INSIDE STANFORD MEDICINE

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How Lucile Packard Children's Hospital Stanford is incorporating water-efficient systems.

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Among teens, sleep deprivation an epidemic

CHRISTOPHER SILAS NEAL

Sleep deprivation increases the likelihood teens will suffer myriad negative consequences, including an inability to concentrate, poor grades, anxiety, depression, thoughts of suicide and even suicide attempts.

By Ruthann Richter

Carolyn Walworth, 17, often reaches a breaking point around 11 p.m., when she collapses in tears. For 10 minutes or so, she just sits at her desk and cries, overwhelmed by unrelenting school demands. She is desperately tired and longs for sleep. But she knows she must move through it, because more assignments in physics, calculus or French await her. She finally crawls into bed around midnight or 12:30 a.m.

The next morning, she fights to stay awake in her first-period U.S. history class, which begins at 8:15. She is unable to focus on what's being taught, and her mind drifts. "You feel tired and exhausted, but you think you just need to get through the day so you can go home and sleep," said the Palo Alto, California, teen. But that night, she will have to try to catch up on what she missed in class. And the cycle begins again.

"It's an insane system. … The whole essence of learning is lost," she said.

Walworth is among a generation of teens growing up chronically sleep-deprived. According to a 2006 National Sleep Foundation poll, the organization's most recent survey of teen sleep, more than 87 percent of high school students in the United States get far less than the recommended eight to 10 hours, and the amount of time they sleep is decreasing — a serious threat to their health, safety and academic success. Sleep deprivation increases the likelihood teens will suffer myriad negative consequences, including an inability to concentrate, poor grades, drowsy-driving incidents, anxiety, depression, thoughts of suicide and even suicide attempts. It's a problem that knows no economic boundaries.

While studies show that both adults and teens in industrialized nations are becoming more sleep deprived, the problem is most acute among teens, said Nanci Yuan, MD, director of the Stanford Children's Health Sleep Center. In a detailed 2014 report, the American Academy of Pediatrics called the problem of tired teens a public health epidemic.

"I think high school is the real danger spot in terms of sleep deprivation," said William Dement, MD, PhD, founder of the Stanford Sleep Disorders Clinic, the first of its kind in the world. "It's a huge problem. What it means is that nobody performs at the level they could perform," whether it's in school, on the roadways, on the sports field or in terms of physical and emotional health.

Social and cultural factors, as well as new forms of information technology, all have collided with adolescent biology to prevent teens from getting enough rest. Since the early 1990s, it's been established that teens have a biologic tendency to go to sleep later — as much as two hours later — than their younger counterparts.

Yet when they enter their high school years, they find themselves at schools that typically start the day at a relatively early hour. So their time for sleep is compressed, and many are jolted out of bed before they are physically or mentally ready. In the process, they not only lose precious hours of rest, but their natural rhythm is disrupted, as they are being robbed of the dream-rich, rapid-eye-movement stage of sleep, some of the deepest, most

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Enzyme malfunction may be why binge drinking can lead to alcoholism, new study finds

By Bruce Goldman

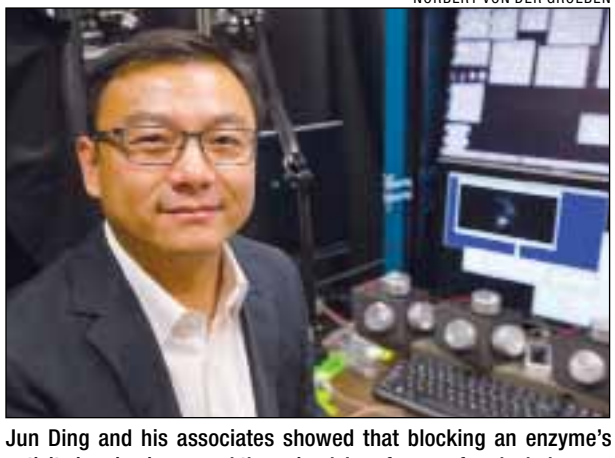
A malfunctioning enzyme may be a reason that binge drinking increases the odds of alcoholism, according to a study by scientists at the School of Medicine.

The scientists identified a previously unsuspected job performed by the enzyme, ALDH1a1, in mice. The discovery could help guide the development of medications that extinguish the urge to consume alcohol, said Jun Ding, PhD, assistant professor of neurosurgery.

Ding is the senior author of the study, which was published Oct. 2 in *Science*. The study's lead author is postdoctoral scholar Jae-Ick Kim, PhD.

Alcoholism is an immense national and international health problem. More than 200 million people globally, including 18 million Americans, suffer from it. Binge drinking substantially increases the likelihood of developing alcoholism. As many as one in four American adults report having engaged in binge drinking in the past month.

NORBERT VON DER GROEBEN



Jun Ding and his associates showed that blocking an enzyme's activity in mice increased the animals' preference for alcohol.

Existing medications for treating alcoholism have had mixed results. Disulfiram (Antabuse) and similar substances, for example, work by inducing unpleasant side effects — including shortness of breath, nausea, vomiting and throbbing headaches — if the person taking it consumes alcohol. "But these drugs don't reduce the craving — you still feel a strong urge to drink," Ding said.

In the new study, Ding and his associates showed that blocking ALDH1a1 activity caused mice's consumption of and preference for alcohol to rise to levels equivalent to those observed in mice that had experienced several rounds of the equivalent of binge drinking. Restoring ALDH1a1 levels reversed this effect.

Previous studies have shown that mutations in the gene for ALDH1a1 are associated with alcoholism, but the reasons for

See ALCOHOL, page 5

New center looks to define concussion

By Ruth Schechter

Paige Fisher was pedaling along a narrow path on her way to a yoga class last January when she crashed head-on into another bicyclist. When she came to, she was bleeding profusely and surrounded by worried bystanders. Despite a visit to the student health clinic, a scan at the emergency room and appointments with her primary care physician, she continued to feel dizzy, sleepy and sensitive to light weeks after her wounds had healed.

NORBERT VON DER GROEBEN

Paige Fisher was treated at the Stanford Concussion and Brain Performance Center.

"I was told I had a concussion and to just rest," said the 22-year-old Stanford graduate. But the lack of activity made her feel lethargic and depressed. "I was not getting better. I felt out of it and not like myself at all."

Fisher was referred

See CONCUSSION, page 5

5 QUESTIONS

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

McDonald on need to learn from diagnostic errors

Most Americans will get at least one faulty diagnosis in their lifetime, sometimes with devastating consequences. "Urgent change is warranted to address this challenge," according to a recent landmark report from the Institute of Medicine.

The September report, by a committee of medical experts, found that despite dramatic improvements in patient safety over the last 15 years, diagnostic errors have been the critical blind spot of health-care providers.

Kathryn McDonald, executive director of Stanford's Center for Health Policy/Center for Primary Care and Outcomes Research, is a member of the committee that wrote the report, "Improving Diagnosis in Health Care."

Recently, Beth Duff Brown, the communications manager at CHP/CPCOR, asked McDonald some questions about the report's findings and also got her suggestions for limiting one of the most overlooked health-care dilemmas today.

1 What surprised or enlightened you most in your findings?

MCDONALD: I learned a lot about the ways that the legal system sets up barriers to transparency even as it tries to protect patients. For example, the current approach to resolving medical liability claims sets up barriers to transparency needed to learn from diagnostic errors. In the aftermath of devastating errors that arise from failures in the diagnostic process and teamwork, many patients want to help make the delivery system safer. Concerns about medical liability prevent clinicians from disclosing medical errors to patients and their families, despite calls from numerous groups that full disclosure is an ethical necessity. It is often complex to understand the multiple forces that result in a diagnostic error.

Learning is important to patients and physicians to prevent repeat problems. We made recommendations about medical malpractice reforms that might be designed to permit patients and health professionals to become allies in trying to make health care safer by encouraging transparency about such errors. We need approaches that would allow patients to be promptly and fairly compensated for injuries that were avoidable while at the same time turning errors into lessons to improve subsequent performance. It's a real shame that we are not there yet, and that evidence is lacking about exactly how to get there. We need folks with medical, law, maybe psychology, and patient safety backgrounds to work on research in this area.

Kathryn McDonald

2 What do you believe is the most significant message and mission of the report?

MCDONALD: The report is packed with reasons and directions for action from all, in ways that support what patients deserve from the health-care system: freedom from worry about inattention to diagnostic errors. That's been the status quo for too long.

