INSIDE STANFORD MEDICINE

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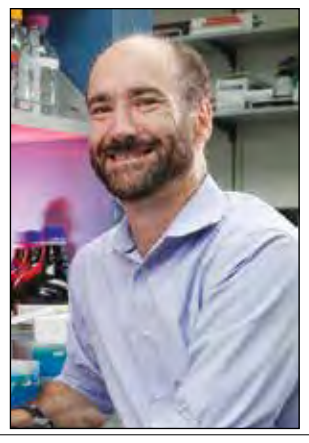

Researchers have developed a method for using genome sequencing to forecast the risk of a deadly vascular condition.

Page 5

Antidepressive effects of ketamine tied to opioid system in brain, scientists say

By Kimber Price

STEVE FISCH

Boris Heifets, Alan Schatzberg, Carolyn Rodriguez and Nolan Williams are co-authors of a paper on the mechanism behind ketamine's antidepressive effects.

Scientists at the School of Medicine have discovered that ketamine works as an antidepressant at least in part by activating the brain's opioid system.

The finding overturns previously held beliefs that the drug's antidepressant effects stemmed solely from its impact on the glutamate system. These beliefs led to the widespread use of ketamine to treat depression and spurred the development of glutamate-blocking drugs for use as antidepressants.

The new finding also highlights the interaction between depression, pain and opioid addiction and presents an opportunity for clinicians to reframe treatment approaches for these three public health crises.

The research is believed to be the first to address how ketamine works in the human brain to provide relief from depression. A paper describing the work was published Aug. 29 in *The American Journal of Psychiatry*.

"Before we did the study, I wasn't sure that ketamine really worked to treat depression. Now I know the drug works, but it doesn't work like everyone thought it was working," said Alan Schatzberg, MD, the Kenneth T. Norris Jr. Professor of Psychiatry and Behavioral Sciences, who shares senior authorship of the paper with Carolyn Rodriguez, MD, PhD, assistant professor of psychiatry and behavioral sciences.

Ketamine's origins

Ketamine was developed in the 1960s and has been used for decades as an anesthetic during surgery. It can cause dissociative side effects, including hallucinations, and has been used as a recreational drug. If used regularly, it can lead to dependence.

Although the Food and Drug Administration has not approved the drug's use for depression, some doctors have prescribed it "off-label" in recent years as a rapid but short-acting antidepressant. Traditional antidepressants, such as selective serotonin reuptake inhibitors, take four to six weeks to have an effect but don't work in two-thirds of patients who try them. Stand-alone ketamine clinics have popped up all over the country to administer expensive intravenous infusions of ketamine to patients, even though some scientists caution that not enough is known about the drug to warrant its widespread use for depression.

Ketamine infusions are also used to treat chronic pain, which is a common condition in depressed patients. Exactly how ketamine blunts pain is not fully understood, but it is known to work at least in part on the opioid system. The Stanford researchers wanted to see if the antidepressive effects of ketamine were also generated by ketamine's activation of the opioid system. They sought to answer this question through a small clinical trial in which people with depression were given an See KETAMINE, page 7

Study: Drought predicts decrease in snakebites

By Tracie White

Grant Lipman, MD, an emergency medicine physician at Stanford Medicine, was running through the brown hills behind the campus a few years ago during a severe drought when he came across a 3-foot-long rattlesnake lying by the trail. When a colleague mentioned he'd experienced a similar rattlesnake sighting, Lipman got to thinking.

"I wondered if there are more snakebites during droughts," said Lipman, clinical associate professor of emergency medicine at the See SNAKEBITE, page 6

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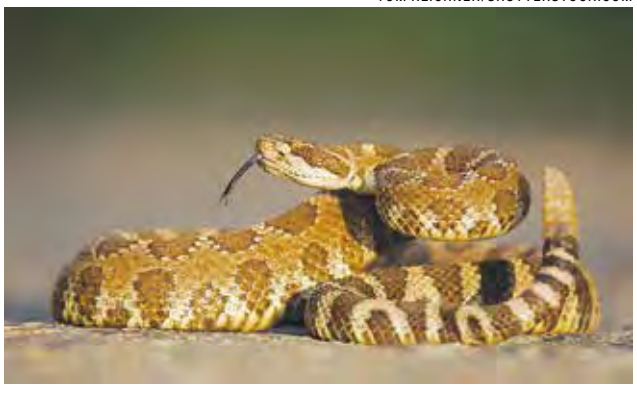

Stanford Medicine honors Chris Dawes, transformational leader in children's health

By Ruthann Richter

Children's hospital founder Lucile Salter Packard never actually met Christopher Dawes. Yet he would serve as the enduring champion of her vision for nearly 30 years.

The longtime CEO of Lucile Packard Children's Hospital Stanford, Dawes retired at the end of August. He was honored Sept. 8 for his decades of leadership during a celebration at the hospital.

The hospital was inspired in part by the Stanford Convalescent Home for Children, where Packard, as a student at Stanford in the 1930s, volunteered in helping sick children as they recuperated outdoors in a camplike setting.

After Packard's namesake hospital opened in 1991, it evolved to become a comprehensive, technology-rich enterprise with a national reputation and reach. Yet it never lost that warm and friendly feel, thanks largely to Dawes' commitment to her establishing vision.

"Under his guiding hand we went from being a very lovely community hospital, nicely designed and family-friendly, to a world-class children's hospital, drawing patients from across the United States and around the world," said Susan Packard Orr, Lucile Packard's daughter, who served on the hospital's board of directors from 1993 to 2017.

STANFORD CHILDREN'S HEALTH

Christopher Dawes joined the staff of the children's hospital in 1989 and was named chief operating officer in 1996 and CEO in 2000.

At the Sept. 8 event, the Lucile Packard Foundation for Children's Health dedicated the front garden, on the hospital's recently expanded campus, in Dawes' honor. The celebration was an opportunity for Dawes' longtime peers and colleagues to wish him well.

Lloyd Minor, MD, dean of See DAWES, page 8

African armed conflict kills more children indirectly than in fighting

By Beth Duff-Brown

More children die from the indirect impact of armed conflicts in Africa than by weapons used in those conflicts, according to a new study led by Stanford researchers.

The research is the first comprehensive analysis of the large and lingering effects of armed conflicts — civil wars, rebellions and interstate conflicts — on the health of noncombatants.

The numbers are sobering: between 3.1 million and 3.5 million infants born within 30 miles of armed conflict died from indirect consequences of battles from 1995 to 2015. That number jumps to 5 million deaths of children ages 5 and younger in those same conflict zones.

"The indirect effects of conflict on children are so much greater than the direct deaths from warfare," said Eran Bendavid, MD, senior author of the study, which was published Aug. 30 in *The Lancet*.

The authors also found evidence of increased mortality risk from as far away as 60 miles from armed conflicts and for eight years after them. Being born in the same year as a nearby armed conflict is riskiest for children younger than 1, the authors found, but the lingering effects remain elevated over the years and, even after a conflict has ended, raise the risk of death for infants by over 30 percent.

In the entire continent, the authors wrote, the number of infant deaths related to armed conflicts from 1995 to 2015 was more than three times the number of direct deaths from these conflicts. Further, they found that among babies born within a 30-mile range of armed conflict, the risk of dying before age 1 was on average 7.7 percent higher than it was for babies born outside that range.

The authors recognize it is not surprising that African children are vulnerable to nearby armed conflict. But they show that this burden is substantially higher than previously indicated.

'Surprisingly poorly understood'

"We wanted to understand the effects of war and conflict, and discovered that this was surprisingly poorly understood," said Bendavid, associate professor of medicine and core faculty member at Stanford Health Policy. "The most authoritative source, the Global Burden of Disease, only counts the direct deaths from conflict, and those estimates suggest that conflicts are a minuscule cause of death."

Paul Wise, MD, MPH, professor of pediatrics and a senior fellow at Stanford's Freeman Spogli Institute for International Studies, has long argued that lack of health care, vaccines, food, water and shelter kills more civilians than bombs and bullets do.

This study has now put data behind the theory when it comes to children.

"We hope to redefine what conflict means for civilian populations by showing how enduring and how far-reaching the destructive effects of conflict can be on child health," said Bendavid, an infectious disease physician.

Eran Bendavid

"Lack of access to key health services or to adequate nutrition are the standard explanations for stubbornly high infant mortality rates in parts of Africa," said Marshall Burke, PhD, an assistant professor of earth systems science and fellow at the Center on Food Security and the Environment. "But our data suggest that conflict can itself be a key driver of these outcomes, affecting health services and nutritional outcomes hundreds of kilometers away and for nearly a decade after the conflict event."

The results suggest efforts to reduce conflict could lead to large health benefits for children, the authors said.

