What I did at neuroscience camp this summer
By Ruth Schechter

The teenagers pushed aside their backpacks, adjusted their sweatshirts and looked up at the imposing man in a white coat at the front of the room. He scanned the room and started to pepper his young audience with questions: How many of you wake up tired? How many of you sleep too much in the morning? How many of you go to sleep after your parents? How many want more sleep?

For each question, every hand in the room shot up.

Serious, engaging and fun, the class, taught by Rafael Pelayo, MD, a pediatric sleep specialist with the Stanford Center for Sleep Sciences and Medicine and a clinical professor of psychiatry and behavioral sciences, is a required course for the Clinical Neuroscience Internship Experience (CNI-X), a summer-long immersion in the clinical and scientific research taking place in the Department of Psychiatry and Behavioral Sciences. More than 100 high school students from around the country attended the program this summer on the Stanford campus.

“With CNI-X, our faculty are taking the most direct route to the future — by introducing incredibly bright, motivated young people to the excitement and diversity of clinical neuroscience,” said program co-director Laura Roberts, MD, MA, professor of psychiatry and behavioral sciences and chief of the psychiatry service at Stanford Health Care. “We introduce novel science to the interns, and they drive the discussion forward and yet also move quickly to issues of social justice and humanity. My guess is that in several years we will see some of these students in our medical school classrooms.”

Students participated in sessions on topics ranging from the neuropsychology of HIV to molecular genetics, forensic psychiatry, eating disorders, boardroom virtual-reality therapeutics. Class formats ranged from introductory seminars to hands-on workshops and laboratory tours.

“The program is designed to build early interest in medicine and psychiatry, destigmatize mental illness and spread knowledge about mental health,” said CNI-X co-director Alan Louie, MD, professor of medicine and associate chair of psychiatry and director of education for the department. “Starting with high-school-age students also allows us to identify promising students interested in careers in mental health.”

Launched in 2015

CNI-X launched last summer with 20 teens heading into their senior year. They participated in a week and a half of sessions. Most were interested in medicine, psychology, law, bioengineering and other fields. Louie said he hoped that what they learned during the program would inform their future careers.

“There are not many programs like this being offered, and apparently there’s tremendous interest,” said Louie. “It benefits everyone when people are better informed about mental health.”

This year Louie and Roberts tweaked and expanded the CNI-X program, and 113 teens from throughout the Bay Area and as far away as Georgia, New York, Wyoming, Texas and Maryland, signed up. There were so many that they were broken into four groups, with classes repeated over two weeks to retain a small-group learning experience.

“I learned so much about neuroscience — I had no idea there were so many

Surgeries found to increase risk of chronic opioid use, study finds
By Tracie White

A study of health insurance claims showed that patients undergoing 11 of the most common types of surgery were at an increased risk of becoming chronic users of opioid painkillers, according to researchers at the School of Medicine.

But the slight overall increase in risk of 0.5 percent in no way suggests that patients should skip surgery over concern of becoming addicted to opioids, the study said. Instead, it’s a reminder that surgeons and physicians should closely monitor patients’ use of opioids after surgery — even patients with no history of using the pain-relieving drugs — and use alternate methods of pain control whenever possible.

The study was published today in JAMA Internal Medicine.

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First-ever restoration of vision achieved in mice, study says
By Bruce Goldman

Experiments conducted under the leadership of a School of Medicine investigator have succeeded, for the first time, in restoring multiple key aspects of vision in mammals.

In experiments in mice described in a study published online today in Nature Neuroscience, the scientists coaxed optic nerve cables, responsible for conveying visual information from the eye to the brain, into regenerating after they had been completely severed, and found that they could retrace their former routes and re-establish connections with the appropriate part of the brain. That unprecedented, if partial, restoration could pave the way to future work that might be used to restore sight to blind people.