What is particularly critical is the huge gap in methods to identify diagnostic errors and near misses, measure their frequency and severity, and figure out a systematic way to make those involved aware of them. As a researcher who has spent most of my life developing patient-safety and quality measures, I know we can do better in this area. At the same time, the challenge is significant. Diagnosis occurs over time and involves varying levels of uncertainty. Real research funding, with an applied focus, is needed. The report calls for this. It includes a carefully crafted definition that is patient-focused in order to set us on a new path for measuring what matters to patients. There is a chapter devoted to measurement: Chapter 3, worth reading if you want a sense of the scope of both diagnostic errors and the challenge of measuring them well enough to help those who want to improve diagnosis.

Part of the challenge is figuring out where to direct energies for the biggest payoff from a public health perspective, while also fostering the culture change needed to focus on learning and improving, sooner rather than later. Definition and measurement are central to this work.

3 How did the committee define a "diagnostic error" and how might this differ from previous definitions?

MCDONALD: We defined diagnostic error from a patient's perspective, and brought together the research so far that clearly shows the opportunity and grave need to improve the current situation. The definition has two parts, both focusing on what patients want and need. Part 1 states that diagnostic error is the failure to establish an accurate and timely explanation of the patient's health problem. This part of the definition is not meant to set an unreachable bar. It is open to establishing what is known at each point in the diagnostic process, sometimes a working diagnosis as more information is collected to rule out the most pressing concerns in the physician's list of possibilities. Part 2 states that a diagnostic error is the failure to communicate that explanation to the patient. No other definitions have anything related to this part, even though it is exactly what patients are looking for, or want for their loved ones if they are not in a state where the communication can occur with them.

Several previous definitions have arisen to accomplish different purposes — often anticipating the measurement challenge. For example, there is a solid stream of research about "missed opportunities" and "triggers" that can be found in a medical record showing that there was a sign that a patient might have a serious condition, but then it wasn't followed up with additional testing in a specific and appropriate time frame. The IOM report's definition built upon previous definitions, but with a clear orientation toward patients and their families.

4 You outline eight goals that physicians and health-care providers should follow in their diagnostic practice. Which do you believe are the most significant?

MCDONALD: They are all important. I know that isn't a satisfying answer, but this is a complex problem that requires a many-pronged, multi-level attack from education to payment system reforms. We tried to be bold and aspirational, while grounded in the existing evidence. I guess if I had to underscore a goal where I am most optimistic that it will make a difference in the short run, I'd point to the teamwork one. There is a growing evidence base that the benefits of teamwork accrue to all members of the team, so this recommendation has the potential to be a win-win for all involved. Improving diagnosis is quite challenging, partly because making a diagnosis is a collaborative effort and involves many, often iterative, steps — few simple ones. These steps can unfold over time, across different health-care settings, and usually involve diagnostic uncertainty. All the moving parts, all the different types of expertise, all the people involved, well that's a call for teamwork. This IOM report and the challenge of improving diagnosis puts health-care organizations on the hook for ensuring that health-care professionals have knowledge and skills to engage in effective teamwork — both interprofessionally and intraprofessionally. And the goal doesn't stop there. We also recommended, as part of this first goal, that health-care professionals and organizations should partner with patients and their families as diagnostic team members, and facilitate patient and family engagement in the diagnostic process, aligned with their needs, values and preferences.

5 The video that was released with the report is very powerful. I think many of us don't realize how often a misdiagnosis can occur and how significant the impact can be.

MCDONALD: The video has two patients for whom things went poorly and one who had a first-class diagnostic experience because of excellent teamwork. And this is one of the key messages of the report. We need less of the old model of diagnosis from one expert to more of a teamwork approach to the diagnostic process. It is well worth watching the video to understand the human side, and the unique patient perspective on this important issue. **ISM**

To watch the video released with the report, visit https://www.youtube.com/watch?t=3e&v=fStBWT6fa3E.

Cancer nanotechnology center receives more than $9 million

By Krista Conger

The National Cancer Institute has awarded nearly $9.5 million to the Center for Cancer Nanotechnology Excellence in Translational Diagnostics at Stanford

The five-year grant is the third award from the NCI to fund the center.

The awards are managed by the NCI's Alliance for Nanotechnology in Cancer, and are meant to bring together researchers from across different disciplines to use emerging nanotechnology advances to aid in early cancer diagnosis, monitoring and therapeutic intervention. Stanford is one of only four institutions across the country that have received all three rounds of funding.

"In contrast to some situations, in which researchers and clinicians try to figure out clinical applications for newly developed technology, the nanotechnology approaches we've developed over the past 10 years were developed with very specific clinical problems in mind," said Sanjiv Gambhir, MD, PhD, professor and chair of radiology, who directs the center.

> "Many of these problems could not be solved without the use of nanotechnology."

"The expectation is that the center will generate nanotechnology that will translate into clinical trials and commercial opportunities," said Gambhir, who described two such efforts developed by the center in the past decade.

One is a tiny magnetic sensor developed in the lab of Shan Wang, PhD, professor of materials science and engineering and of electrical engineering at Stanford, that is capable of detecting minute changes in magnetic fields that occur when cancer-associated biomarkers are bound by magnetic nanoparticles. This technique could potentially be used to quickly assess the presence of cancer anywhere in the body with just a small sample of blood or another bodily fluid.

Another is a way to use novel nanoparticles that are delivered into the body to detect cancer. "Using special imaging instruments and novel nanoparticles we can hopefully detect very early aggressive tumors," said Gambhir, who also holds the Virginia and D.K. Ludwig Professorship for Clinical Investigation in Cancer Research.

According to Gambhir, the real strength of the center lies in its ability to bring together researchers from very diverse disciplines. "We've been able to leverage Stanford's many strengths by drawing in collaborators from across the university, including researchers from the schools of Medicine, Engineering, and Humanities and Sciences," he said. "In particular, we've attracted physical scientists and engineers to tackle difficult clinical problems in the field of cancer detection, diagnosis and treatment. Many of these problems could not likely be solved without the use of nanotechnology, and the success of the center brings together faculty from all over campus." **ISM**

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STANFORD MEDICINE

Seven scientists awarded grants for high-risk, high-return research

Seven Stanford scientists have received awards totaling $11.5 million to pursue high-risk, high-reward research, the National Institutes of Health announced Oct. 6.

They are among the 78 recipients of the 2015 Pioneer, New Innovator, Transformative Research and Early Independence awards from the NIH. The awards are designed to encourage scientists to pursue creative research projects with the potential of leading to big improvements in health care.

"Our scientists exemplify the spirit of excellence and innovation for which Stanford's research program is known," said Lloyd Minor, MD, dean of the School of Medicine, which is home to six of this year's Stanford recipients. "I congratulate all of the award winners on this tremendous honor and thank them for helping Stanford Medicine lead the biomedical revolution in precision health."

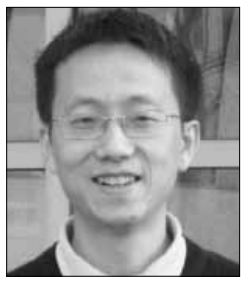
This year, the NIH handed out 13 Pioneer Awards, 41 New Innovator Awards, eight Transformative Research Awards and 16 Early Independence Awards. The total funding came to about $121 million.

"This program has consistently produced research that revolutionized scientific fields by giving investigators the freedom to take risks and explore potentially groundbreaking concepts," said NIH director Francis Collins, MD, PhD. "We look forward to the remarkable advances in biomedical research the 2015 awardees will make."

Tony Wyss-Coray

Sanjay Basu

Jessica Feldman



Liang Feng

Juliana Idoyaga

Daniel Jarosz

Manu Prakash

Pioneer Award

TONY WYSS-CORAY, PhD, professor of neurology and neurological sciences and a senior research career scientist at the Palo Alto Veterans Administration, received a Pioneer Award. The $2.5 million grant, dispensed over five years, goes to scientists proposing creative, potentially high-impact research in the biomedical and behavioral sciences.

Wyss-Coray's group studies the role of immune and injury responses in brain aging and neurodegeneration, with a focus on Alzheimer's disease. Wyss-Coray's research has revealed insights into how functional defects in the brain's own immune cells, microglia, can contribute to neurodegeneration, as well as how factors in blood can advance or retard cognitive decline.