Gathering the data

The researchers matched data on 15,441 armed-conflict events with data on 1.99 million births and subsequent child survival across 35 African countries. The primary conflict data came from the Uppsala Conflict Data Program's Georeferenced Event Dataset, which includes detailed data about the time, location, type and intensity of conflicts from 1946 to 2016.

The authors also used all available data from the Demographic and Health Surveys, funded by the U.S. Agency for International Development, conducted in 35 African countries from 1995 to 2015 as the primary sources on child mortality in their analysis.

The data, they said, show that the indirect toll of armed conflict among children is three to five times greater than the estimated number of direct casualties in conflict. The total burden is likely even higher, since the authors focused on children and not the effects on women and other vulnerable populations.

Zachary Wagner, PhD, a former postdoctoral scholar at Stanford and lead author of the study, said he knows few are surprised that conflict is bad for child health.

"However, this work shows that the relationship between conflict and child mortality is stronger than previously thought, and children in conflict zones remain at risk for many years after the conflict ends," Wagner said.

Another Stanford co-author was Sam Heft-Neal, PhD, a research scholar at Center for Food Security and the Environment and Department. **ISM**

Scientists prevent immune response to gene therapy in mice

By Bruce Goldman

School of Medicine researchers have demonstrated that gene therapy can be effective without causing a dangerous side effect common to all gene therapy: an autoimmune reaction to the normal protein, which the patient's immune system is encountering for the first time.

The researchers showed this in a mouse model that accurately recapitulates Duchenne muscular dystrophy. One in every 5,000 boys is born with this crippling disease, which leaves patients wheelchair-bound by mid-adolescence and is typically fatal by young adulthood. It stems from a genetic defect that deprives skeletal and cardiac muscles of a working version of a protein called dystrophin.

"Gene therapy is on the cusp of becoming a mainstream approach for treating single-gene disorders," said Lawrence Steinman, MD, professor of neurology and neurological sciences and of pediatrics at Stanford. "But there's a catch: If you give a gene that's a recipe for a normal protein to someone with a faulty version of the gene, whose body never made the normal protein before, that person's immune system will mount a reaction — in some cases, a lethal one — to the normal protein, just as it would to any foreign protein. We think we've solved that problem."

The findings are described in a study published online Sept. 3 in the *Proceedings of the National Academy of Sciences*. Steinman, who holds the George A. Zimmermann Professorship, is the study's senior author.

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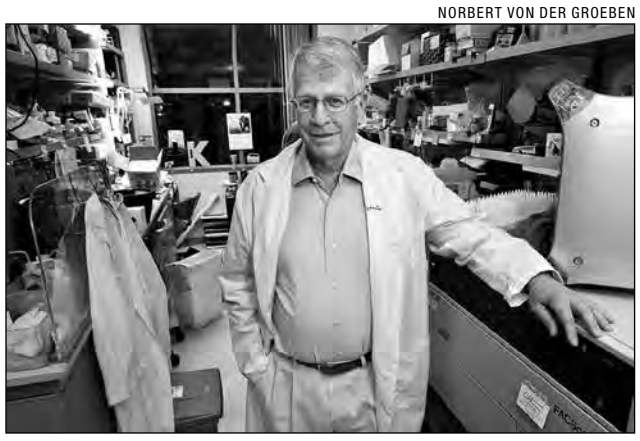

Lawrence Steinman and his colleagues demonstrated that they can stave off a dangerous side effect of gene therapy in mice.

The lead author is senior research scientist Peggy Ho, PhD.

Going viral

Duchenne muscular dystrophy is the result of a single defective gene, making it an excellent candidate for gene therapy, in which a patient's faulty gene is replaced with the correct version. One way to do this is by co-opting viruses, which are simple entities that are adept at infecting cells and then forcing every invaded cell's reproductive machinery to copy their own viral genes. For gene therapy, viruses are modified by ridding them of unwanted genes, retaining the ones necessary for infectivity and adding the therapeutic gene to be delivered to a patient.

The gene encoding dystrophin is far too big for a gene-hauling virus to take onboard. Fortunately, a mere fraction of the entire gene is enough to generate a reasonably functional version of dystrophin, called microdystrophin. The abridged gene fits snugly into a viral delivery vehicle designed some time ago by Jeffrey Chamberlain, PhD, a co-author of the study and a professor of neurology, medicine and biochemistry at the University of Washington.

But there's still that sticky autoimmunity problem. To get around it, Steinman and his colleagues spliced the gene for microdystrophin into a different kind of delivery vehicle called a plasmid.

Plasmids are tiny rings of DNA that bacteria often trade back and forth to disseminate important traits, such as drug resistance, among one another. The particular bacterial plasmid the investigators co-opted ordinarily contains several short DNA sequences, or motifs, that the immune system recognizes as suspicious and to which it mounts a strong response.

Inducing tolerance

But some years ago, Steinman and a few other Stanford scientists — including Ho and study co-author William Robinson, MD, PhD, professor of immunology and rheumatology — figured out how to replace those troublesome DNA motifs with another set of DNA sequences that, far from exacerbating the immune response, subdue it. This immune-tolerance-inducing plasmid has been deployed in clinical trials for two different autoimmune conditions, with promising results.

For the new study, the researchers used a one-two punch to deliver gene therapy and protection against autoimmunity to the mice: viral delivery of the microdystrophin gene, followed by the plasmid-assisted induction of tolerance to microdystrophin.

Fifteen 6-week-old mice — an age roughly equivalent to that of a young child — bioengineered to lack functioning dystrophin were injected with the virus carrying microdystrophin. Starting a week later, they were divided into three groups and given weekly injections for 32 weeks of either a dummy solution; the dummy solution and the plasmid absent the microdystrophin gene; or the plasmid with the microdystrophin gene.

At the end of the 32-week period, by which time the mice were the human equivalent of young adults, the ones that got the microdystrophin-loaded plasmid had significantly greater muscular strength and substantially more dystrophin-producing muscle fibers. They had lower levels of key bloodborne signaling chemicals that carry inflammatory messages between immune cells, and they had weakened antibody responses to normally immunogenic portions of microdystrophin.

"It's still early days here — this was, after all, a mouse experiment — but it seems we can induce tolerance to a wide assortment of formerly immunogenic proteins by inserting the gene for the protein of interest into the plasmid," Steinman said. **ISM**

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STANFORD MEDICINE

Diseased heart muscle cells have abnormally shortened telomeres

By Krista Conger

People with a form of heart disease called cardiomyopathy have abnormally short telomeres in heart muscle cells responsible for contraction, according to a new study by researchers at the School of Medicine.

A telomere is a DNA sequence that serves as a protective cap on the ends of chromosomes.

The finding dovetails with a previous study showing that people with Duchenne muscular dystrophy, a genetic muscle-wasting disease, also have short telomeres in their heart muscle cells, or cardiomyocytes. These patients often die at an early age from heart failure.

Although it's not yet known whether the stunted telomeres directly affect the function of the cardiomyocytes or arise as a result of heart failure, the finding opens the door to an intriguing line of research and drug discovery. It also may one day allow researchers and clinicians to identify people at risk for heart failure due to cardiomyopathy.

"The shortening of telomeres in cardiomyocytes appears to be a reliable hallmark of cardiac failures that arise due to genetic defects, and it's very specific to cells that require the missing contractile proteins such as dystrophin, troponin T or myosin heavy chain, among others," said Helen Blau, PhD, professor of microbiology and immunology and member of the Stanford Cardiovascular Institute.

Blau, the Donald E. and Delia B. Baxter Foundation Professor and director of the Baxter Laboratory for Stem Cell Biology, is the senior author of the study, which was published online Aug. 27 in *Proceedings of the National Academy of Sciences*. Alex Chang, PhD, an instructor of cardiovascular medicine and of microbiology and immunology, is the lead author.

Shortening with cell division

In most cells, telomeres naturally shorten each time the cell divides. But cardiomyocytes divide infrequently, and their telomere lengths remain relatively stable throughout one's life.

In humans, Duchenne muscular dystrophy, which is caused by a mutation in the dystrophin gene, is characterized by progressive muscle weakness and eventual death due to cardiac complications. In earlier work, Blau and her colleagues observed that although mice with the corresponding mutation in dystrophin displayed the muscle wasting symptoms, their hearts functioned normally. The researchers realized that a key difference between humans and mice is the length of each species' telomeres: Human telomeres are relatively short at 5-15 kilobases, but mice have telomeres approaching 40 kilobases. When the investigators introduced a second mutation in the mice that reduced telomere length to more closely match that of humans, the animals began to display the typical symptoms of the disease, including heart failure.

Helen Blau

A subsequent study in the Blau lab found that, in mice, telomere shortening triggered a DNA-damage response that compromised the function of the cells' energy generators, or mitochondria. As a result, cardiomyocytes were unable to efficiently pump blood throughout the body.