The animals’ condition prior to the scientists’ efforts to regrow the eye-to-brain connections resembled glaucoma, the second-leading cause of blindness after cataracts. Cataracts can often be surgically removed, but there’s no cure for glaucoma, said the study’s senior author, Andrew Huberman, PhD, an associate professor of neurobiology, Jung Hwan Albert Lim, a graduate student at the University of California-San Diego, is the lead author.

Glaucoma, caused by excessive pressure on the optic nerve, affects nearly 70 million people worldwide. Vision loss due to

A “nutrition surveillance” app could help boost nutrition for children in some of the world’s poorest and most remote regions.
Cheek blood test can discriminate between bacterial, viral infections

By Jennie Dusheck

Researchers at the School of Medicine have made an important breakthrough in their ongoing efforts to develop a diagnostic test that can tell health-care providers not whether a patient has a bacterial infection but will benefit from antibiotics.

The study was published July 6 in Science Translational Medicine.

Antibiotics have saved millions of lives and created a world in which complex and lifesaving surgeries are possible. But the overuse of antibiotics threatens to create a global scourge of antibiotic-resistant pathogen. Because of this problem, public health ex- pertists regularly remind physicians to prescribe antibiotics only for bacterial infections. But too often there’s no easy way for doctors to tell whether a patient’s illness is bacterial or viral, or, sometimes, if there’s any infection at all.

“A lot of times you can’t really tell what kind of infec tion someone has,” said Timothy Sweeney, MD, PhD, an infectious disease expert at the National Insti tute for Immunity, T ransplantation and Infection and leader author of the paper. “If someone comes into the clinic, a bacterial or a viral infection often look exactly the same.”

“The idea to look for a diagnostic test came from our previous paper in Immunity last year,” said assistant professor of medicine Purvesh Khatri, PhD, the senior author. “In that paper, we found a common response by the human immune system to multiple viruses that is distinct from that for bacterial infections. We wondered whether we could exploit that difference to improve the diagnosis of bacterial or viral infections. But we needed a gene signature consisting of far fewer genes for the test to be cost-effective.”

Blood test

The team used publicly available patient gene expres sion data to pinpoint just seven human genes whose activity changes during an infection.

When pathogens infect the cells of the body, the in fection sets off a chain reaction involving the immune system that changes the activity, or expression, of hun dreds of genes. Gene expression is the process by which cells extract information from genes and render it in the form of either proteins or RNA. Cells have the capac ity to express more or less of each molecule, creating a pattern of gene expression that changes in response to external influences, including infections.

The seven-gene test is a vast improvement over earlier tests that look at the activity of hundreds of genes, the researchers said. Because so few genes are involved, the new test will be cheaper and faster, while remaining accurate, they said.

A study in Nepal co-authored by assistant professor of medicine Jason Andrews, MD, revealed that only 5 percent of patients who received antibiotics actually needed them, said Khatri. The Nepalese patients were treated because the drug was cheaper than trying to figure out if they actually needed it. “If we really want to make a difference,” Khatri said, “our test has to be more cost-effective than the drug itself.”

That’s an important breakpoint, he said, since it could allow health-care systems to use antibiotics appropri ately and save money at the same time.

The work is part of a global response to the need to reduce the use of antibiotics, driven in part by President Obama’s National Action Plan for Combating Anti biotic-Resistant Bacteria. Today, drug-resistant bacteria cause 2 million illnesses and 23,000 deaths each year in the United States alone, according to the Centers for Disease Control and Prevention. And, of the 154 million antibiotic prescriptions written in U.S. doctors’ offices and emergency departments each year, it’s esti mated that 1 in 3 are unnecessary. A 2014 review of anti microbial resistance reported that unless something is done to stop the evolution of antibiotic-resistant bacteria, such so-called superbugs could cost the world $100 trillion in gross-domestic-product losses by 2050.

Finally, besides promoting the evolution of drug resistant microbes, antibiotics increase the risk of side effects such as tendon rupture or kidney damage, and can damage gut and other microorganisms that are essen tial to overall health.

