strenuous exercise gradually and take regular rests when it's hot. All of these measures are known to reduce exercise-related fatality rates, regardless of whether individuals have sickle cell trait, the study said.

"Another critical difference between our study and the earlier, population-based studies is that in our study, we knew the sickle cell status of everyone in the population," said Kurina. She and her team looked only at soldiers whose sickle cell status was confirmed by blood tests taken during their years of service, instead of from self-reported sickle cell status or past medical history, as had been done in the other studies.

"The most important thing to come out of this study is the really reassuring news that under conditions of universal precautions against dehydration and overheating, we don't see an elevation in the risk of mortality in people with sickle cell trait," said Kurina. It happens, she noted, that the lead author of the 1987 paper went on to propose and validate the measures adopted by the Army to mitigate dehydration and overheating.

The study's results call into question the need to screen service members with sickle cell trait, especially with better safety precautions during intense exertion, Kurina said.

Big data at Stanford

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill, and could not have been done without the Stanford Military Data Repository.

Kurina said she values collaborating with the military on health research. "In each of these projects," she said, "it's critical to be able to have these really productive partnerships with military partners." Kurina said she'd like to see the work repeated and confirmed in a civilian population.

Researchers from the Army, the University of Texas and the Army-Baylor University Graduate Program in Health and Business Administration contributed to the study.

This research was supported by the National Heart, Lung and Blood Institute in collaboration with the Uniformed Services University of the Health Sciences. All data used in the study were provided under a cooperative agreement with the U.S. Army Medical Command.

Stanford's Department of Medicine also supported the work. ISM

Of Note

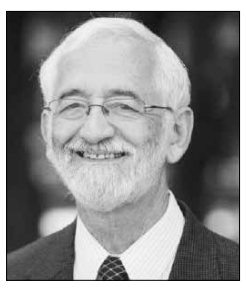
continued from page 8

Manali Patel

George Poultsides

Rajat Rohatgi

Julien Sage



Kelley Skeff

Anne Villeneuve

effective Aug. 1. Patel is an oncologist and health services researcher. Her research focuses on improving the delivery of equitable, high-value cancer care. Patel is also a staff oncologist and researcher at the VA Palo Alto Health Care System and a faculty affiliate at Stanford's Center on Health Policy/Center on Primary Care and Outcomes Research.

GEORGE POULTSIDES, MD, was promoted to associate professor of surgery, effective April 1. His research and clinical work focuses on the treatment of hepatic, pancreatic and gastrointestinal cancer, and on clinical trials of new diagnostic and therapeutic approaches.

RAJAT ROHATGI, MD, PhD, was promoted to associate professor of biochemistry and of medicine, effective Jan. 1. His research focuses on the mechanisms of cell-to-cell communication in developmental biology and cancer.

JULIEN SAGE, PhD, was promoted to professor of pediatrics and of genetics, effective Jan. 1. His research focuses on the mechanisms that control the proliferation of mammalian cells, with an emphasis on stem cells and cancer.

KELLEY SKEFF, MD, PhD, the George DeForest Barnett Professor and professor of medicine, delivered the 2016 commencement address at the Georgetown University School of Medicine, which gave him an honorary degree. He is co-director and co-founder of the Stanford Faculty Development Center for Medical Teachers.

ANNE VILLENEUVE, PhD, professor of developmental biology and of genetics, has been selected to join the American Academy of Arts and Sciences. AAAS is one of the nation's oldest and most prestigious academic societies and policy research centers. Villeneuve will be inducted in October in Cambridge, Massachusetts. ISM