Wyss-Coray plans to use his award to reprogram the genetic code in mice so that specific cells or tissues will synthesize proteins containing "designer" amino acids that can be chemically tagged. Researchers can then identify, track or isolate these proteins. This will allow researchers to study the collection of proteins within specific cell types and tissues during aging and in neurodegenerative diseases, including Alzheimer's disease.

New Innovator Award

The New Innovator Award provides $1.5 million over five years to fund innovative research by an investigator who has not yet received a research project grant or the equivalent from the NIH.

SANJAY BASU, MD, PhD, assistant professor of medicine, specializes in the development of mathematical models that help improve disease-prevention programs, in part by predicting unexpected or adverse health consequences of public health, fiscal and regulatory policies. He investigates how such programs can help prevent chronic diseases, especially obesity and Type 2 diabetes, that disproportionately affect low-income populations around the world.

For example, his recent work on the Supplemental Nutrition Assistance Program found that adding grocery stores well-stocked with fresh produce in inner-city "food deserts" does not increase the amount of fruits and vegetables that people buy and eat. But preliminary work suggests that delivering food stamp benefits weekly instead of monthly may increase how much people spend on fruits and vegetables by encouraging weekly shopping at local stores instead of monthly shopping at big box stores. With his New Innovator Award, Basu plans to bring in two new postdoctoral scholars and purchase some expensive data sets that would otherwise be unavailable.

Basu is a member of the Stanford Prevention Research Center, an affiliate of the Stanford Center for Poverty and Inequality and a senior fellow of the Stanford Center for Innovation in Global Health.

JESSICA FELDMAN, PhD, assistant professor of biology, studies cell specialization, which is a critical step in development and for normal physiology. Cells specialize by expressing different proteins that give them unique identities, but they must also shape and form themselves in unique ways to be able to carry out specific functions.

A critical regulator of cell form is the microtubule cytoskeleton, a network of polymers that becomes spatially organized within cells during development. Feldman studies how this cytoskeleton forms in *C. elegans*, a tiny, transparent worm. She aims to understand the mechanisms that regulate microtubule organization during development, specifically the molecules that control and contribute to microtubule organization and how specific microtubule organization is coupled to the cell cycle and cell polarization.

Feldman will use the award to identify new molecules that link microtubules to specific sites in the cell, and also to uncover the regulatory mechanisms that control microtubule organization during development. She hopes that by understanding these basic principles, scientists can better understand the cause and consequences of aberrant microtubule organization that occurs in specific birth defects and in cancer.

LIANG FENG, PhD, assistant professor of molecular and cellular physiology, will use his award to study the molecular mechanisms of Alzheimer's disease and to explore new therapeutic strategies. During the course of this work, he plans to develop new tools that might also find applications in a variety of biological systems.

The Feng group has focused on proteins embedded in or anchored on biological membranes. These membranes act as selective barriers separating the interior of cells from their outside environment. Membrane proteins play crucial roles in a wide range of biological and physiological processes and are targeted by a large number of pharmacologically active compounds.

Feng's research interest lies primarily in understanding the mechanism and regulation of these dynamic membrane proteins, and in developing new tools and approaches to understand their functions. To further that understanding, his group employs biochemical, biophysical, structural, computational and engineering approaches.

JULIANA IDOYAGA, PhD, assistant professor of microbiology and immunology, wants to create better treatments for autoimmune diseases. As many as 24 million Americans are affected by autoimmune diseases. There are currently no clinically approved therapies that can cure or prevent these diseases without causing side effects due to generalized immunosuppression.

Idoyaga's research focuses on the function and biology of dendritic cells, which are specialized antigen-presenting cells that initiate and modulate our body's immune responses. She aims to use her award to design new immunotherapies that harness the natural capacity of dendritic cells to generate antigen-specific regulatory T cells. These regulatory T cells can silence the undesired immune responses that lead to autoimmunity. She has found strong evidence in experimental models that engaging selected dendritic cell subsets can be used as a safe therapeutic approach for autoimmune diseases.

As a graduate student at the Massachusetts Institute of Technology, New Innovator Award recipient **DANIEL JAROSZ**, PhD, investigated how mutations are made in DNA. After graduating in 2007, he pursued postdoctoral training at the Whitehead Institute with Susan Lindquist, a pioneer in the field of protein folding. Jarosz joined the Stanford faculty in 2013 as an assistant professor of chemical and systems biology and of developmental biology. His research explores how organisms balance competing needs to retain their genetic integrity yet also adapt to new environments. Jarosz's work has revealed that links between protein folding and environmental stress strongly influence the evolution of new traits, the effects of disease-related mutations and developmental processes.

Recently the team has investigated whether wrongly folded proteins are always a problem. Prions, which are misfolded proteins that act as templates to create more misfolded proteins, are best known for causing neurodegenerative disease. But Jarosz's work in fungi suggests that they can also drive beneficial traits.

Jarosz plans to use his award for new work characterizing prionlike complexes formed by molecules that regulate cellular information flow: transcription factors and RNA binding proteins.

MANU PRAKASH, PhD, assistant professor of bioengineering, works in the broad area of organismic biophysics and frugal science, developing low-cost, precision measurement tools for the masses. For example, he and his group invented the Foldscope, a $1 origami microscope assembled out of folded paper. Foldscopes are now being used by a worldwide community in applications ranging from environmental monitoring to science education (http://microcosmos.foldscope.com). Foldscopes can also be configured for diagnostic applications, with ongoing field-validation studies in Kenya for a number of diseases including helminth infections and schistosomiasis.

For his latest work, Prakash is studying disease vectors such as mosquitoes that transmit deadly diseases like malaria and dengue. These vector-borne diseases take a huge toll on human health. Yet no high-throughput, high-resolution tools exist for mosquito surveillance and the pathogens they harbor. With the support of this new award, Prakash aims to bring his low-cost, scalable design approach to creating a toolbox to enable the assessment of spatial-temporal population dynamics of mosquitoes and corresponding human pathogens in field conditions. If applicable broadly, these tools could provide a new window into host-pathogen dynamics in mosquitoes at ecological scales. **ISM**

Hospital expansion to tap sustainable water practices

By Ruth Schechter

SKYHAWK PHOTOGRAPHY

The Discovery Garden, now under construction as part of the hospital expansion, will incorporate underground cisterns for its watering needs.

Hospitals by their very nature require massive amounts of water to maintain complex medical systems and equipment critical to patient care. Heating and cooling systems, and specialty services such as laundry, sterilization, sanitation, food service and integrated computer systems, call for an ongoing source of water. And lots of it.

In fact, hospitals today are the third most water-intensive public buildings, behind senior care facilities and hotels, using an average of 570 gallons of water per staffed bed per day, according to *Healthcare Design* magazine. In comparison, the U.S. Environmental Protection Agency estimates that an average person uses about 80 to 100 gallons of water per day.

In this era of water conservation, architects, designers and planners for the Lucile Packard Children's Hospital Stanford expansion are working to significantly reduce water consumption. The facility, scheduled to open in the summer of 2017, will add 521,000 square feet to the approximately 300,000-square-foot existing hospital, streamlining care for children, expectant mothers and their families.

Landscaping priorities

An inherent sense of environmental responsibility is a driving force behind the children's hospital expansion, which makes sustainability and "green" systems a top priority. The building integrates nature seamlessly into its layout, with almost four acres of gardens and green space for patients, families, visitors and staff to enjoy. The landscapes also will provide natural habitats for local birds and insects.

A water-sensitive approach to the expansion was factored in long before California's current drought made low-water landscaping and reduced water usage a major concern. "Seven years ago, when we started planning, we knew there was not enough rainfall to sustain even the most efficient hospital's needs," said Robin Guenther, principal at Perkins+Will and the lead designer of the hospital expansion. "That presented the option of finding ways to reuse water as much as possible."

The landscaping will feature native and hardy adapted plants that require minimal water, such as drought-tolerant varieties of yarrow, flax lily, mountain lilac, lavender and sage. A specially designed blend of grasses that require little or no water will be planted instead of a traditional lawn. Expanses of greenery and permeable paving allow rain to be absorbed into the region's groundwater rather than run off into the bay.

"Nature is an important part of the hospital's identity, and landscape has been embraced as a central design concept," Guenther said. "Everything from selection of plant material and retention of trees to the form and functionality of the gardens is customized to the ecological setting of the site, the climate and the users."