Hurdles ahead

The new gene-expression test for bacterial infec tion faces two hurdles before it can be made available to doctors in a few years. First, it must be thoroughly tested in a clinical setting. Until now, the data and test results for this ongoing work have all come from pre xisting, online digital data sets of gene expression from patients with different kinds of infections — not from current patients.

The study tested the seven-gene test on blood samples from 96 critically ill children and found that the test was accurate. But it needs to be further validated in larger numbers of patient blood samples, the researchers said.

Second, the test needs to be incorporated into a de vice that can give a result in an hour or less. The preliminary version of the blood test takes four to six hours to run and is too expensive for many patients who have sepsis, for example, the risk of death goes up by 6 to 8 percent for every hour that antibiotics are de layed, so it’s critically important to act quickly.

“Someone who is obviously severely ill and Sweene y, prescribing antibiotics would be the default. But often patients have early bacterial infections and doc tors don’t yet realize the patient is in danger. The gene expression test could remove doubt in a matter of min utes, allowing doctors to prescribe antibiotics sooner and save money.”

For that reason, Sweeney and Khatri are working with other researchers on a way to engineer the gene expression test to provide results in under an hour. The plan is to combine an 11-gene test they created a few months ago with the more recent seven-gene test. The 11-gene test reveals if the patient has an infection at all. If they do have an infection, the seven-gene test reveals if it is bacterial or viral. Both tests would be run at the same time.

Researchers envision the two tests as a decision tree. “When you put the new seven-gene set together with the 11-gene set, we can make a decision tree that really helps tell how to proceed,” said Sweeney. “First we ask, ‘Is an infection present?’ Because some people present with an inflammation, a fever, a high heart rate, but it’s not due to an infection. Then we ask, ‘If it is, what kind is it?’”

The 18-gene combination test would first be used in hospitals, Sweeney said. It’s possible, he said, that an even cheaper test just using the seven genes could be used in outpatient clinics.

The work is an example of Stanford Medicine’s focus on precision health — that is, being able to know how to think about a patient,” said Sweeney. “First we ask, ‘Is an infection present?’ Because some people present with an inflammation, a fever, a high heart rate, but it’s not due to an infection. Then we ask, ‘If it is, what kind is it?’”

The new institute “is clearly poised to make significant contributions to cancer research,” the science — occurring at Stanford University, its programs encompassing laboratory research, clinical care and community outreach and education.

The institute’s mission is to support and coordinate the wide range of cancer-related activities — in basic, trans lational, clinical and population-based science — occurring at Stanford University, Stanford Health Care and Lucile Packard Children’s Hospital Stanford, along with its partner institution, the Cancer Prevention Institute of Calif ornia. Its nearly 400 members include scientists and physicians from a wide range of disciplines, all collaborating to translate research advances into improved cancer treatments.

Building from a base of exceptional discovery research and patient care, the institute achieved its initial NCI “cancer center” designation in 2007, and in less than eight years has expanded its reach and its programs to earn the coveted “comprehensive” status.

“I’d like to thank the leaders of Dr. Beverly Mitchell, who has worked tirelessly since becoming the SCI director in 2008 to achieve this prestigious honor for Stan ford Medicine,” said Lloyd Minor, MD, provost and dean of the School of Medicine. “The combined effort of the institute’s multidisciplinary membership has shown how we are applying precision health to complex diseases and improving patient outcomes.

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The leadership and dedication of faculty from a variety of scientific disciplines, combined with extraordinary institutional and community support, has positioned the institute for continued growth and achievement in the future, according to the NCI officials who visited Stanford and reviewed its application for “comprehensive” status. The NCI’s site review summary noted that the institute “is clearly poised to make significant contributions to cancer research in the next five years.”

“This achievement is a testament to the talent and dedication of our members and staff working together every day to improve understanding of cancer, and to reduce its burden on patients and families.”