"Because we found in a previous study that cardiomyocytes from boys who had died of Duchenne muscular dystrophy had telomeres that were about 50 percent shorter than those from individuals without the disease," Blau said, "we wondered whether people with other genetic heart conditions, such as cardiomyopathies, might also have cardiomyocytes with abnormally shortened telomeres." Blau and Chang collaborated with several other members of Stanford's Cardiovascular Institute to investigate the question.

Using iPS cells

A cardiomyopathy is a condition in which the heart is unusually large, thickened or stiff. This affects its ability to pump blood effectively. One of every 500-2,500 people worldwide is affected, and cardiomyopathies are a leading cause for heart transplantation. Dilated cardiomyopathy occurs when the left ventricle is enlarged, while hypertrophic cardiomyopathy is caused by a thickening of the heart muscle.

Chang compared the telomere length in cardiomyocytes from 11 patients with dilated or hypertrophic cardiomyopathy due to genetic mutations with nine people who had died from causes unrelated to heart disease. He found that telomeres from the cardiomyopathy patients were about 25-40 percent shorter than those of the control subjects. In contrast, the telomere length in nonbeating heart cells of the blood vessels did not vary significantly between the two groups.

Chang saw similar results in cardiomyocytes generated from induced pluripotent stem cells: Those generated from people with cardiomyopathies had significantly shorter telomeres than those generated from unaffected relatives.

"Within 20 days we could see the telomere shortening happening in the laboratory-grown cardiomyocytes from diseased patients, suggesting this is a cell-intrinsic property," Blau said.

The ability to use iPS cell technology to generate affected cardiomyocytes also means that it should be possible to quickly and easily test for compounds or drugs that interfere with the telomere shortening, with a view to finding drugs to abrogate the disease in humans, the researchers believe.

"Now we can study this phenomenon in the lab in real time and start to ask questions about cause and effect," Blau said. "We'd love to know, for example, how this shortening might impact the DNA damage response, mitochondrial dysfunction and cell-death pathways. It opens up a whole new line of investigation." **ISM**

State of Stanford Medicine is scheduled for Sept. 17

Exciting announcements about the year ahead. Updates on key issues. Behind-the-scenes perspectives.

Stanford Medicine's leadership will address a variety of topics and discuss the future of the School of Medicine and the two hospitals at the State of Stanford Medicine at noon Sept. 17 at the Li Ka Shing Center for Learning and Knowledge.

Lloyd Minor, MD, dean of the School of Medicine; David Entwistle, president and CEO of Stanford Health Care; and Dennis Lund, MD, interim president and CEO of Stanford Children's Health, will:

- Share the latest on affordability, space, construction and more.
- Detail progress with the integrated strategic plan and its rollout.
- Showcase cutting-edge research shaping the future of medicine.

Attendees will also receive lunch and Stanford Medicine giveaways.

Members of the Stanford Medicine community can register at https://stan.md/2NX3epp. To view the event via livestream, fill out the form at https://stan.md/2M8qSKF. **ISM**

Same mutations underpin spread of cancer in individuals

By Hanae Armitage

Scientists have arrived at a key understanding about how cancers in individual patients spread, or metastasize, a study from the School of Medicine and other collaborating institutions reports.

The study found that mutations that drive cancer growth are common among metastases in a single patient.

Johannes Reiter

Most cancer-related deaths are caused by metastases, or secondary tumors in distant locations of the body that have spread away from the original, primary tumor. While primary tumors can often be surgically removed, metastatic tumors typically require treatment such as standard chemotherapy or targeted therapy. The success of such new targeted therapies depends on the presence of a specific mutation in all cancer cells, in particular in metastatic tumors.

Until now, most studies that aimed to decode the genetic variability, or heterogeneity, of cancers focused mainly on primary tumors. And while that information is still extremely valuable, it leaves much of the story untold; cancer cells are notorious for their ability to change, evolve and evade treatments, particularly as they spread in the body.

"We took samples from multiple untreated metastases of each patient, and we observed a mix of overlapping and differing driver mutations," said Johannes Reiter, PhD, an instructor of radiology at Stanford. "But through computational analyses, we inferred that the driver mutations that were most likely to contribute to cancer development were shared among all metastases in each patient."

Mutation X

A tumor comprised of billions of cells is riddled with genetic mutations; cancer cells and normal cells acquire multiple mutations as they divide. Identifying the driver mutations that significantly contribute to cancer development is critical to precision oncology, in which doctors aim to treat a patient's cancer based on its genetic composition.

"Doctors might take a sample of the primary tumor and find some mutation — call it mutation X — in a driver gene and then treat it with a drug that targets that driver gene to specifically kill all cells that have mutation X," Reiter said. "But what if that particular mutation is only present in some of the metastases of the patient?" Only the metastases comprised of cells with mutation X would respond to treatment and shrink or go extinct; those without mutation X would continue to grow. In the end, the doctor wouldn't see a remission of the patient's cancer if driver mutations were different across its metastases. "So that's why it's very important for us to know whether or not the driver gene mutations are the same across all metastases of the patient," Reiter said.

The paper was published Sept. 7 in *Science*. Reiter; postdoctoral scholar Alvin Makohon-Moore, PhD, at Memorial Sloan Kettering Cancer Center; and graduate student Jeffrey Gerold, at Harvard University, share lead authorship. Martin Nowak, PhD, professor of biology and of mathematics at Harvard University, is the senior author.

Driver mutations occur in genes known to be involved in tumor genesis — such as genes that typically control cell division. When mutated, these genes may spur a cell to divide in an uncontrolled fashion, generating cancer. While hundreds of driver genes have been identified across cancer types over the last decades, relatively few mutations are thought to be important in the development of an individual's cancers. Likewise, it's hard to know which ones are truly culpable and which are "passenger mutations," or innocuous mutations that occur by happenstance and are just along for the ride — even if they occurred in a driver gene.

To see whether driver gene mutations were the same across all metastases of a patient's cancer, Reiter and his colleagues analyzed DNA samples from 76 untreated metastases from a group of 20 patients with eight different cancer types, making sure at least two distinct metastases were sampled in each person.

Like choosing the right suspects in a lineup, the scientists picked out the mutations that occurred in known driver genes and investigated whether or not they were found in all the sampled metastases of an individual patient. In some cancers, the researchers only identified two driver gene mutations; in others, there were as many as 18.

By analyzing their data against massive databases that hold mutational data of more than 25,000 previously sequenced cancers, they found that the driver gene mutations that were shared among all metastases in an individual were also frequently mutated in previously sequenced cancers, indicating that these mutations are the true drivers of the disease and play a critical role during cancer development.

The scientists also saw that the few driver gene mutations that were not found across all metastases of a patient's cancer were predicted to have weak or no functional consequences. In other words, the mutations not shared among all metastases were likely passenger mutations, despite their occurrence in driver genes, and likely did not play a critical role during cancer development. This finding could open new avenues to understanding and interpreting tumor biopsies in the future, Reiter said.

Confirming driver mutations

Reiter said that, for now, it's too early to generalize these findings due to the small cohort size. But the study does suggest that tumor samples from a single metastasis typically represent the full set of functional driver mutations of a patient's cancer. Next, Reiter hopes to expand the study to more patients with different cancer types.

"It's rare that we can access untreated metastases, and that's fortunate for the patients, but we do want to look at the concept of our findings in a larger cohort," Reiter said. **ISM**

Researchers' model could help stem national opioid crisis

By Tom Abate

Stanford researchers have developed a mathematical model that could help public health officials and policymakers curb an opioid epidemic that took the lives of an estimated 49,000 Americans last year.

The model includes data about prescriptions, addictions and overdoses in the United States. It can be used to consider "what if" scenarios similar to those that business leaders run through to project how changing product features or prices are likely to affect sales and profits, said Margaret Brandeau, PhD, the Coleman F. Fung Professor in the School of Engineering and a professor of management science and engineering.

Margaret Brandeau

Brandeau is the senior author of a paper that describes how the model analyzes opioid use and addiction among Americans whose initial exposure to these drugs came either from being prescribed pills or gaining illicit access to pills.

The paper was published Aug. 23 in the *American Journal of Public Health*. The lead author is graduate student Allison Pitt.

'Like squeezing a balloon'

Using models is relatively new in the realm of public health, where responsibility for solving problems is widely diffused among a variety of governmental and private sector decision-makers, said co-author Keith Humphreys, PhD, the Esther Ting Memorial Professor and a professor of psychiatry and behavioral sciences.

"Confronting this crisis is like squeezing a balloon," said Humphreys, an expert on substance abuse. "When you touch one aspect of the situation, an unpleasant consequence often pops up somewhere else."