Designed with attention to the demands of security, comfort and safety unique to a hospital setting, each outdoor area will incorporate plants and amenities for different needs —places where kids can play, parents can relax and staff can mingle and unwind.

The centerpiece will be the Discovery Garden, which will feature private meditation niches and nooks framed by hedges for privacy and quiet. The Emerald Garden will feature an open lawn, a children's play area, stone retaining walls and shaded walkways. The Rainbow Garden, a respite for physicians and staff, will be linked to the campus shuttle system. Courtyards and roof gardens will be easily accessible and allow natural light to filter into the corridors.

Underground storage

These water-efficient landscapes will be irrigated with rainwater and condensate water —water that is extracted from dehumidifying indoor air — that will be collected in two 55,000-gallon underground cisterns. The distilled water that is used continuously in dialysis equipment also will be routed to the cisterns, ensuring that water will be available even when there is no rainfall. Constructed of steel-reinforced polyethylene, each cistern is 70 feet long and 40 feet wide — about half as big as an Olympic-size swimming pool — and 10 feet deep.

"Because we are using water from multiple, constant sources, we do not need to rely on storm-water runoff, which is inconsistent, especially during an extended drought," said Henry Phillips, project manager at Sandis, a civil engineering firm that specializes in sustainable design. "Water is routed to the cisterns through a pumping system and can be diverted to an integrated bypass system if the tanks are full."

These sources for irrigation will save as much as 800,000 gallons of water per year, said Michele Charles, project engineer for the expansion, adding that the system can be adapted to add more cisterns in the future. Hospital designers did an extensive analysis before construction to determine how much water the gardens would require so they could set the baseline for the expected supply of condensate water, Phillips said.

Conserving resources

The existing hospital facility also maintains its grounds in a water-wise manner. Designed during a drought in the late 1980s and opened in 1991, the gardens consist primarily of drought-tolerant plants. An ongoing program to monitor and maintain broken sprinkler heads limits runoff, while use of mulch to protect plantings helps retain moisture, said Patrick Connor, administrative director of support services. "No-mow" turf with an efficient irrigation system, which looks and feels like traditional lawn, invites families and visitors to lounge and play, he said.

The new building incorporates an extensive external shading system, and windows are positioned to avoid direct sunlight throughout the year. Limiting direct sunlight helps to reduce solar gain — the increase in temperature caused by the sun — while reducing the need for air conditioning, which has energy and water needs of its own. The hospital also has located its data center on the roof rather than in the basement, so that it can be cooled by ambient air rather than air conditioning. That move alone has reduced energy needs by 60 percent compared with other Northern California hospitals, Guenther said.

The hospital also plans to install water-conserving dishwashers and sterilizers, which are projected to use about 80 percent less water than their standard counterparts. Water-cooled pumps and air compressors will be replaced, and on-demand sinks and low-flow bathroom fixtures, both of which also are being phased into the existing hospital, are expected to save 2.5 million gallons of water a year. Together, these systems in the new building are expected to use 38 percent less water than in a comparable standard hospital, according to Guenther. An electronic dashboard in the main lobby will display the building's ongoing water and energy usage.

"Throughout the design process, we looked at sustainability as a key feature," said Jill Sullivan, RN, MSN, vice president of hospital transformation and space planning. "Using water wisely makes an impact on the whole community and saves money in the long term. Plus, it's simply the right thing to do."

More about the Stanford University Medical Center Renewal Project can be found at http://sumc.org. **ISM**

Ruth Schechter is a freelance writer and editor.

NORBERT VON DER GROEBEN

A good fit

First-year PhD students in biochemistry await their moment onstage during the lab coat ceremony Sept. 30 in Berg Hall at the Li Ka Shing Center for Learning and Knowledge. New graduate students in the 14 bioscience programs and in bioengineering were on hand for the annual rite, during which they were introduced and helped into their new white coats. A reception followed.

Alcohol

continued from page 1

this have been obscure. A key finding in the new study is that in certain nerve cells strongly implicated in addictive behaviors, ALDH1a1 is an essential piece of a previously unknown biochemical assembly pathway for the manufacture of an important neurotransmitter called GABA. Neurotransmitters are chemicals that bind to receptors on nerve cells, promoting or inhibiting signaling activity in those cells.

GABA is the brain's main inhibitory neurotransmitter. It was previously thought that GABA was made in mammalian brains only via a different biochemical assembly line that doesn't involve ALDH1a1.

An alternative assembly line

While GABA is produced widely throughout the brain, the novel GABA-production assembly line identified by Ding's group was observed only in a group of nerve cells known to play a powerful role in addiction. The new finding has potentially great clinical significance because a drug that could increase GABA synthesis through this alternative assembly line — by boosting ALDH1a1 levels in the brain — could potentially restore the balance in neural circuitry that's been thrown out of kilter by excessive alcohol consumption without dangerously elevating GABA levels elsewhere in the brain.

Another neurotransmitter substance, dopamine, is famous among neuroscientists for its involvement in modulating motion and motivation. Dopamine supercharges the machinery of the brain's so-called reward circuit, which is involved in all types of addictive behavior from cocaine, morphine and alcohol abuse to compulsive gambling.

The reward circuit is a network of nerve cells and connections found in the brains of living creatures from flies to humans and every animal in between. It guides individuals' behavior — and ensures species' survival — by offering pleasurable sensations as a reward for eating, sleeping, having sex and making friends. Key components of this circuit are fueled by dopamine.

"Every time I publish a paper, my dopamine-producing nerve cells go crazy, but I don't get addicted. Why not?"

Until recently, neuroscientists widely assumed that each type of nerve cell in the brain can release one and only one neurotransmitter. But in a study published in *Nature* in 2012, Ding, then a postdoctoral scholar at Harvard Medical School, and his colleagues demonstrated that dopamine-producing nerve cells can manufacture and release other types of neurotransmitters, too, including GABA. These cells not only produce both dopamine and GABA but release them simultaneously.

"We wondered what GABA is doing in there," Ding said. "Why does one nerve cell need two neurotransmitters?"

Ding also had another question. "All of us normally encounter countless reward-inducing situations without getting addicted," he said. "Every time I publish a paper, my dopamine-producing nerve cells go crazy, but I don't get addicted. Why not?"

GABA's role in countering addiction

To find out whether GABA in dopamine-producing cells might have something to do with addiction, Ding and his associates initially tried to examine GABA's effects by blocking its production through the conventional assembly line — that is, the only one known at the time — while stimulating only dopamine-producing cells in mice's brains. To their surprise, these tried-and-tested methods failed to reduce GABA levels in these cells or the neurotransmitter's effects on nearby downstream nerve cells. That was puzzling.

Curious, Ding began a literature search to see if there were any other ways that biological systems manufacture GABA. He learned that in plants, GABA can be produced via a biochemical assembly line quite separate from the common, previously known one our brains use. He found that one step in this alternative GABA-manufacturing pathway is performed by a family of enzymes, aldehyde dehydrogenases, that are better known for being involved in the breakdown of alcohol. Ding also found that aldehyde dehydrogenases are expressed not only in the liver, where most of the alcohol we drink gets metabolized, but in some parts of the brain that, to Ding — whose professional career has focused on the brain's dopamine-producing nerve circuitry — looked anatomically identical to the dopamine-producing nerve cells that feed the reward circuit. Ding's team verified that the specific family member at work in those dopamine-producing cells was ALDH1a1.

Using laboratory methods to impair ALDH1a1 activity in mice, the scientists saw GABA levels in dopamine-producing nerve cells drop, just as they did when mice with normal ALDH1a1 activity underwent repeated bouts of high alcohol intake — the equivalent of binge drinking. In behavioral tests, the ALDH1a1-deficient mice showed the same increased alcohol preference and intake as did otherwise normal "binge-drinker" mice. These effects were reversed by manipulations that raised ALDH1a1 levels in the mice.

Ding said he thinks that GABA's co-release with dopamine, and GABA's inhibitory character, may be what prevents everyday pleasurable sensations from causing most of us, most of the time, to become addicted to the behaviors that produce them. Mutations in ALDH1a1, he said, may predispose some people to alcoholism by disabling this brake on our reward machinery. His lab is now exploring whether the same molecular mechanisms may be at work in other forms of addiction.

Additional Stanford co-authors of the study are postdoctoral scholars Subhashree Ganesan, PhD, Yu-Wei, PhD, and Esther Park, PhD; and Lu Chen, PhD, associate professor of neurosurgery and of psychiatry and behavioral sciences.