By Michael Claeys

The Stanford Cancer Institute has been designated a Comprehensive Can cer Center by the National Cancer Institute, a part of the National Institutes of Health and the world’s leading cancer research organization.

The designation is recognition of the institute’s robust and integrated programs encompassing laboratory research, clinical care and community outreach and education.

The institute’s mission is to support and coordinate the wide range of cancer-related activities — in basic, translational, clinical and population-based science — occurring at Stanford University, Stanford Health Care and Lucile Packard Children’s Hospital Stanford, along with its partner institution, the Cancer Prevention Institute of California. Its nearly 400 members include scientists and physicians from a wide range of disciplines, all collaborating to translate research advances into improved cancer treatments.

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group of rare blood cancers responds to new drug treatment

Maleness as well as malabsorption and weight loss.

About 90 percent of patients with advanced SM have a particular mutation known as D816V in the KIT protein, which encodes a protein called KIT that controls the growth of mast cells. KIT is a member of a class of proteins called tyrosine kinases that modulate the activity of many signaling pathways within a cell. Mutations that cause kinases to be overactive are responsible for many types of cancers, including advanced SM.

Drugs known as protein kinase inhibitors are often used to block the activity of the mutated kinases in order to slow or stop disease progression. However, the drug currently approved for treatment of advanced SM, a kinase inhibitor marketed by Novartis as ima- tinib, or Gleevec, is not active against the KIT protein with the D816V mutation—leaving most patients without an effective treatment.

Lack of options

Goltib, a hematologist, pioneered the testing of midostaurin for advanced SM after becoming frustrated with the lack of treatment options.

In 2002, as a pathology fellow at Stanford, he treated a patient who was severely ill with another type of blood cancer caused by a mutated tyrosine kinase. The patient initially responded to imatinib, but developed another mutation in his cancer cells within a few months that led to resistance to the drug. Although Goltib was unable to save that patient, the experience remained with him.

Shortly thereafter, researchers at Har- vard showed that the imatinib-resistant cancer that Goltib's patient developed was the same as a midostaurin-resistant cancer in a mouse model of the disease.

“I wondered if midostaurin could work against another type of blood cancer cell, he said. Goltib realized that ad- vanced SM might be a good disease in which to test the drug, given that the majority of patients suffering from it carry the mutated KIT D816V protein, which imatinib cannot.”

A dramatic response

“I didn’t have any patients with ad- vanced SM at the time, but another physician in my division was treating someone with mast cell leukemia, a highly fatal variant of sys- temic mastocytosis,” Goltib said. He convinced Novar- tis to allow him to give the patient midostaurin under the company’s compassion- ate-use program. “We saw a dramatic response. The pa- tient, who was near death, improved enough to be re- leased from the hospital, go home and begin cooking meals again.”

Although the patient’s disease was controlled for only a few months, the experience established the potential activity of midostaurin in ad- vanced SM. As a result, Goltib, along with colleagues from Stanford and else- where, initiated further trials of mid- ostaurn in the United States in 2005, as well as the current, international trial, which was launched in 2009.

Study findings

Sixty percent of patients in the cur- rent trial experienced complete or partial resolution of organ damage related to the disease. As a result, responding patients were less likely to need blood transfusions or platelet transfusions and they experi- enced improvements in liver function and fewer signs of malabsorption such as weight loss.

Patients treated with midostaurin who experienced improvement in organ function or a significant decrease in the percentage of abnormal mast cells in the bone marrow survived significantly longer than those who did not receive these responses. The median overall sur- vival of patients was 28.7 months.

The survival benefit among patients with a severe subtype of the disease called mal cell leukemia was particularly striking, according to Goltib. Although most peo- ple succumb to this form of the disease within six months of diagnosis, the me- dian overall survival of the patients treated with midostaurin was 9.4 months.

Of 39 patients whose spleen size was evaluated, nearly 80 percent saw a reduction in the en- largement that is a common marker of advanced SM that contributes to abdominal pain and decreased appetite.