The paper cites the daunting facts of the opioid crisis: Between 1990 and 2010, there was a 400 percent spike in prescriptions for opioid painkillers. Today, roughly 3.5 million Americans have become addicted to opioids as a result of an initial exposure to opioid pills. Yet, as doctors have begun responding to the crisis by reducing prescriptions, overdose deaths have increased because former pill addicts, unable to get the quality-controlled drug, have started buying and overdosing on heroin.

Against this bleak backdrop, the Stanford model projects that if doctors can cut prescriptions by 25 percent over a 10-year period, while policymakers expand drug treatment programs, addictions and deaths will start falling by 2026.

"People want this to be over sooner, but the model shows that we've dug ourselves such a deep hole that it will take time to climb out," Brandeau said.

Putting the puzzle together

Humphreys said the model the authors created puts multiple parts of the opioid-crisis puzzle together so that government and private-sector officials can see how addressing any given aspect of the crisis will affect the big picture.

"This is perhaps the most complex public health challenge we've ever faced," Humphreys said. "We need this tool to avoid policy paralysis."

Keith Humphreys

Pitt, the lead author, spent the last two years collecting data on opioid use and addiction and other variables. The researchers based their model on data from 2015. Thereafter the model made projections for such variables as what fraction of American adults experience moderate to severe pain each year; how many opioid painkillers are prescribed; how many people have become addicted to opioids by starting with pills; and how many Americans who initially became addicted through exposure to pills die each year from overdoses of other pharmaceutical opioids or heroin.

In 2015, when 188 million opioid prescriptions were issued, 3.5 million Americans were already addicted to opioids through initial exposure to pills. Of these, the researchers estimated that roughly 16,000 died as a result of a pill overdoses. Another 22,000 who were initially hooked on pills died that year from heroin overdoses. This crossover from pills to street drugs, which often occurs when pill addicts can no longer get prescription medications, is one tragic aspect of the opioid crisis. In addition to these 38,000 deaths related to pill exposure, an estimated 26,000 more Americans died of overdoses from other drugs, mainly from cocaine and methamphetamine in 2015. But the Stanford study does not factor these deaths into the model.

Instead, the researchers focused on overdoses that could be traced to pill exposure and projected forward 10 years to make educated guesses about how different scenarios would be likely to decrease addiction and death rates stemming from pharmaceutical opioids. The first, or baseline, scenario was to project the status quo. If current trends prevail, the model projects that 188 million prescriptions would still be written in 2026, and that by then an estimated 4.3 million Americans would have become addicts through an initial exposure to pills. Pill-connected overdose deaths would likely soar to an estimated 50,000, compared with 38,000 in 2015.

Considering the 'what ifs'

After establishing this baseline, the researchers considered various scenarios by which the epidemic might be slowed: What if physicians reduced new prescriptions across the board? What if there were controls on refills? What if there were easy ways for patients to get rid of their excess pills so they don't get misused? What if various post-addiction treatments were made more available?

The scenario that assumes physicians reduce opioid prescriptions by 25 percent resulted in 2,500 fewer overdoses over 10 years than the status quo. "We must restrict the supply of pills to have any hope of bringing this crisis under control," Brandeau said.

The model considers the likelihood that as pills become unavailable, more opioid addicts will buy street heroin — a deadlier opioid with a higher chance of overdose. The researchers highlighted two treatment measures that, when combined with prescription cutbacks, seem most effective at reducing overdose deaths. The first policy is to greatly increase the availability of naloxone, a drug that can reverse the effects of an overdose if administered before the person's body shuts down from what physicians call opioid poisoning. "Emergency rooms can administer naloxone if a person is brought to them in time, but we have to get this life-saving treatment more broadly into the hands of first responders," Humphreys said.

The researchers also advocate greatly expanding post-addiction drug treatment programs by, for instance, helping opioid addicts quit by providing them with methadone to alleviate the physical symptoms of withdrawal.

The researchers say that these three measures — a 25 percent reduction in prescriptions, greater access to naloxone and greatly expanded methadone treatment — could together reduce overdose deaths by 6,000 over 10 years compared with the status quo estimate of roughly 50,000.

"To effectively combat the epidemic, we need a portfolio of interventions," said Brandeau. "We need policies to prevent individuals from becoming addicted in the first place, but we also need policies to treat addiction and mitigate its effects." ISM

Liquid biopsy predicts lymphoma therapy success within days

By Krista Conger

A blood test can predict which patients with a type of cancer called diffuse large B cell lymphoma are likely to respond positively to initial therapy and which are likely to need more aggressive treatment, according to a multicenter study led by researchers at the School of Medicine.

The study validates the clinical usefulness of tracking the rise and fall of circulating tumor DNA, or ctDNA, in the blood of patients before and after therapy. It suggests that clinicians may soon be able to determine how a patient is responding to treatment within days or weeks of starting therapy rather than waiting until therapy is completed five to six months later.

"Although conventional therapy can cure the majority of patients with even advanced B cell lymphomas, some don't respond to initial treatment," said associate professor of medicine Ash Alizadeh, MD, PhD. "But we don't know which ones until several months have passed. Now we can predict nonresponders within 21 days after the initiation of treatment by tracking the levels of ctDNA in a patient's blood. We can look earlier and make a reliable prediction about outcome."

The study was published online Aug. 20 in the *Journal of Clinical Oncology*. Alizadeh shares senior authorship with associate professor of radiation oncology Maximilian Diehn, MD, PhD. Instructor of medicine David Kurtz, MD, PhD, and postdoctoral scholar Florian Scherer, MD, are the lead authors.

Varying responses to treatment

Diffuse large B cell lymphoma, a blood cancer, is the most common type of non-Hodgkin lymphoma. Because it is highly biologically variable, patients vary widely in their response to treatment. Although most people are cured by conventional therapy, about one-third are not. Being able to predict early in the course of treatment those who will need additional or more aggressive therapies would be a significant boon to both clinicians and patients.

Circulating tumor DNA is released into the blood by dying cancer cells. Learning to pick out and read these DNA sequences among the thousands or even millions of other noncancerous sequences in the blood can provide valuable insight into the course of the disease and the effectiveness of therapy. Recently, Diehn and Alizadeh showed that ctDNA tracking can also predict lung cancer recurrence weeks or months before any clinical symptoms arise.

"Combined with our recent study on lung cancer, our new findings speak to the power and likely utility of using ctDNA to assess how well cancer treatments are working in an individual patient. We are very hopeful that the approach will ultimately be extensible to most if not all cancer types," Diehn said.

MARK TUSCHMAN

Maximilian Diehn and Ash Alizadeh are senior authors of a study that found a blood test could show whether patients with a type of blood cancer were responding well to initial treatment or needed more agressive treatment.

In this study, the researchers tracked ctDNA levels in 217 people with diffuse large B cell lymphoma who were treated at six medical centers — three in the United States and three in Europe. For each patient, they compared levels of ctDNA before treatment began with the levels after the first and second rounds of conventional chemotherapy. They then correlated those changes with each patient's outcome.

They found that ctDNA was detectable prior to the initiation of therapy in 98 percent of the people studied. And, as would be expected, the amount of ctDNA in the blood dropped in all patients once treatment began. But the precipitousness of the decline varied. Those people whose ctDNA levels dropped a hundredfold after the first round or three-hundredfold by the second round were much more likely to live 24 months or more without experiencing a recurrence of their disease than those whose ctDNA levels declined more slowly.

"We found that ctDNA levels serve as a very sensitive and specific biomarker of response to therapy within as few as 21 days," Kurtz said. "Every year, about 30,000 people in the United States are diagnosed with diffuse large B cell lymphoma and, for the most part, they're treated with six cycles of combination therapy. But we know that not all patients need six cycles. A large fraction could be cured with fewer cycles — maybe even just two. If we can identify those people who are responding extremely well, we could spare them additional treatments. Conversely, we could intensify the therapy or seek other options for those who are not responding as well as we would have hoped." ISM

Risk of deadly vascular condition forecasted from DNA sequences

By Hanae Armitage

A new approach that distills deluges of genetic data and patient health records has identified a set of telltale patterns that can predict a person's risk for a common, and often fatal, cardiovascular disease, according to a new study from the School of Medicine.

Although the method, which uses a form of artificial intelligence called machine learning, has so far only been used to predict the likelihood of this particular condition — called abdominal aortic aneurysm, or AAA — it's proof that such an approach could decipher the molecular nuances that put people at risk for just about any complex genetic disease.

"Right now, genome sequencing is starting to make its mark," said Michael Snyder, PhD, professor and chair of genetics at Stanford. "It's being used a lot in cancer, or to solve mystery diseases. But there's still a big open question: How much can we use it for predicting disease risk?"