The study was funded by National Institutes of Health, the National Institute of Mental Health and the Klingenstein Foundation.

Stanford's Department of Neurosurgery also supported the work. **ISM**

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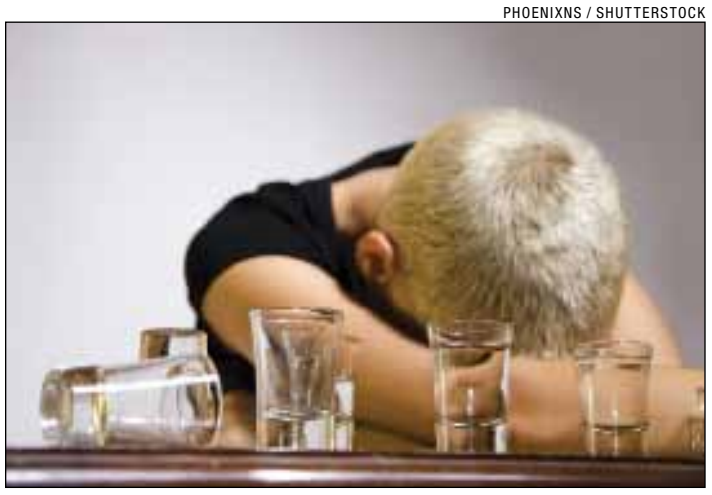

Binge drinking substantially increases the likelihood of developing alcoholism.

Concussion

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to the Stanford Concussion and Brain Performance Center, where she underwent a series of tests to track her response rate and attention span. She was put on a regimen of treadmill training and vestibular rehabilitation therapy, an exercise program that retrains the brain to regain balance control and minimize dizziness.

"The center used metrics, measurements and data to track my progress, so it wasn't just that I felt better — I could see the measurements of my improvement," Fisher said. "I had been feeling like it was all in my head, so that was a real morale booster."

A growing concern

The Stanford Concussion and Brain Performance Center was established last year to define objective criteria for diagnosing concussions, and to treat adults and children based on the physical response of the brain.

"Concussion remains the most underreported, underdiagnosed and underestimated head injury. It affects how we think, even though physical function may be intact," said Jamshid Ghajar, MD, PhD, clinical professor of neurosurgery and director of the center. "It mainly affects the ability to focus — how a person interacts with the outside world. Poor attention is the most common cognitive impairment."

Jamshid Ghajar

Concussion injuries are gaining attention because of their prevalence among young athletes. Approximately 3.8 million people suffer concussions from sports and recreational activities in the United States each year — an estimated 100,000 of them among high school athletes. Almost half of all athletes do not report feeling any symptoms after a concussive blow, but people who have had a concussion are three times more likely to have a similar event and to experience slower neurological recovery the second time.

Currently, there is no universally accepted scientific definition of concussion, and both diagnosis and treatment often vary from physician to physician. Symptoms can range widely and vary in intensity and duration. Doctors typically diagnose the condition by observing symptoms such as headache and dizziness, and sometimes by testing reaction time, memory and comprehension. Brain scans, using magnetic resonance imaging or computed tomography, often show no physiological change.

"Concussion remains the most underreported, underdiagnosed and underestimated head injury."

Ghajar defines a concussion as a change in brain function after a direct or indirect force to the head, sometimes followed by a temporary loss of consciousness that results in neurological and cognitive dysfunction, such as disorientation, balance, slowed reaction time, blurred vision and impaired memory. The condition resolves by itself in a week in 92 percent of the cases, he said.

Response to impact

A concussion begins with an impact to the head, neck or torso, which causes a metabolic cascade within the frontal lobe of the brain, affecting the way it responds to stimuli. The result is a timing gap in the way the brain interprets and predicts what is taking place in the outside world. Ghajar likens it to the way a tennis player anticipates where and when to swing the racket to hit the ball at the right time and place. When the system is disrupted, the result is a delayed and variable reaction time.

"What I think is disrupted in concussion is prediction or anticipation," he said. "The brain is not synchronized properly with the outside world, and its moment-to-moment prediction is impaired. It's all about the timing."

Ghajar has developed an eye-tracking device to evaluate how well a patient can anticipate the progression of a dot of light moving in a circle, a measure of how well one can synchronize with outside stimuli. Cameras track the eye's ability to follow the dot's movement, which tests predictive ability. A person with a concussion cannot track the light well, resulting in "jitters" in the eye movement in relation to the target. The system works, Ghajar said, because visual tracking and attention share similar neural areas in the brain.

He is involved in a large-scale study of military personnel, high school athletes and other groups to determine whether the degree of disruption in eye movements detected by the device correlates with concussion and recovery. Using this eye-tracking technology, he and his colleagues plan to establish measurable criteria for concussion and to determine when it's safe for a patient to go back to normal activities. Ghajar is president of the Brain Trauma Foundation, an organization focused on developing best practice guidelines, conducting clinical research and educating medical professionals and consumers about concussion.

For Fisher, watching her progression on Ghajar's eye-tracking system showed tangible proof that she was, indeed, recovering from her concussion. After almost four months of gradually building up her strength and focus, she finally was able to get back to all her usual activities — including bicycling.

Jessica Little, PhD, clinical assistant professor of neurosurgery, is director of clinical research and operations at the center. Anna Viet, RN, is the center's nurse coordinator.

Other Stanford Medicine brain specialists, including Jaime Lopez, MD, associate professor of neurology and neurological sciences; Viet Nguyen, MD, clinical assistant professor of neurology and neurological sciences; Gerald Grant, associate professor of neurosurgery; and Paul Fisher, MD, professor of pediatrics and of neurology and neurological sciences (no relation to Paige Fisher), regularly collaborate with the center. **ISM**

Ruth Schechter is a freelance writer and editor.

Sleep

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productive sleep time, said pediatric sleep specialist Rafael Pelayo, MD, with the Stanford Sleep Disorders Clinic.

"When teens wake up earlier, it cuts off their dreams," said Pelayo, a clinical professor of psychiatry and behavioral sciences. "We're not giving them a chance to dream."

Understanding teen sleep

On a sunny June afternoon, Dement maneuvered his golf cart, nicknamed the Sleep and Dreams Shuttle, through the Stanford University campus to Jerry House, a sprawling, Mediterranean-style dormitory where he and his colleagues conducted some of the early, seminal work on sleep, including teen sleep.

Beginning in 1975, the researchers recruited a few dozen local youngsters between the ages of 10 and 12 who were willing to participate in a unique sleep camp. During the day, the young volunteers would play volleyball in the backyard, which faces a now-barren Lake Lagunita, all the while sporting a nest of electrodes on their heads.

MONKEY BUSINESS / DOLLAR PHOTO CLUB

Social and cultural factors, as well as new forms of information technology, all have collided with adolescent biology to prevent teens from getting enough rest.

At night, they dozed in a dorm while researchers in a nearby room monitored their brain waves on 6-foot electroencephalogram machines, old-fashioned polygraphs that spit out wave patterns of their sleep.

One of Dement's colleagues at the time was Mary Carskadon, PhD, then a graduate student at Stanford. They studied the youngsters over the course of several summers, observing their sleep habits as they entered puberty and beyond.

Dement and Carskadon had expected to find that as the participants grew older, they would need less sleep. But to their surprise, their sleep needs remained the same — roughly nine hours a night — through their teen years. "We thought, 'Oh, wow, this is interesting,'" said Carskadon, now a professor of psychiatry and human behavior at Brown University and a nationally recognized expert on teen sleep.

Moreover, the researchers made a number of other key observations that would plant the seed for what is now accepted dogma in the sleep field. For one, they noticed that when older adolescents were restricted to just five hours of sleep a night, they would become progressively sleepier during the course of the week. The loss was cumulative, accounting for what is now commonly known as sleep debt.

"The concept of sleep debt had yet to be developed," said Dement, the Lowell W. and Josephine Q. Berry Professor in the Department of Psychiatry and Behavioral Sciences. It's since become the basis for his ongoing campaign against drowsy driving among adults and teens. "That's why you have these terrible accidents on the road," he said. "People carry a large sleep debt, which they don't understand and cannot evaluate."

The researchers also noticed that as the kids got older, they were naturally inclined to go to bed later. By the early 1990s, Carskadon established what has become a widely recognized phenomenon — that teens experience a so-called sleep-phase delay. Their circadian rhythm — their internal biological clock — shifts to a later time, making it more difficult for them to fall asleep before 11 p.m.