The most frequent side effects of midostaurin were low-grade nausea, vomit- ing and diarrhea. The drugs were usually responsive to treatment with the drug and anti-nausea medicines. Patients other- wise reported a significant improvement in disease-related symptoms and quality of life. Midostaurin is currently available on a compassionate-use basis for pa- tients with advanced SM. Goltib said the investigators hope to evaluate its use in earlier-stage patients whose dis- ease is responsive only to standard clinical approaches or to prepare more advanced-stage patients for a bone mar- row transplant in an attempt to cure the disease.

“This is an evolution of a treatment that originated in 2002 with a patient with an entirely different disease,” Goltib said. “We hypothesized that midostaurin might work for patients with advanced SM, and the drug performed ul- timately the current international trial. Our study represents more than a decade of work and collaboration between aca- demia, the pharmaceutical industry, and the SM patient community, and we are very hopeful that it will lead to approval of a new treatment for this rare, devastat- ing disease.”

The Charles and Ann Johnson Foun- dation and Stanford’s Department of Medicine also supported the work.

By Krista Conger

Group of rare blood cancers responds to new drug treatment

By Erin Digitale
Latching chemotherapy drugs onto proteins that seek out tumors could provide an effective way of treating tumors in the brain or with limited blood supply.

more but will be cleared quickly from the bloodstream, possibly reducing its effectiveness.

Cochran is a member of Stanford Bio-X, the Child Health Research Institute, the Stanford Cancer Institute, Stanford CH-E-H and the Stanford Neurosciences Institute.

The work was supported by the National Institutes of Health, the Stanford Child Health Research Institute, Stanford Bio-X, Stanford CH-E-H, the National Science Foundation and the Anne T. and Robert M. Bass Endowed Fellowship in Pediatric Cancer and Malnutrition.

Stanford’s Department of Bioengineering also supported the work. The department is jointly operated by the School of Medicine and the School of Engineering. ISM
Physicians innovate to protect children’s health in Guatemala

By Nicole Feldman

Stanford pediatrician Paul Wise, MD, MPH, stooped below the black tarp roof of a cinderblock house in Guatemala to offer his condolences to a mother who had just lost her child.

“Doctor Pablo,” as he is known in the communities around San Lucas Toliman, talked softly as he relayed his sympathies to the mother, whose 9-year-old son had been a patient of his.

The boy’s genetic disorder would have been terminal anywhere, but thanks to Wise and local health promoters, the boy’s family had years with him instead of months. They found the doctor through the Guatemala Rural Child Health and Nutrition Program, a collaboration between Wise and the health promoters to eliminate death by malnutrition for children under 5.

While Wise spoke to the heartbroken mother, his Stanford research assistant, Alejandro Chavez, helped the promoters set up inside a local community center to measure the weight and height of local kids to determine their nutrition level.

Chavez and the promoters had worked together for months to create an app for tablets that will make it easier to find malnourished children.

The app they designed will decrease training time for new health promoters and expand the program. The goal is to distribute the app globally to help programs in other countries tackle malnutrition.

Children in crisis

As recently as 2005, about one of every 20 children in this rural area of Guatemala died before their fifth birthday. Almost half the deaths were associated with undernutrition.

“The death of any child is always a tragedy, but the death of any child from preventable, treatable causes is unjust,” said Wise, a Stanford Health Policy core faculty member and a professor of pediatrics at the School of Medicine.

Along with other faculty from the Freeman Spogli Institute for International Studies and the medical school, Wise created the Children in Crisis Initiative to improve the health of children in areas of the world plagued by conflict and political instability. The program brings together Stanford researchers and students across disciplines.

Nowhere are their efforts better illustrated than in the rural communities around San Lucas Toliman, in the central mountains of Guatemala.

The program’s effectiveness rests on a deep respect for the local communities merged with innovation by Stanford researchers.