OF NOTE

reports on significant honors and awards for faculty, staff and students


Raag Airan


Philip Beachy


Jonathan Bernstein


Paul Bollyky


Alexander Butwick


Lisa Chamberlain


Anne Lynn S. Chang


Lu Chen


Benjamin Chung


A. Dimitrios Colevas


Anna Cunningham


Amit Etkin


Summer Han


Brian Hargreaves


Andrew Huberman


Erik Ingelsson


Vinicio de Jesus Perez


Ioannis Karakikes


Abby King


Christin Kuo


Carolyn Lee


I. Ross McDougall


David Miklos


Thomas Montine


Mark Nicolls

RAAG AIRAN, MD, PhD, was appointed assistant professor of radiology, effective July 1. Airan, who earned his graduate degrees at Stanford, is a neuroradiologist, a bioengineer and member of the Stanford Neurosciences Institute and Stanford Bio-X. His research centers on developing translational techniques for targeted drug delivery to the central nervous system and for noninvasive neuromodulation.

PHILIP BEACHY, PhD, the Ernest and Amelia Gallo Professor, professor of biochemistry and of developmental biology, received the 2016 Katharine Berkan Judd Award Lectureship from the Memorial Sloan Kettering Cancer Center. The award recognizes a researcher who has made significant contributions to understanding cancer. Beachy delivered a lecture at the center titled "Stem cells and signaling pathways in regeneration and malignancy."

JONATHAN BERNSTEIN, MD, PhD, was promoted to associate professor of pediatrics, effective April 1. His research focuses on the genetics of autism and other developmental disorders.

PAUL BOLLYKY, MD, PhD, assistant professor of medicine and of microbiology and immunology, received a Grand Challenges Explorations grant from the Bill & Melinda Gates Foundation. He will receive $100,000 for one year and have the opportunity to compete for a $1 million grant. In collaboration with **K.C. HUANG**, PhD, associate professor of bioengineering and of microbiology and immunology, and **ERIC NELSON**, MD, PhD, instructor of pediatrics, Bollyky will investigate whether bacteriophages lead to structural changes in the lining of the intestines, which could promote the growth of healthy bacteria.

ALEXANDER BUTWICK, MD, was promoted to associate professor of anesthesiology, perioperative and pain medicine, effective March 1. His research focuses on preventing and treating postpartum hemorrhage. He is investigating risk factors for postpartum hemorrhage and postpartum anemia following cesarean deliveries.

LISA CHAMBERLAIN, MD, associate professor of pediatrics and medical director of Lucile Packard Children's Hospital Stanford's Pediatric Advocacy Program, received an Excellence in Healthcare Award from the *Silicon Valley Business Journal* for her work helping low-income children. Her research focuses on child health policy and on nonclinical factors that affect care for children with chronic illnesses.

ANNE LYNN S. CHANG, MD, was promoted to associate professor of dermatology, effective Feb 1. She is the director of the Advanced Basal Cell Carcinoma Clinic and of adult dermatologic clinical trials. Her research and clinical work focuses on aggressive basal cell carcinomas and on the mechanisms of healthy skin aging.

LU CHEN, PhD, was promoted to professor of neurosurgery and of psychiatry and behavioral sciences, effective Jan. 1. Her research focuses on the molecular mechanisms of synaptic plasticity and memory formation. She is particularly interested in investigating synaptic and cognitive dysfunction in autism spectrum disorders.

BENJAMIN CHUNG, MD, was promoted to associate professor of urology, effective May 1. He is the director of robotic surgery, and his clinical focus is the surgical treatment of prostate and kidney cancer using minimally invasive robotic techniques. His research focuses on urologic cancer outcomes and on the epidemiology of urologic cancers.

A. DIMITRIOS COLEVAS, MD, was promoted to professor of medicine, effective April 1. His interests include head and neck cancer treatment and developmental therapeutics.

ANNA CUNNINGHAM, a graduate student in chemical and systems biology, was a thematic best poster winner in the bioinorganic catalysts category at the 2016 American Society for Biochemistry and Molecular Biology meeting. Her poster was on coevolution and disease-causing mutations in glucose-6-phosphate dehydrogenase.

AMIT ETKIN, MD, PhD, was promoted to associate professor of psychiatry and behavioral sciences, effective July 1. His research focuses on understanding the neural basis of emotional disorders and their treatment, then using that knowledge to create improved therapies.