Teens are also biologically disposed to a later sleep time because of a shift in the system that governs the natural sleep-wake cycle. Among older teens, the push to fall asleep builds more slowly during the day, signaling them to be more alert in the evening.

"It's as if the brain is giving them permission, or making it easier, to stay awake longer," Carskadon said. "So you add that to the phase delay, and it's hard to fight against it."

Pressures not to sleep

After an evening with four or five hours of homework, Walworth turns to her cellphone for relief. She texts or talks to friends and surfs the Web. "It's nice to stay up and talk to your friends or watch a funny YouTube video," she said. "There are plenty of online distractions."

While teens are biologically programmed to stay up late, many social and cultural forces further limit their time for sleep. For one, the pressure on teens to succeed is intense, and they must compete with a growing number of peers for college slots that have largely remained constant. In high-achieving communities like Palo Alto, that translates into students who are overwhelmed by additional homework for Advanced Placement classes, outside activities such as sports or social service projects, and in some cases, part-time jobs, as well as peer, parental and community pressures to excel.

At the same time, today's teens are maturing in an era of ubiquitous electronic media, and they are fervent participants. Some 92 percent of U.S. teens have smartphones, and 24 percent report being online "constantly," according to a 2015 report by the Pew Research Center. Teens have access to multiple electronic devices they use simultaneously, often at night. Some 72 percent bring cellphones into their bedrooms and use them when they are trying to go to sleep, and 28 percent leave their phones on while sleeping, only to be awakened at night by texts, calls or emails, according to a 2011 National Sleep Foundation poll on electronic use. In addition, some 64 percent use electronic music devices, 60 percent use laptops and 23 percent play video games in the hour before they went to sleep, the poll found. More than half reported texting in the hour before they went to sleep, and these media fans were less likely to report getting a good night's sleep and feeling refreshed in the morning. They were also more likely to drive when drowsy, the poll found.

The problem of sleep-phase delay is exacerbated when teens are exposed late at night to lit screens, which send a message via the retina to the portion of the brain that controls the body's circadian clock. The message: It's not nighttime yet.

Yuan, a clinical associate professor of pediatrics, said she routinely sees young patients in her clinic who fall asleep at night with cellphones in hand.

"With academic demands and extracurricular activities, the kids are going nonstop until they fall asleep exhausted at night. There is not an emphasis on the importance of sleep, as there is with nutrition and exercise," she said. "They say they are tired, but they don't realize they are actually sleep-deprived. And if you ask kids to remove an activity, they would rather not. They would rather give up sleep than an activity."

> "I think high school is the real danger spot in terms of sleep deprivation."

The role of parents

Adolescents are also entering a period in which they are striving for autonomy and want to make their own decisions, including when to go to sleep. But studies suggest adolescents do better in terms of mood and fatigue levels if parents set the bedtime — and choose a time that is realistic for the child's needs. According to a 2010 study published in the journal *Sleep*, children are more likely to be depressed and to entertain thoughts of suicide if a parent sets a late bedtime of midnight or beyond.

In families where parents set the time for sleep, the teens' happier, better-rested state "may be a sign of an organized family life, not simply a matter of bedtime," Carskadon said. "On the other hand, the growing child and growing teens still benefit from someone who will help set the structure for their lives. And they aren't good at making good decisions."

According to the 2011 sleep poll, by the time U.S. students reach their senior year in high school, they are sleeping an average of 6.9 hours a night, down from an average of 8.4 hours in the sixth grade. The poll included teens from across the country from diverse ethnic backgrounds.

American teens aren't the worst off when it comes to sleep, however; South Korean adolescents have that distinction, sleeping on average 4.9 hours a night, according to a 2012 study in *Sleep* by South Korean researchers. These Asian teens routinely begin school between 7 and 8:30 a.m., and most sign up for additional evening classes that may keep them up as late as midnight. South Korean adolescents also have relatively high suicide rates (10.7 per 100,000 a year), and the researchers speculate that chronic sleep deprivation is a contributor to this disturbing phenomenon.

By contrast, Australian teens are among those who do particularly well when it comes to sleep time, averaging about nine hours a night, possibly because schools there usually start later.

Regardless of where they live, most teens follow a pattern of sleeping less during the week and sleeping in on the weekends to compensate. But many accumulate such a backlog of sleep debt that they don't sufficiently recover on the weekend and still wake up fatigued when Monday comes around.

Moreover, the shifting sleep patterns on the weekend — late nights with friends, followed by late mornings in bed — are out of sync with their weekday rhythm. Carskadon refers to this as "social jet lag."

"Every day we teach our internal circadian timing system what time it is — is it day or night? — and if that message is substantially different every day, then the clock isn't able to set things appropriately in motion," she said. "In the last few years, we have learned there is a master clock in the brain, but there are other clocks in other organs, like liver or kidneys or lungs, so the master clock is the coxswain, trying to get everybody to work together to improve efficiency and health. So if the coxswain is changing the pace, all the crew become disorganized and don't function well."

This disrupted rhythm, as well as the shortage of sleep, can have far-reaching effects on adolescent health and well-being, she said.

"It certainly plays into learning and memory. It plays into appetite and metabolism and weight gain. It plays into mood and emotion, which are already heightened at that age. It also plays into risk behaviors — taking risks while driving, taking risks with substances, taking risks maybe with sexual activity. So the more we look outside, the more we're learning about the core role that sleep plays," Carskadon said.

Many studies show students who sleep less suffer academically, as chronic sleep loss impairs the ability to remember, concentrate, think abstractly and solve problems. In one of many studies on sleep and academic performance, Carskadon and her colleagues surveyed 3,000 high school students and found that those with higher grades reported sleeping more, going to bed earlier on school nights and sleeping in less on weekends than students who had lower grades.

Sleep is believed to reinforce learning and memory, with studies showing that people perform better on mental tasks when they are well-rested. "We hypothesize that when teens sleep, the brain is going through processes of consolidation — learning of experiences or making memories," Yuan said. "It's like your brain is filtering itself — consolidating the important things and filtering out those unimportant things." When the brain is deprived of that opportunity, cognitive function suffers, along with the capacity to learn.

"It impacts academic performance. It's harder to take tests and answer questions if you are sleep-deprived," she said.

That's why cramming, at the expense of sleep, is counterproductive, said Pelayo, who advises students: Don't lose sleep to study, or you'll lose out in the end.

Research has shown that sleep problems among adolescents are a major risk factor for suicidal thoughts and death by suicide, which ranks as the third-leading cause of fatalities among 15- to 24-year-olds. And this link between sleep and suicidal thoughts remains strong, independent of whether the teen is depressed or has drug and alcohol issues, according to some studies.

"Sleep, especially deep sleep, is like a balm for the brain," said Shashank Joshi, MD, associate professor of psychiatry and behavioral sciences at Stanford. "The better your sleep, the more clearly you can think while awake, and it may enable you to seek help when a problem arises. You have your faculties with you. You may think, 'I have 16 things to do, but I know where to start.' Sleep deprivation can make it hard to remember what you need to do for your busy teen life. It takes away the support, the infrastructure."

Sleep is believed to help regu-

See SLEEP, page 7

Mom's higher blood sugar tied to baby's heart-defect risk

By Erin Digitale

Pregnant women with elevated blood-sugar levels are more likely to have babies with congenital heart defects, even if their blood sugar is below the cutoff for diabetes, according to a new study from the School of Medicine and Stanford Children's Health.

The study, which was published online today in *JAMA Pediatrics*, extends the scope of prior findings on the connection between maternal diabetes and fetal heart defects. It is the first to show the link in women without a diabetes diagnosis.

"Diabetes is the tail end of a spectrum of metabolic abnormalities," said James Priest, MD, the study's lead author and a postdoctoral scholar in pediatric cardiology. "We already knew that women with diabetes were at significantly increased risk for having children with congenital heart disease. What we now know, thanks to this new research, is that women who have elevated glucose values during pregnancy that don't meet our diagnostic criteria for diabetes also face an increased risk." Priest treats patients with congenital heart defects at the Children's Heart Center at Lucile Packard Children's Hospital Stanford.

Pregnancy normally involves metabolic changes that make blood sugar — glucose — more available to the fetus than to the mother, an important adaptation for ensuring that the fetus gets enough nourishment. However, in some women, especially those who are obese or who have a family history of diabetes, these changes progress too far, to the point that the mother develops gestational diabetes. Although the risks of gestational diabetes have been well-studied, less attention has been paid to smaller metabolic changes in pregnancy.