“It’s absolutely essential to any program that the people in need be part of the solution,” said Wise, who is the Richard E. Behrman Professor of Child Health and Society. Unlike many non-governmental organizations and health programs, Wise believes the way to create a sustainable health system is for the locals to run it, so the health promoters manage the program’s day-to-day activities.

This leaves the Stanford team free to focus on innovation, such as the new app. They believe the technology could change child health programs around the world. Wise’s team has partnered with Medic Mobile, a nonprofit that creates open-source software for healthcare workers, which plans to distribute the app to other areas suffering from malnutrition.

The six Android tablets purchased by Children in Crisis are enough to monitor the program’s 1,500 kids through the app.

Role of nutrition

When done well, nutrition surveillance is very effective at decreasing child mortality in poor countries.

“Nutrition contributes enormously to health and well-being,” Wise said as he walked through Tierra Santa, a small community near San Lucas, making house calls. “So the focus of our work turned to improving young child nutrition. It’s not an easy thing to do in a place that’s extremely poor.”

Wise and his Stanford colleagues — medical student Victoria Bawel and associate professor of pediatrics Lisa Chamberlain, MD, MPH — made their rounds during their visit in March. Evidence of poverty was everywhere.

Here, clean tap water is a dream and even the sturdy homes often lack four walls or paned windows, though the children were nearly dressed in T-shirts or colorful “traje,” traditional Mayan clothing.

It’s hard to provide proper nutrition when most families can’t find enough work to buy adequate food. But a little help can make a big difference.

Bawel, a first-year medical student who plans a career improving health in areas of poverty, set up inside a local community center to measure the weight and height of local kids to determine their nutrition level.

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“Think about what it is to try to explain a graph to someone for the first time.”

It takes the health workers about three years to learn to graph and then interpret the results for intervention.

Wise said, “So we all get together and we say, ‘How do we make this easier to do?’”

The app was the answer.

‘Let’s create an app’

Enter Alejandro Chavez, a recent Stanford computer science graduate and Stanford Health Policy research assistant. He developed the app, which helps users collect health data on children and then determine whether they are malnourished and need an intervention.

“The major goal was to lower training requirements and make programs like this simpler to start and maintain,” said Chavez, who travels often to work in Guatemala, where he gets feedback from the health promoters.

Every two months, the promoters gather each community’s children to measure their weight and height. Children and their mothers sit patiently, waiting for their turn. The children enjoy a cup of Incaparina, and their mothers eagerly listen to the promoters’ tips for keeping their children healthy.

“It’s very important to me,” said Elsie Rosibel Samayoa, who brought her 2-year-old to be measured. “There are mothers who don’t understand the importance of monitoring their children’s weight, but I do.”

Since its implementation in 2009, the Stanford program has slashed nutrition-based mortality in the participating communities by about 80 percent and decreased severe malnutrition by more than 60 percent, saving hundreds of children.

However, nutrition surveillance and intervention isn’t easy. Tracking nutrition takes training and expertise, and when the local population rarely exceeds the tobacco of cornmeal, soy and essential nutrients. The sweet, mealy drink helps the program’s most malnourished children get back on track.

“The tablet automatically generates the information we need to know,” she said. “It becomes easier to confirm that a child is malnourished and needs supplements.”

Looking forward

With the app’s launch, it looks like training time for the promoters will be reduced from three years to less than six months. That means new communities can be incorporated into the program quickly, creating broader access to care. Meanwhile, many health programs around the world are waiting to see how well the Stanford app works in Guatemala.

Josh Nebbit, a Stanford alumnus and Medic Mobile CEO, said, “As more health programs recognize the importance of nutrition and implement community-based interventions, screening and surveillance tools will be critical. We must learn from Dr. Wise’s success.”

First-year medical student Victoria Bawel plans a career improving health in areas of poverty. Through the Children in Crisis Initiative, children like Fátima are getting the nutritional supplements they need.

Three researchers receive awards to study epilepsy Three Stanford researchers have received early-career awards from the American Epilepsy Society.