It turns out, quite a bit.

Typically, researchers and health care providers use genetic testing to look for DNA sequences that may correspond to an increased risk for a particular illness. Mutations in the BRCA1 and BRCA2 genes, for instance, may signal an increased risk of breast cancer. But the method that Snyder and his colleagues developed doesn't work like that. It's not looking for one standout gene or mutation; it's looking for a slew of complex mutational patterns, and how those genetic errors play into a person's health and risk for disease.

The method seeks to identify any likely disease-causing culprits in an "agnostic" manner, meaning that it combs through an onslaught of genetic information from patients with AAA, looking for commonalities. This, Snyder said, is the key to unraveling any number of genetic diseases. It's not often the case that one, two or even a handful of genes take sole responsibility for a condition. Far more likely is that it's a whole bunch of them. The idea is that it takes a village to cause a disease, and by using this new method, those villagers can be identified.

The study was published Sept. 6 in *Cell*. Snyder and Philip Tsao, PhD, professor of medicine, share senior authorship. Instructor Jingjing Li, PhD; research manager Cuiping Pan, PhD; and postdoctoral scholar Sai Zhang, PhD, are the lead authors.

Typically diagnosed at death

AAA afflicts upward of 3 million people every year and is the 10th-leading killer in the United States. Patients with AAA have an enlarged aorta, the main artery of the body, which slowly balloons over time until, in the worst of cases, it ruptures. To make matters worse, these types of aneurysms rarely show symptoms. So in many cases, the condition silently escalates, which is in part what makes it so dangerous.

Yet AAA is pretty amenable to behavioral change. Things like smoking and high blood pressure intensify the condition, while higher levels of HDL, or "good" cholesterol, help decrease the risk. So, if people know they are at risk early on, they can ideally adjust their lifestyle to avoid exacerbation or onset altogether.

"What's important to note about AAA is that it's irreversible, so once your aorta starts enlarging, it's not like you can unenlarge it. And typically, the disease is discovered when the aorta bursts, and by that time it's 90 percent lethal," said Snyder, the Stanford W. Ascherman, MD, FACS, Professor in Genetics. "So here's this irreversible disease, no way to predict it. No one has ever set up a predictive test for it and, just from a genome sequence, we found that we could actually predict with about 70 percent accuracy who is at high risk for AAA." When other details from electronic patient records were added, like whether a patient smoked and his or her cholesterol levels, accuracy increased to 80 percent, Snyder said.

The method Snyder and his team devised relies on an algorithm they call the Hierarchical Estimate From Agnostic Learning, or HEAL, which analyzed genomic data from 268 patients with AAA and scanned the mass of information for any genes that were found to be mutated across the population. The algorithm identified 60 genes that were hypermutated in the AAA patients. Some genes played roles in blood-vessel function and aneurysm development — a nod to HEAL's accuracy — but others, more surprisingly, were associated with regulation of immune function, revealing that the mutational landscape of this disease is complex, involving niches of physiology that weren't necessarily expected.

PAUL SAKUMA

Michael Snyder and his colleagues used an approach that draws on genetic data and patient health records to predict a person's risk for an often fatal type of cardiovascular disease.

The team further confirmed their findings using HEAL in a control group, double-checking that the AAA-related mutational patterns were not seen among 133 healthy individuals. And indeed, there was no significant overlap.

For other diseases

"HEAL could, therefore, uncover new research directions and potential therapeutic targets for devastating diseases such as AAA," said Tsao, who is also the director of the Veterans Affairs Palo Alto Epidemiology Research and Information Center for Genomics.

The key, Snyder said, is that the findings were entirely unbiased. The researchers didn't say, "We think gene X, Y and Z might play a role in AAA." They fed the genetic information into HEAL and asked if there were genes or sets of genes that were enriched for mutation. "We let machine learning figure it out, and that's something that, to our knowledge, has never been done before," Snyder said.

In their next phase of work, Snyder and his group are looking into using HEAL to detect the elusive genetic underpinnings of preterm birth and autism.

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 research was funded by National Institutes of Health, the University of California and the Veterans Affairs Office of Research and Development

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

New issue of magazine explores the vision for Stanford Medicine

By Patricia Hannon

Stanford's three medical organizations this summer unveiled a plan that, for the first time, lays out how they will work together to achieve a shared vision.

With an eye toward leveraging their combined strengths, the entities — the School of Medicine, Stanford Children's Health and Stanford Health Care — are tapping into opportunities to improve health care locally and around the globe.

The new issue of *Stanford Medicine* explores the process they undertook to weave an integrated strategic plan, as well as how their vision is playing out in research, education and health care. The process included input from about 4,000 people at the three entities, known collectively as Stanford Medicine.

"Several people who have been here for years have come up to me and said, 'You know, the School of Medicine and the hospitals have never worked as well together as they are now,'" said Lloyd Minor, MD, dean of the School of Medicine. "And that's very meaningful to me. That holds promise not just for Stanford Medicine, but for all the lives we hope to improve."

In a story about developing the unified plan, you'll hear how priorities were set and how the plan addresses the objectives of being value-focused, digitally driven and uniquely Stanford.

Several articles highlight research that reflects those objectives:

- A palliative care specialist and an informatics expert are using a tool that combines artificial intelligence with medical expertise to help clinicians make more informed and humane decisions about end-of-life care.
- At Stanford's Precision Health and Integrated Diagnostics Center, researchers use machine learning and assessments of the health of individuals to better understand the impact on them of cardiovascular disease, diabetes, cancer and neurological and mental health. Researchers aim to diagnose diseases earlier and stop them before they cause real damage, but their ultimate goal is to prevent disease entirely.
- Stanford Medicine's goal for precision health to improve the lives of billions of people around the globe is gaining traction. The approach uses expertise in data science and statistics to pinpoint problems and remedies; uses medical knowledge and economic analysis to improve patient-centered care in a cost-effective way; and draws on technology to bring advanced training and tools to a new generation of medical leaders. Examples include helping develop and improve ambulance services in India and Nepal; efforts to eliminate hepatitis B in China; and a video outreach project that promotes breastfeeding to mothers in South Africa.
- Stanford's fast-growing drug-development program, SPARK, has given hundreds of academic researchers around the world the training and connections to get their discoveries out of labs and into the hands of doctors and patients.
- Microbiologists and immunologists are developing tools to define and manipulate our gut microbiota in a battle against such disorders as inflammatory bowel disease, obesity and heart disease.

Also in this issue is the story of a professor who allowed research colleagues to analyze the genetic and molecular makeup of healthy and diseased cells from his lungs after he was diagnosed with cancer. The gesture marked the beginning of what could be the world's largest study into what goes wrong when lung cells become cancerous.

Additionally, the magazine details how a dermatologist's distant memory of learning about a rare disease helped her diagnose a woman who was nearly bedridden from debilitating pain for almost a year.

The magazine is available at http://stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at 723-6911 or by sending an email to medmag@stanford.edu. ISM

OBITUARY

Robert Rouse, professor emeritus of pathology, dies at 70

By Bruce Goldman

Robert "Bob" Rouse, MD, professor emeritus of pathology at the School of Medicine and former chief of pathology and the laboratory medicine service at the Veterans Affairs Palo Alto Health Care System, died July 28 after a brief hospitalization for complications from Parkinson's disease. He was 70.

Respected by his peers for his contributions to basic immunology and surgical pathology, Rouse was known for his wry sense of humor, unflappable demeanor, precise language and incisive mind. He baked bread on a daily basis and would wear a bowtie at special events — on selected occasions, one made of wood.

Rouse exuded a preternatural calmness, recalled Roger Warnke, MD, professor emeritus of pathology, who first met Rouse in 1974, when Warnke was a resident pathologist at Stanford and Rouse was applying for his residency there.

"You'd think maybe he was asleep during a presentation, but when the talk was over he'd ask incisive, pertinent questions," Warnke said. "He'd been totally engaged all that time, although you wouldn't have known it."

Rouse displayed unerring decency as a mentor and a co-worker, said Kristin Jensen, MD, associate professor of pathology, who in 2015 succeeded Rouse as chief of the VA-Palo Alto's pathology and laboratory medicine service, a diagnostic testing facility with about 80 employees. "He was always checking in on how you were doing, and he was very gracious — always willing to step aside and let someone else take credit," Jensen said.

Robert Rouse

Many who sat across or around a microscope with him, Jensen said, will recall his ability to scrutinize slides with his naked eye. "He could tell you with high accuracy what kind of tissue it was and, often, what the biopsy was for," said Jensen of this offbeat skill, which amused trainees and colleagues alike.

"Bob was tall, lanky, thoughtful and very serious-looking," Jensen said. "It was only when you got to know him a little better that his wry sense of humor came out."