Two serious heart defects

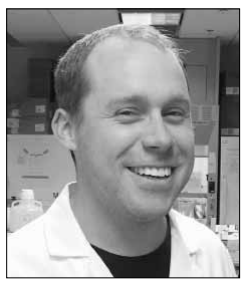
In the new study, the researchers examined blood samples taken from 277 California women during the second trimester of pregnancy.

The control group comprised 180 women carrying infants without congenital heart disease. The others had infants affected by one of two serious heart defects. Fifty-five infants had tetralogy of Fallot, which is characterized by structural problems in the heart and in the blood vessels that connect the heart to the lungs; it is the most common of the heart defects that cause blue baby syndrome, in which a baby is getting too little oxygen. The remaining 42 infants had dextrotransposition of the great arteries, in which the positions of the two main arteries leading from the heart are swapped, preventing oxygenated blood from the lungs from circulating to the body.

The blood samples were collected at different times of the day, and the women were not asked to fast before sample collection. The researchers measured the women's levels of glucose, the main form of blood sugar, and insulin, a hormone that controls blood sugar.

The researchers found that average blood glucose levels were higher in women carrying fetuses with tetralogy of Fallot than in women in the control group, but were not elevated in women whose fetuses had dextrotransposition of the great arteries. However, women whose fetuses had dextrotransposition of the great arteries had significantly elevated insulin levels.

The scientists used a mathematical model that accounted for both glucose and insulin levels, and was adjusted for the woman's age and ethnicity and whether she had diabetes. In the model, higher glucose levels were correlated with the odds of having a baby with tetralogy of Fallot, but not with dextrotransposition of the great arteries. In the model, however, the relationship with insulin levels was not significant for either birth defect.



James Priest

Fuel for cells

Glucose is a fundamental fuel for cells, Priest noted, so it is unlikely that it is high glucose itself that damages the fetal heart. "It has to act via some mechanism," he said, adding that the cell's machinery for handling glucose overlaps with important developmental signaling mechanisms, such as the insulin-like growth factor receptors.

"I'm excited by this research because it opens up a lot of questions about how physiologic processes in the mother may be related to congenital heart disease," Priest said. "Most of the time we don't have any idea what causes a baby's heart defect. I aim to change that."

The work is an example of Stanford Medicine's focus on precision health by generating care that is proactive, predictive and personalized.

The study's senior author, Gary Shaw, DrPH, professor of pediatrics in neonatal and developmental medicine, added, "There are several other kinds of structural birth defects, in addition to heart defects, that have been linked with overt diabetes. This new work will motivate us to ask if underlying associations with moderately increased glucose levels may be similarly implicated in risks of some of these other birth defects."

Other Stanford-affiliated authors of the study are Wei Yang, data analyst in pediatrics; Gerald Reaven, MD, professor emeritus of medicine; and Joshua Knowles, MD, PhD, assistant professor of cardiovascular medicine. Reaven, Knowles and Shaw are members of the Stanford Child Health Research Institute.

The research was supported by the National Institutes of Health, the Stanford Cardiovascular Institute and the American Heart Association. Biospecimens and data used in the study were obtained from the California Biobank Program.

Stanford's Department of Pediatrics also supported the work. **ISM**

Sleep

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late emotions, and its deprivation is an underlying component of many mood disorders, such as anxiety, depression and bipolar disorder. For students who are prone to these disorders, better sleep can help serve as a buffer and help prevent a downhill slide, Joshi said.

Rebecca Bernert, PhD, who directs the Suicide Prevention Research Lab at Stanford, said sleep may affect the way in which teens process emotions. Her work with civilians and military veterans indicates that lack of sleep can make people more receptive to negative emotional information, which they might shrug off if they were fully rested, she said.

"Based on prior research, we have theorized that sleep disturbances may result in difficulty regulating emotional information, and this may lower the threshold for suicidal behaviors among at-risk individuals," said Bernert, an instructor of psychiatry and behavioral sciences. Now she's studying whether a brief nondrug treatment for insomnia reduces depression and risk for suicide.

Sleep deprivation also has been shown to lower inhibitions among both adults and teens. In the teen brain, the frontal lobe, which helps restrain impulsivity, isn't fully developed, so teens are naturally prone to impulsive behavior. "When you throw into the mix sleep deprivation, which can also be disinhibiting, mood problems and the normal impulsivity of adolescence, then you have a potentially dangerous situation," Joshi said.

Some schools shift

Given the health risks associated with sleep problems, school districts around the country have been looking at one issue over which they have some control: when school starts in the morning. The trend was set by the town of Edina, Minnesota, a well-to-do suburb of Minneapolis, which conducted a landmark experiment in student sleep in the late 1990s. It shifted the high school's start time from 7:20 a.m. to 8:30 a.m. and then asked University of Minnesota researchers to look at the impact of the change. The researchers found some surprising results: Students reported feeling less depressed and less sleepy during the day and more empowered to succeed. There was no comparable improvement in student well-being in surrounding school districts where start times remained the same.

With these findings in hand, the entire Minneapolis Public School District shifted start times for 57,000 students at all of its schools in 1997 and found similarly positive results. Attendance rates rose, and students reported getting an hour's more sleep each school night — or a total of five more hours of sleep a week — countering skeptics who argued that the students would respond by just going to bed later.

Other studies have reinforced the link between later start times and positive health benefits. One 2010 study at an independent high school in Rhode Island found that after delaying the start time by just 30 minutes, students slept more and showed significant improvements in alertness and mood. And a 2014 study in two counties in Virginia found that teens were much less likely to be involved in car crashes in a county where start times were later, compared with a county with an earlier start time.

Bolstered by the evidence, the American Academy of Pediatrics in 2014 issued a strong policy statement encouraging middle and high school districts across the country to start school no earlier than 8:30 a.m. to help preserve the health of the nation's youth. Some districts have heeded the call, though the decisions have been hugely contentious, as many consider school schedules sacrosanct and cite practical issues, such as bus schedules, as obstacles.

In Fairfax County, Virginia, it took a decade of debate before the school board voted in 2014 to push back the opening school bell for its 57,000 students. And in Palo Alto, where a recent cluster of suicides has caused much communitywide soul-searching, the district superintendent issued a decision in the spring, over the strenuous objections of some teachers, students and administrators, to eliminate "zero period" for academic classes — an optional period that begins at 7:20 a.m. and is generally offered for advanced studies.

Certainly, changing school start times is only part of the solution, experts say. More widespread education about sleep and more resources for students are needed. Parents and teachers need to trim back their expectations and minimize pressures that interfere with teen sleep. And there needs to be a cultural shift, including a move to discourage late-night use of electronic devices, to help youngsters gain much-needed rest.

"At some point, we are going to have to confront this as a society," Carskadon said. "For the health and well-being of the nation, we should all be taking better care of our sleep, and we certainly should be taking better care of the sleep of our youth." **ISM**

Committee appointed to conduct search for new CEO of Stanford Health Care

Stanford Health Care's board of directors has appointed a committee to immediately begin a nationwide search for a new CEO.

The current CEO, Amir Dan Rubin, will step down Jan. 4.

The committee is co-chaired by John Levin, chair of the SHC Board of Directors, and Lloyd Minor, MD, dean of the School of Medicine. The other members of the committee are Christopher Dawes, CEO of Lucile Packard Children's Hospital Stanford; Norman Rizk, MD, chief medical officer of SHC; Robert Jackler, MD, professor and chair of otolaryngology; and SHC board members Bret Comolli, John Gunn, Fred Harman, Ron Johnson, Linda Meier and Mariann Byerwalter, who is former chair of the board.

"We are grateful to the members of the search committee for undertaking this critical role," Minor and Levin said in a statement. "Our goal is to find a truly outstanding leader for SHC as is befitting the unique and preeminent role that Stanford Health Care plays not only in our community but nationally. We will be reaching out to the multiple constituencies of the Stanford Medicine family for input in this process. We are fortunate that we have excellent leadership at all levels of the organization that will continue the exciting momentum of SHC while we conduct this search." **ISM**

Public health impact of e-cigarettes will be subject of forum set for Oct. 26

The public health ramifications of e-cigarettes will be the focus of the next Stanford Health Policy Forum, scheduled for noon Oct. 26 in Berg Hall at the Li Ka Shing Center for Learning & Knowledge.