JULIET KNOWLES, MD, PhD, a chief resident in neurology, received an AES Research and Training Fellowship for Clinicians, which includes a $50,000 award to study the effect of recurrent seizures on myelin structure and plasticity.

RICHAN KYET, PhD, a postdoctoral scholar in comparative medicine, received an AES Postdoctoral Research Fellowship, which includes a $45,000 award to study the inhibitions of interneurons in a model of temporal lobe epilepsy.

CHRISTOPHER MAKARENOS, PhD, a postdoctoral scholar in nephrology and neurological sciences, received an AES/Wishes for Elliott Postdoctoral Research Fellowship, which includes a $45,000 award to use a 3-D human culture platform to test therapies for a type of epilepsy caused by a genetic mutation known as SCN8A.
Researchers at the School of Medicine have developed a possible treatment for lymphedema, the severe swelling of an arm or leg that can occur when the lymph system is blocked. Using scaffolding composed of specially patterned collagen nanofibers, the researchers coaxed lymph vessels to grow around lymph blockages. The technique was effective at treating lymphedema in pigs, the scientists report in a study published online June 7 in *Biomaterials.*

“We were able to take a cue from nature about what makes these vessels grow, but also think outside the box and use this nanoscale scaffolding to bridge the blockages,” said Ngan Huang, PhD, assistant professor of medicine and anesthesia at Stanford, and co-senior author of the study. “I think combining the two was really key.”

**A disease without a cure**

The lymphatic system is responsible for draining fluids from the body’s tissues and filtering this lymph fluid. When a lymphatic vessel is blocked, as in the case in lymphedema, fluid can get backed up into a limb, causing painful swelling.

In developed countries including the United States, lymphedema is most often seen in cancer patients whose lymph nodes are affected by their cancer. But infections and genetic conditions can also cause lymph blockages. In some cases, the underlying cause of the disease — such as an infection — can be treated. But for many, physical therapy, massage and compression garments are the best options to treat the disease and provide just temporary relief.

“Lymphedema is a chronic, debilitating disease with profound functional and psychosocial implications,” said Stanley Rockson, MD, professor of medicine and anesthesia at Stanford and the senior author of the study. “Current treatments are extremely limited. While transplantation of healthy lymph nodes represents a theoretically viable treatment option for cancer survivors and others, the success rate of these procedures has been disappointing.”

Rockson holds the the Allan and Tina Neill Professorship in Lymphatic Research and Medicine.

**Nanofibers**

Huang’s lab, in collaboration with the Union City, California-based company Fibralgin, has been studying how nanofibers of collagen can be used in medicine. Collagen, the most abundant protein in the human body, acts as a structural support in a variety of tissues. The scientists have designed nanofibers, dubbed “BioBridge,” that mimic collagen’s different arrangements.

The unique feature of the BioBridge scaffolds is that they’re not just noodles on a nanoscale,” said Huang. “They have patterning that’s physiologically relevant.” The scaffolds used in the recent work, she and pain treatment how collagen is naturally arranged in some connective tissues in the body. The threadlike fibers are each about a third of a millimeter wide.

Previously, Huang’s group has studied how the BioBridge scaffolds can be used to guide new blood vessels. As new cells that make up the vessels grow, they align themselves along the nanofibers. But lymph vessels, at a molecular level, are similar to blood vessels. So Huang and her collaborators wondered whether the fibers could also be used to coax and direct new lymph vessel growth as well.

**Bridging lymph blockages**

The scientists coated stretches of the BioBridge nanofibers with fragments of lymph nodes, since the molecules spur vessel growth, but also think outside the box and use this nanoscale scaffolding to bridge the blockages,” said Ngan Huang, PhD, assistant professor of medicine and anesthesia at Stanford, and co-senior author of the study. “I think combining the two was really key.”

**Moving to humans**

So far, the BioBridge approach has only been tested in pigs. But Fibralgin has a clinical trial planned in Latin America, and Rockson is putting together a Stanford-based study to test the treatment in breast cancer patients with lymphedema.