Native of St. Louis

Born Dec. 13, 1947, in St. Louis, Missouri, Rouse graduated with a bachelor's degree in engineering from Northwestern University in 1970. He earned a medical degree from Washington University in 1974. At Stanford, he completed an internship in anatomic pathology; a two-year postdoctoral fellowship in the lab of Irving Weissman, MD, now a professor of pathology and of developmental biology; and a medical fellowship in surgical pathology.

In 1980, he was named an acting assistant professor of pathology at Stanford. In 1983, he was appointed an assistant professor as well as co-director, with Warnke, of the medical center's tissue immunodiagnosis laboratory — a position he held until 2006. He was promoted to associate professor in 1991 and to full professor in 2001. In 2006, he assumed the role of chief of the pathology and laboratory medicine service at the Stanford-affiliated VA Palo Alto Health Care System. Although he retired from Stanford in 2015, he remained active as a part-time staff pathologist at the VA until December 2017.

Early in his career, Rouse co-authored a number of scientific journal articles on immunology with Weissman and other Stanford faculty researchers. These focused particularly on phenomena related to the maturation of lymphocytes known as T cells in the thymus. He later turned his immunological training to uses in pathology, such as the development of practical diagnostic applications of immunohistochemistry.

A surgical pathologist, he was an early adopter in the application of antibodies to tissue sections in order to get more-precise diagnoses. From 1988 through 1998, he served on the World Health Organization's committee for the histological typing of thymic tumors.

"Diagnostic pathology is more subjective than many of us would like to admit," Jensen said. To render the procedure more concrete, in the mid-1990s Rouse initiated a website, surgpathcriteria.stanford.edu, that emphasized textual, as opposed to pictorial, histologic descriptions, as well as differential diagnostic and grading criteria, in the belief that text allowed for more precision, consistency and accessibility than did images, whose interpretations could be somewhat subjective.

"Anybody could access that website," Jensen said. "It's becoming widely used nationally and internationally by practitioners and, increasingly, by patients around the world."

A masterful gardener who with his wife, Bichtien, hosted annual garden parties at his home on the Stanford campus, Rouse was also a gourmet baker. "He would bake bread on a daily basis and bring it in to share with his coworkers," Warnke said.

Rouse was a member of the College of American Pathologists, the California Society of Pathologists and the South Bay Pathology Society. He co-authored more than 100 peer-reviewed journal articles and numerous reviews and book chapters, and served on the editorial boards of *Advances in Anatomic Pathology* and the *Journal of Histochemistry and Cytochemistry*, and on the editorial review panel of *Human Pathology*.

In addition to his wife, Rouse is survived by a daughter, Liensa Rouse Vidra of New York City, and a son, Nicholas Rouse of Atlanta.

A small memorial was held with close family and friends. In lieu of flowers or gifts, his family suggested considering a donation to the Michael J. Fox Foundation to honor his memory. ISM

Snakebite

continued from page 1

School of Medicine, who routinely treats patients with venomous snakebites.

Lipman launched a study with a team of researchers to investigate the question. What they found defies conventional wisdom: The number of snakebites actually decreases after a drought but goes up after periods of rainy weather. The study also reported that the increase in weather extremes caused by climate change has a direct influence on snakebite incidence in California. This could be useful to help guide public health measures, such as determining the best allocation of antivenom supplies, the study said.

PAUL SAKUMA

Grant Lipman and his colleagues found that snakebites in California occurred more frequently after periods of high rainfall and decreased after times of drought, contrary to long-held beliefs.

Lipman shares lead authorship with Caleb Phillips, PhD, adjunct assistant professor of computer science at the Univeristy of Colorado-Boulder. The senior author is Derrick Lung, MD, assistant clinical professor of medicine at the University of California-San Francisco. The study was published Sept. 5 in *Clinical Toxicology*.

Little scientific evidence links drought to an increase in snakebites, and yet everyone seems to believe there's a connection, including emergency medicine providers, since that's what they're taught during training, Lipman said. A quick Internet search of headlines from the popular press quickly confirmed this: "Deadly Snakebites Set to Skyrocket During Record-breaking Drought," reads one in 2018 in the *Daily Mail.* Another, "Snakes Cross Paths with Humans in Bay Area Due to Drought," was reported on ABCNews.com in 2015. The prevailing theory goes that snakes wander further to forage for food during times of drought, plus they are simply more active in warmer weather.

"We set out to prove that, yes, there are more snakebites during high drought time especially since that's what we were taught," Lipman said.

20 years of snakebite data

The researchers collected and examined 20 years of snakebite data from every phone call made to the California Poison Control System from 1997 to 2017. Details included the date and time of the bite; the patient's age and sex; where the bite occurred on the body; call site; treatment; and medical outcomes. Cases were also grouped by the callers' ZIP codes to one of California's 58 counties.

A total of 5,365 snakebites were reported, all of them from rattlesnakes. Five deaths were reported over the 20-year period. The median age of the patients was 37. They were most likely to be male, and the bites most often occurred at home in the backyard. The majority of bites occurred during the spring or summer and in counties dominated by shrub or scrub growth. Mariposa County topped the list with the most bites at 96 bites per 1 million people. In Santa Clara County, where Stanford is located, there were 4 bites per 1 million people.

> "It's important information for people who work and play in California."

"The most common comment I usually hear from snakebite victims in the emergency room is: 'I was just minding my own business,'" Lipman said. "Usually, though, it's the snakes that were minding their own business, having a nice nap. It's people who tend to disturb them."

'More snakes, more snakebites'

The study found that snakebite incidence decreased 10 percent following a drought but increased by 10 percent following high levels of precipitation. The researchers developed their own theory that an increase in rain results in more shrub growth and, with that, an increase in rodents, the snakes' primary food source.

"More food, more snakes, more snakebites," Lipman said. "But that's just our theory."

After accounting for seasonal trends, researchers observed that precipitation was a strong predictor of snakebites. The numbers of bites peaked following the heavy precipitation years of 2006 and 2011, the study found.

"While we were writing this up, we were seeing all these catastrophic weather events around the world," Lipman said. "Massive droughts, powerful hurricanes and floods. We were seeing this global climate change, and we started looking at the recent worst California drought followed by the state's highest precipitation levels on record."

By looking at reports of the wettest and driest years during the 20-year period, researchers saw quite visible comparative trends across the state in all 58 counties. After adjusting for population, the researchers found that the incidence of snakebite fell during two periods of extreme drought between 2002-05 and from 2007-10. From 2015-16, the most severe drought on record in California, the number of snakebites reached their nadir, the study said.

As weather grows increasingly extreme, it grows ever more important to know when to be prepared for perhaps increasingly high incidences of snakebites, Lipman said.

"We can predict a big snakebite season because of prior wet winters and have antivenom in places where there are a lot of hikers or trail runners," Lipman said. "It's important information for people who work and play in California."

Reminding outdoorsy Californians of snakebite-prevention practices is also helpful, particularly when risks of snakebites might be high, Lipman said. Such practices include staying at least two snake-lengths away from rattlesnakes, which can strike fast. Lipman noted that because snakes don't have ears, stomping on the ground works best to scare them away, and that antivenom is effective (but expensive) and needs to be administered quickly to snakebite victims with signs of poisoning.

Researchers from the University of Colorado-Boulder, UCSF and St. Joseph Hospital in Orange, California, contributed to the study.

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

■ OBITUARY

John 'Jack' Farquhar, prevention-research visionary, dies at 91

By Hanae Armitage

John "Jack" Farquhar, MD, a giant in prevention research and professor emeritus of medicine and of health research and policy at the School of Medicine, died Aug. 22 of natural causes. He was 91.

A boundary-busting cardiologist for his time, Farquhar was one of the first scientists to see cardiovascular disease prevention through the lens of public health. He focused on environmental and behavioral risk factors that spanned whole cities, envisioning interventions that could change the health behaviors of entire communities and ultimately prevent disease and improve public health.

"Jack was a visionary in disease-prevention research. His forward thinking helped usher in the precision health revolution," said Lloyd Minor, MD, dean of the School of Medicine. "His passing is a tremendous loss for the Stanford community and beyond."

Farquhar founded the Stanford Prevention Research Center and launched a handful of health programs at Stanford, including the Health Improvement Program for faculty and staff, and the Preventive Cardiology Clinic. Outside Stanford, he was a founding member of the International Heart Health Society and a member of the Committee to Prevent the Spread of Cardiovascular Disease into Developing Countries, an effort supported by the National Academy of Medicine. Farquhar was elected to the academy (formerly the Institute of Medicine) in 1978.

Native of Canada

Farquhar was born in Winnipeg, Canada, in 1927 and grew up there until he was 13, when he and his family moved to Pasadena, California. He was an athlete in high school, playing football and soccer. At 16, he won a Golden Gloves amateur boxing competition.