SUMMER HAN, PhD, was appointed assistant professor (research) of neurosurgery and of medicine, effective Dec. 1, 2015. Her research interests include statistical genetics, health-policy modeling and risk-prediction modeling.

BRIAN HARGREAVES, PhD, was appointed associate professor of radiology, effective Feb. 1. He directs the Body MRI research group, which develops and implements new magnetic-resonance imaging techniques, particularly in cardiovascular, abdominal, breast and musculoskeletal imaging.

ANDREW HUBERMAN, PhD, was appointed associate professor of neurobiology, effective April 1. He studies the function of the neural circuits underlying sight and how to repair them after damage from conditions such as glaucoma and traumatic brain injury. His work has implications for treating disorders of brain development, including autism and Williams syndrome.

ERIK INGELSSON, MD, PhD, was appointed professor of medicine, effective May 1. In his research, he combines analyses of large-scale studies in genomics, transcriptomics, epigenomics, proteomics and metabolomics with functional model systems to develop new insights into the pathophysiology of cardiovascular disease and related conditions, identify novel biomarkers and discover targets for drug development.

VINICIO DE JESUS PEREZ, MD, assistant professor of medicine, received a Young Physician-Scientist Award from the American Society for Clinical Investigation. The award recognizes junior researchers whose work is notable for its insight into the mechanisms of disease and the potential for new therapies. De Jesus Perez's research and clinical focus is pulmonary hypertension and lung fibrosis.

IOANNIS KARAKIKES, PhD, was appointed assistant professor (research) of cardiothoracic surgery, effective May 1. His research focuses on delineating the molecular mechanisms underlying the pathogenesis of familial cardiomyopathies using patient-specific cardiomyocytes derived from human induced pluripotent stem cells, as well as the development of biological therapies for heart failure.

ABBY KING, PhD, professor of health research and policy and of medicine, will serve as one of two co-chairs of the U.S. Department of Health and Human Services 2018 Physical Activity Guidelines Advisory Committee. The guidelines serve as the authoritative federal document providing guidance on physical activity, fitness and health. King's work focuses on chronic disease prevention and health promotion using behavioral and social ecological approaches.

CHRISTIN KUO, MD, was appointed assistant professor of pediatrics, effective May 1. She specializes in pediatric pulmonary medicine, and her research focuses on the development and function of lung neuroendocrine cells in order to improve diagnostic and therapeutic approaches for pediatric neuroendocrine-related respiratory disorders and adult neuroendocrine tumors.

CAROLYN LEE, MD, PhD, was appointed assistant professor of dermatology, effective Feb. 15. Her research focuses on discovering and functionally characterizing new oncogenes and tumor-suppressor genes in skin cancer.

I. ROSS MCDOUGALL, PhD, MB, ChB, professor emeritus of radiology and of medicine, received the Georg Charles de Hevesy Nuclear Pioneer Award from the Society of Nuclear Medicine and Molecular Imaging. The award recognizes outstanding contributions in the field of nuclear medicine. McDougall's clinical and research focus is the diagnosis and treatment of thyroid disease.

DAVID MIKLOS, MD, PhD, was promoted to associate professor of medicine, effective May 1. His research and clinical work focuses on allogeneic hematopoietic stem cell transplantation and on the use of immunotherapy to treat blood cancers.

THOMAS MONTINE, MD, PhD, was appointed professor of pathology, effective May 1. He chairs the department, having succeeded professor of pathology Stephen Galli, MD. Montine's research focuses on the structural and molecular bases of cognitive impairment in the elderly and how they give rise to Alzheimer's disease and nonmotor features of Parkinson's disease.

MARK NICOLLS, MD, was promoted to professor of medicine, effective March 1. His research focuses on the relationship between inflammation and the development of pulmonary hypertension. He also studies how microvascular health affects lung transplants.

MANALI PATEL, MD, MPH, MS, was appointed assistant professor of medicine, **See OF NOTE, page 7**