The forum, "E-Cigarettes: A Threat or an Opportunity for Public Health?," is free and open to the public.

Debating the issue will be David Abrams, PhD, professor of health, behavior and society at Johns Hopkins University; Bonnie Halpern-Felsher, PhD, professor of pediatrics at Stanford; and Robert Jackler, MD, professor and chair of otolaryngology at Stanford. Each will bring their expertise to bear on the question of whether e-cigarettes are a threat or a benefit to public health.

Paul Costello, chief communications officer for the School of Medicine, will moderate the discussion.

The Stanford Health Policy Forum is an ongoing series of discussions and presentations designed to inform public debate about major health policy issues. **ISM**

Stanford Medicine reports on why a healthy childhood matters, including some surprises

By Rosanne Spector

You've forgotten most of your childhood experiences. That's normal. But your body remembers many of those experiences without you knowing it, and that's normal, too. Medical researchers are discovering your body doesn't forget, and that some of those early events will have far-reaching consequences for your health.

In the new issue of *Stanford Medicine*, produced with the support of Lucile Packard Children's Hospital Stanford, you'll read how researchers are developing techniques to prepare children for the healthiest possible adulthood.

"Some people think kids are protected by virtue of being kids. In fact, the opposite is true," said pediatric psychiatrist Victor Carrion, MD, in the issue, which includes the special report "Childhood: The road ahead." Carrion, a professor of psychiatry and behavioral sciences and director of the Stanford Early Life Stress and Pediatric Anxiety Program, discussed the long-term effects of childhood trauma, but the same goes for other types of early damage: Kids might seem resilient, but they carry hidden scars.

Certain consequences of childhood hardship or disease are easily predicted: Children with diabetes, for example, are likely to develop foot sores or eye disease when they grow up — a result of the nerve destruction diabetes is known to cause. Other reverberations emerge because survivors of once-fatal conditions are living longer: Those who've come through childhood cancer are at higher risk of infertility, early-onset bone weakness and development of other cancers, among other problems, all because of the long-term effects of the treatment that saved them. And then there are some repercussions that defy traditional medical expectations — like heart disease, liver disease and obesity affecting trauma survivors at higher rates than others.

The magazine also includes a Q&A with former President Jimmy Carter on discrimination against women and girls, which he considers the most serious human rights problem on Earth. "The human rights issue was brought to a highly personal level when we saw the horrible and surprising abuse of women and girls all around the world, including in the United States," he said in the interview. The online version of the magazine includes audio of the Carter conversation.

Highlights of the magazine's special report include:

- An article on the devastating toll inadequate sleep takes on teens, with an update on efforts, including a Stanford project, to fix the problem.
- A report on the growing need for support of chronically ill children making the jump to adult care, and on the progress that's being made.
- A story about a high school student's return to health after an assault, and the new type of therapy that helped her.
- A feature about three rocket-combustion experts teaming up with a pediatrician to analyze the breath of critically ill children at warp speed.
- An article on blending Western medicine into traditional culture to reduce newborn mortality in the developing world.
- A quick look at a new way to study the toll of childhood disease on bones.

The issue also includes an article on a surprising role for viruses in human embryos, as well as a report from India on how vision, investment and medical know-how has brought about an ambulance system — now 10 years old and one of the most important advances in global health today. The online version includes a video showing the ambulance system in action.

The magazine is online at http://stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at (650) 723-6911 or by sending an email to medmag@stanford.edu. **ISM**

OF NOTE

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

HELEN BLAU, PhD, the Donald E. and Delia B. Baxter Professor and director of the Baxter Laboratory for Stem Cell Biology, has received the Glenn Award for Research in Biological Mechanisms of Aging from the Glenn Foundation for her contributions as a leader in the field. Blau will receive the $60,000 prize to augment research in her laboratory. She has developed molecular approaches to rejuvenating diverse cell types, counteracting fundamental mechanisms of aging and identifying therapeutic strategies for increasing the regenerative capacity of muscle stem cells and restoring muscle strength in the elderly.

HOWARD CHANG, MD, PhD, professor of dermatology and director of the National Institutes of Health Center of Excellence in Genomic Science, was awarded the Paul Marks Prize for Cancer Research by the Memorial Sloan Kettering Cancer Center for discovering a new class of genes called long noncoding RNAs and for revealing their role in cancer. He is the first Stanford researcher to receive this prize. Chang will receive $50,000 and will speak at a scientific symposium Dec. 3 at the center in New York. The prize was created to honor Paul Marks, MD, president emeritus of the center.

JAMES CHANG, MD, the Johnson & Johnson Distinguished Professor in Surgery and chief of the Division of Plastic Surgery, was elected vice-president of the American Society for Surgery of the Hand. The ASSH is the oldest and largest professional organization in hand surgery, with over 3,500 members worldwide. The focus of Chang's research is improving the treatment of hand trauma, peripheral nerve injuries and congenital hand problems by applying new techniques in tissue engineering and microsurgery. Chang will automatically become ASSH president in 2017.

SUSAN HINIKER, MD, an instructor of radiation oncology, will receive an Annual Meeting Travel Award from the American Society for Radiation Oncology in recognition of the scientific abstract she submitted to its 57th annual meeting. Hiniker will receive the $1,000 award to offset travel costs to the Oct. 18-21 meeting in San Antonio.

CHIA-SUI (SUNNY) KAO, MD, was appointed assistant professor of pathology, effective July 1. Her clinical specialty is in diseases of the genitourinary tract, and her research interests are in testicular and bladder neoplasms.

MICHAEL LONGAKER, MD, the Deane P. and Louise Mitchell Professor in the School of Medicine and co-director of the Institute for Stem Cell Biology and Regenerative Medicine, was honored by the American College of Surgeons on Oct. 6 in Chicago. The ACS dedicated its 2015 Scientific Forum to Longaker in recognition of his accomplishments in surgical research and for his work in the areas of developmental biology, epithelial biology and tissue repair, tissue engineering and stem cell biology.

KARL LORENZ, MD, MSHS, was appointed professor of medicine, effective July 1. Lorenz will serve as the new section chief of the Veterans Health Administration-Stanford programs in palliative care. His prior research includes developing simple measures of pain for use in the clinic, improving the quality of patient care and improving end-of-life care for people living with advanced chronic illnesses. His work focuses on providing more patient- and family-centered care for the seriously ill, as well as on ways to encourage health providers to engage in simple yet often-neglected clinical practices, such as speaking to patients about their prognoses, health goals and pain management.

STEPHEN MONTGOMERY, PhD, assistant professor of pathology and of genetics, will receive a $1.4 million grant over three years from the National Human Genome Research Institute and the National Cancer Institute to develop methods for interpreting noncoding genetic variation and for predicting disease-causing variants in genomes. Montgomery, the study's principal investigator, and his team plan to develop various statistical models based on large amounts of information from individuals and identify variants that contribute to hundreds of diseases and traits. **ISM**


Helen Blau


Howard Chang


James Chang


Susan Hiniker


Michael Longaker


Karl Lorenz


Stephen Montgomery

Anna Deavere Smith to discuss school-to-prison pipeline on Oct. 23 with Victor Carrion

Playwright and actress Anna Deavere Smith will join Victor Carrion, MD, professor of psychiatry and behavioral sciences, onstage for a conversation on the impact of adversity, trauma and limited educational opportunities in the development of children — and the role medicine and art can play in alleviating the problem.


Anna Deavere Smith

The event, which is free and open to the public, is scheduled for noon Oct. 23 in the Clark Center auditorium.

"For many poor children, a lack of resources leads to their entanglement in the justice system early in life, limiting opportunity and education further and leading to the school-to-prison pipeline that Anna refers to in her most recent work," said Carrion, an expert on childhood stress and trauma.


Victor Carrion

In this latest work, *The Pipeline Project*, Deavere Smith examines what propels young people in underserved communities from school to incarceration and a lifelong interaction with the criminal justice system. She had called it "the moral dilemma of our time."

A recipient of the prestigious MacArthur Foundation Fellowship and the National Humanities Medal, Smith is credited with creating a new form of theater: solo documentaries in which she portrays multiple characters to illuminate complex social issues.

For more information about the event and to register to attend it, visit https://med.stanford.edu/psychiatry/community/TalkwithAnnaDeavereSmith.html. **ISM**