Farquhar attended the University of California-Berkeley, where he earned a bachelor's degree in medicine, after which he enrolled in medical school at UC-San Francisco. He completed part of his residency at UCSF and part at the University of Minnesota, and then moved east for a fellowship as a research associate at Rockefeller University, where he dabbled in biochemistry, studying diet and blood lipids. In 1962, Farquhar packed his bags and headed west to accept a position as an assistant professor of medicine at Stanford.

John Farquhar

Over the course of Farquhar's first decade at Stanford, which included a sabbatical at the London School of Hygiene & Tropical Medicine, his views on cardiovascular disease began to shift. He was among the first to explore the idea that heart disease was largely attributable to one's environment.

"Jack was a true pioneer," said David Maron, MD, clinical professor of medicine at Stanford and director of preventive cardiology. "He understood the relationship between lifestyle and cardiovascular disease." He was a new kind of investigator whose goal was to change lifestyle by changing communities, Maron said.

A force for preventive medicine

The first manifestation of Farquhar's vision debuted in 1972, when he and colleagues Nathan Maccoby, PhD, professor of communication, and Peter Wood, PhD, DSc, professor emeritus of medicine, led the launch of a large-scale field study that aimed to address disease risk by changing the behavior of entire communities. The landmark trial facilitated health-education campaigns and implemented health-improvement tactics, such as programs that offered healthy lunch options at schools, organized community footraces and taught about the dangers of smoking. Initially, the intervention started with three communities. When the National Institutes of Health saw success in those health campaigns, it granted massive funding to the trial that allowed for a new, bigger trial launch in five California cities. It became known as the Stanford Five Cities trial.

"Researchers traditionally randomized individual patients to a new therapy or drug, but here was Jack, randomizing entire cities to receive versus not receive community-based health campaigns," said Christopher Gardner, PhD, professor of medicine, who trained under Farquhar and holds the Rehnborg Farquhar Professorship. "What Jack brought was really paradigm-shifting; he brought a multidisciplinary approach with a focus on behavior and environment."

The Stanford Five Cities trial served as a way for Farquhar to promote the importance of community-based intervention and explain the importance of bringing multiple forces to bear in a community to reduce heart-attack risk, said William Haskell, PhD, professor emeritus of medicine at Stanford and friend and colleague of Farquhar's.

Farquhar made sure that the Five Cities study reached all members of a community. He was particularly cognizant of the importance of diversity and inclusion at a time when the health of most ethnic groups was ignored, said Marilyn Winkleby, PhD, MPH, professor emerita of medicine at the Stanford Prevention Research Center. "Health campaign billboards stood along the highways in Salinas and Monterey in Spanish, and he would have his health column run in the local paper in Spanish," Winkleby said. "He was thoughtful about subgroups that were often overlooked, especially those that have the highest risk and the fewest resources to enhance their health."

To effectively carry out the Five Cities trial and what followed — the NIH grant included funds to monitor the cities for 10 years after the health interventions were completed — Farquhar began to recruit experts from a variety of fields, many of whom, such as Haskell, helped him found the Stanford Prevention Research Center.

"Jack may or may not have said so, but he was one of the key academic leaders in the country to put community health research on the map decades ago," said Marcia Stefanick, PhD, professor of medicine at the center. "He pulled together amazing people who were capable of conducting both lifestyle and drug trials, like the Lipid Research Clinical Trial and Prevalence Study, thereby redirecting preventive medicine."

Compassionate mentor

Farquhar helped launch the careers of multiple researchers at Stanford who are still here today — Maron, Stefanick, Gardner and Abby King, PhD, professor of health research and policy and of medicine, to name a few — through a postdoctoral training program he established in 1975, called the SPRC Research Fellowship Program in Cardiovascular Disease Prevention. Today, Gardner is the program's director.

"We're now in our 43rd year, and if you look across campus there are about 40 of these postdoc training awards, but none are older than Jack's program," Gardner said. "More than 100 investigators were trained as postdocs through this program."

Among his many awards, Farquhar received the Gold-Headed Cane from UCSF in 1952; the American College of Physicians' James D. Bruce Award for Distinguished Contributions in Preventive Medicine in 1983; the Dana Foundation Award in 1992; and the Fries Prize for Improving Health in 2005.

Farquhar is survived by his wife, Christine Farquhar, and his two children, Meg and John Farquhar.

In lieu of flowers, the family suggests contributions to the John W. Farquhar, MD, SCRDP Postdoctoral Research Fund. The contributions should be sent to the attention of Diana Fox at the Stanford Prevention Research Center, 3300 Hillview Ave., Suite 100, Office 102, Palo Alto, CA, 94304-1334. ISM

Ketamine

continued from page 1

opioid-receptor blocker prior to taking ketamine.

The study enrolled adults with treatment-resistant depression, meaning their condition had not improved after multiple treatment efforts. Twelve participants received infusions of ketamine twice — once preceded by naltrexone, an opioid-receptor blocker, and once with placebo. Neither the study participants nor the researchers were told whether active drug or placebo was administered during each test. The researchers found that ketamine reduced depressive symptoms by about 90 percent for three days in more than half of the participants when administered with a placebo, but had virtually no effect on depressive symptoms when it was preceded by naltrexone.

"This was purely a mechanistic study, not a treatment trial," said Nolan Williams, MD, clinical assistant professor of psychiatry and behavioral science. "And the results were so clear that we ended the study early to avoid exposing additional patients to the ineffective combination treatment." Williams shares lead authorship of the paper with Boris Heifets, MD, PhD, clinical assistant professor of anesthesiology, perioperative and pain medicine.

Understanding how it works

Because the field of anesthesia has long regarded ketamine specifically as a nonopioid drug, Heifets was skeptical when Williams approached him about joining the research effort. "Everything that I was taught, and everything that I've always taught my students — all of the evidence supports the fact that ketamine is not an opioid," he said. "I was really surprised at the results."

Although some small studies have shown that ketamine had rapid, although transient, antidepressant effects, Schatzberg said the researchers wanted to understand how ketamine works. He said he came to suspect that ketamine's effects might be linked to the brain's opioid system when Rodriguez published a report on ketamine's ability to reduce symptoms of obsessive-compulsive disorder, which was similar to previous Stanford research using the opioid morphine.

The prevailing hypothesis for ketamine's antidepressant effect was that the drug blocked a receptor for glutamate, an excitatory neurotransmitter in the brain that is implicated in memory and learning. "But ketamine's mechanism is complicated, as it acts on many different receptor types beyond glutamate receptors, and it acts in three distinct phases — rapid effects, sustained effects and return to baseline," Rodriguez said.

Schatzberg noted that no other glutamate-receptor blocker has an antidepressant effect like ketamine and that attempts to develop similar drugs have largely failed.

The researchers said the findings from the new study may explain why ketamine works so quickly as an antidepressant: It activates the brain's opioid receptors during its first phase of activity. The glutamate system may be responsible for the sustaining effects after ketamine is metabolized, they said.

The authors say that revealing the role of the opioid system in the antidepressant effects of ketamine is critical in the effort to develop new antidepressants. For instance, glutamate receptor blockers may not have rapid antidepressant effects unless they also involve the opioid system, Williams said.

"Psychiatry used opioids, barbiturates and high doses of stimulants to treat depression 50 or 60 years ago," Schatzberg said. "We have to properly examine the risks associated with using drugs of abuse — even in low doses — to treat depression. It's not limited to ketamine; other antidepressant drugs that target the opioid system are in development now, too."

While a standard opioid like morphine initially has an antidepressant effect, it promotes depression after repeated use, Williams said. People who are depressed take as much as 2.4 times as many opioids immediately after painful surgeries than those who aren't depressed, he said. "There is truly a link between depression, pain and opioid use," Heifets said. "You can't go after one without addressing the others."

Other Stanford co-authors of the study are research psychologist Christine Blasey, PhD; instructor Keith Sudheimer, PhD; medical student Jaspreet Pannu; life science researcher Heather Pankow; Jessica Hawkins, clinical research manager; Justin Birnbaum, MD, clinical professor of psychiatry; and David Lyons, PhD, professor of psychiatry. Lyons, Rodriguez and Schatzberg are members of the Stanford Neuroscience Institute. Schatzberg is also a member of Stanford Bio-X.

Rodriguez has consulted for Allergan, BlackThorn Therapeutics and Rugen Therapeutics. Schatzberg has consulted for Alkermes and Avanir, has equity in Corcept and Merck, and received a grant from Janssen Pharmaceuticals.

The study was funded by the National Institutes of Health (through a grant to Spectrum, the Stanford Center for Clinical and Translational Research and Education), the Brain and Behavior Research Foundation, the Avy L. and Roberta L. Miller Foundation and the Pritzker Family Fund.

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

Unplanned comment leads doctor to champion gun violence prevention

By Amy Jeter Hansen

For Dean Winslow, MD, one comment last fall served as an ending and a beginning.

At his confirmation hearing before the Senate Armed Services Committee, two days after the mass shooting at a church in Sutherland Springs, Texas, the Stanford professor of medicine and retired Air Force colonel opined that it was "insane … that in the United States of America a civilian can go out and buy a semiautomatic weapon like an AR-15."

Dean Winslow

He quickly fell out of contention for assistant secretary of defense for health affairs. But the reaction from friends and colleagues in the medical community — and his own subsequent reflection — spurred Winslow to do something he'd never before considered: spearhead a nonprofit organization for health care professionals working to address the dangers of gun violence.

The group is called Scrubs Addressing the Firearms Epidemic, or SAFE, and aims to unify voices of physicians, nurses and medical students. The mission is to reduce gun violence by promoting firearm safety education for caregivers, supporting research and advocating for evidence-based policies that reflect responsible gun ownership and respect the Second Amendment.

First national event Sept. 17

The organization's first national event, Stand SAFE, will take place on Sept. 17. Medical students and health professionals are encouraged to wear scrubs customized with the SAFE logo, convene briefly in a show of solidarity at noon local time, and hold gun violence-related education activities.

"We're looking at this from the perspective of people who care for victims of gun violence — including children — and as people that also have actually seen gun violence up close," Winslow said. "And we really feel that our country can do better in terms of reducing the terrible toll."

Stanford's SAFE rally will be held at noon on the Dean's Lawn, next to the Clark Center, followed by an educational event at 12:30 p.m. at the Li Ka Shing Center for Learning and Knowledge. Confirmed speakers include Winslow; John Donahue, JD, PhD, professor of law at Stanford; and David Spain, MD, professor of surgery at Stanford. First-year medical students also will receive training on how to respond to a life-threatening bleeding emergency before paramedics arrive.

> **"We really feel that our country can do better in terms of reducing the terrible toll."**

A common goal: Keep people healthy

Recognizing the nation's political deadlock on firearms, SAFE focuses on the public health aspect of gun violence prevention — an area of agreement among numerous medical organizations.

The idea, said SAFE co-chair Sarabeth Spitzer, is to emphasize a common goal of keeping people healthy.

"We need to do thorough, nationwide research to figure out what are the most effective ways to prevent these injuries," said the fourth-year Stanford medical student, who has published work on the cost of hospitalizations for firearm injuries. "And once we have evidence to show certain policies are effective, we should implement those policies as soon as possible."

The approach has resonated in the health care community, where projects with a similar focus have sprouted. SAFE intends to provide an umbrella for like-minded professionals: Many physicians, academics and students have signed on to the team and advisory board, and in a matter of weeks, three dozen medical schools have established chapters.

The participation of future physicians, along with the nonpartisan, clinical focus, distinguishes the effort, said Michelle Sandberg, MD, a member of the SAFE advisory board who also was a founding board member of Moms Demand Action for Gun Sense in America.

"What is really compelling to me is this passionate, engaged younger generation of doctors interested in bringing together a large group of health care providers to take a more active role in this issue," said Sandberg, a pediatrician and clinical instructor at Stanford.

In the immediate future, plans for SAFE include coordinating with other entities to add firearms safety measures to medical education. Leaders also will gather soon to hammer out details of a long-term agenda.

Winslow and Spitzer know that meeting their goals will be challenging, but they remain hopeful about making progress, even if it is slow to come.

"I really do believe the time is right for this," Winslow said. "I'm a Midwesterner, so I'm congenitally optimistic about things." ISM

Dawes

continued from page 1

the School of Medicine, said Dawes' imprint will be felt many years to come.

"Chris' impact on maternal and child health programs at Stanford has been and continues to be enormous," Minor said. "Chris has been an inspiration for me and for all of us. His passion and dedication are infectious. The hospital he built will continue to thrive because of his vision."

Easy-going and unflappable

Dawes, who had held senior positions in several other Bay Area medical centers, joined the hospital's staff in 1989 and was named chief operating officer in 1996 and CEO in 2000.

In the early days, he said the hospital was much like a startup, with limited resources and faculty and no national profile. For instance, there were no pediatric surgeons on staff, and very few surgeries were done in young patients.

To build the enterprise, he hired the best people he could find, and he listened to their advice. With his easy-going, unflappable style, he worked well with those at all levels, whether it was the parent of a child or a university official, and maintained close relationships with the medical staff, a key to the hospital's success, said David Stevenson, MD, the Harold K. Faber Professor in Pediatrics and senior associate dean for maternal and child health at the School of Medicine.

"He was always listening to the doctors, asking the question, 'What do we have to do to make this place great?'" Stevenson recalled.

The answer, Dawes found, was to build exceptional programs, known as centers of excellence, with a focus on six major areas of care: heart, cancer, brain and behavior, transplantation, pulmonary, and pregnancy and newborn care. The hospital was fortunate in that the David and Lucile Packard Foundation had decided to invest $300 million, including $200 million to be matched through community fundraising.

In the next five years, he would work with the School of Medicine to recruit more than 100 new faculty — the best in their fields — and help create the facilities needed to support them. In 2008, Packard opened new pediatric-dedicated operating rooms, a cancer center and a cardiovascular intensive care unit.

Dawes also recognized that the best children's hospitals in the country not only provide great clinical care, but also support strong research to advance maternal and child health. He helped to establish and became a champion of the Maternal and Child Health Research Institute, which supports Stanford investigators conducting transdisciplinary research in the pre-clinical, clinical and basic sciences with the goal of improving the health of pregnant women and children. The institute has provided $52.3 million in grant funding to nearly 700 projects in its 10-year history, leading to numerous transformative discoveries.

Importance of academic programs

"Chris understands how important the academic programs are to a children's hospital," said Harvey Cohen, MD, PhD, the Deborah E. Addicott-John A. Kriewall and Betsy A. Haehl Family Professor in Pediatrics. "As such, he was able to get the faculty to identify themselves with the children's hospital, in addition to their identities as faculty members. That was the attribute that allowed him to lead us from a reasonably good regional children's hospital to one of the best children's hospitals in the country."

Over time, the demand for the hospital's services outgrew the building's roots. The hospital's top-ranked specialties were attracting patients from near and far, but didn't have the beds to accommodate them all. Moreover, health care was changing, and the hospital needed to change with it to be sustainable.

In 2012, under Dawes' direction, the hospital began developing a network of clinics and hospital partnerships in the Bay Area and nationwide so patients could benefit from its high-level services without having to travel long distances. The network, Stanford Children's Health, now has over 60 locations in Northern California and is the only

BETH BARTON/DNK DIGITAL

Dawes and Susan Packard Orr cut the ceremonial ribbon at a Nov. 30, 2017, celebration to mark the completion of the hospital's new main building, which opened its doors the following month.

health system in the region — and one of the few in the country — exclusively dedicated to pediatric and obstetric care.

Hospital officials also began planning for a major expansion on the Palo Alto campus. The hospital would double in size to 521,000 square feet, add a state-of-the-art surgery and imaging center and an additional 149 patient beds.

Jill Sullivan, vice president of strategic space planning, worked closely with Dawes for nearly a decade on the hospital's expansion. "Chris was instrumental in ensuring that the design of the building upheld Lucile Packard's founding vision to provide the best possible care to patients and families," Sullivan said.

The expansion plan set aside 3.5 acres for gardens and green space and was designed to provide the kind of warm, healing, family-oriented environment Packard had envisioned. The hospital's new main building opened its doors to its first patients in December 2017.

Advocate for children's health

Dawes also gained national stature for his advocacy on behalf of the nation's youth. As chair of the board of the National Association of Children's Hospitals and Related Institutions, Dawes frequented Washington, D.C., during the development of the Affordable Care Act in 2009 and 2010, working with colleagues to create guidelines for coverage of children.

He was formative in the creation of the Children's Hospital Association, which joined two national children's organizations into a major public policy and purchasing group for hospitals around the country.

"Chris has been transformational in the development of our children's hospitals on a national level," said Mark Wietecha, president and CEO of the association. "He was a founding trustee of CHA, a steady contributor to our national collaborative to improve pediatric care, and a tireless advocate and supporter of our work in Washington. Our children's hospitals and our children are better for his many contributions."

Dawes said he did not accomplish all of this alone, "I tend to listen to people's ideas, observations and concerns," he said. "I have always had the philosophy that I want to surround myself with people who are smarter and more experienced than I am."

"Collectively we have created an organization that is admired nationally and a place that attracts great faculty and staff," he added. "We have a terrific future." ISM