The lead author of the paper is Catara Hadiamktary, MD, of the Helios Clinic in Hildesheim Germany. The other senior author is John Cooke, MD, PhD, formerly a professor of medicine at Stanford who is now at the Houston Methodist Research Institute in Texas. Other Stanford co-authors are former postdoctoral scholar Magdalena Bazalova-Carter, PhD; postdoc-toral scholar Luquia Hou, PhD; research associate Yuka Matsuzuki; assistant professor of medicine Rajesh Dash, MD, PhD; and associate professor of medicine Philip Yang, MD, MD. They collaborated with researchers from the University of Victoria, Veterans Affairs Palo Alto Health Care System, Surpass Inc., IntrocOpt Medical Corp. and Fibralign Corp., which produces the aligned nanofibrillar collagen scaffolds used in this study. Had- diamktary and Cooke have received subscription rights in Fibralign.

The study was funded by the U.S. Army Medical Research & Materiel Command and the National Science Foundation.

Stanford’s Department of Cardiothoracic Surgery also supported the work.

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By Sarah C.P. Williams

**Study describes how nanofiber scaffolds could treat lymphedema**

Opioid continued from page 1

risk, as they were roughly five times more likely than a control group of nonsurgi-cal patients to end up using opioids chronically, followed by those undergoing gall bladder surgery, whose risk was three- and-a-half times greater than those in the control group.

“We also found an increased risk among women following cesarean sec-tion, which was somewhat concerning since it is a very common procedure,” adding that the risk was 28 percent higher than among the control group, Sun said.

Other factors that contributed to an increased risk of opioid use included being male, elderly, taking antidepressants or abusing drugs.

The opioid abuse epidemic

Since prescription painkillers became cheap and plentiful in the mid-1990s, drug overdose death rates in the United States have more than tripled, according to the Centers for Disease Control and Prevention. In the eight Americas, as many as every day from an opioid overdose, it approaches 100,000

Previous studies have shown increased risk of chronic opioid use post-surgery, but unlike past studies, Sun and colleagues set out to examine pa-tients who hadn’t received prescriptions for opioids at least one year prior to surgery. Among the opioid prescription histories examined in the study were hydrocodone, oxycodone and fentanyl — the drug responsible for the recent accidental overdose death of legendary music star Prince.

The researchers examined health claims from 643,941 privately insured patients between the ages of 18 and 64 who had not filled an opioid prescription in the year prior to surgery, then compared them with about 18 million nonsurgical patients, who also hadn’t received opioid prescriptions for at least a year prior to surgery.

For minor procedures known to be somewhat pain-free, such as a cataract surgery and laparoscopic appendectomy, all 11 types of surgery were associated with an increased risk of chronic opioid use, the study said.

Other pain-control measures

“The message isn’t that you shouldn’t have surgery,” Sun said.

“Rather, there are things that anesthesiologists can do to reduce the risk by finding other ways of controlling pain and using less opioids for when possible,” Sun said.

Opioid

**continued from page 1**

Sun said he and his colleagues in surg-ery and anesthesiology at Stanford try to use topical anesthetics when possible and reduce the need for opioids post-surgery.

He added that patients should also be encouraged to consider non-pharmacological pain management alternatives such as Tynol following surgery.

“Even when taken exactly as prescribed, opioids can carry significant risks and side ef-fects,” said study co-author Beth Darnall, PhD, clinical associate professor of an-esthesiology and author of the book *Less Pain, Fewer Pills: Avoid the Dangers of Prescription Opioids and Take Control over Chronic Pain.* “Ideally, opioids are avoided in treating chronic pain, and when treatment is required to ensure comprehensive care, including physical therapy, pain psychology and self-management strategies.”

As a pain psychologist and clinician-scientist, Darnall emphasizes alternate methods of pain management based on evidence-based techniques that can help calm the nervous system such as dia-phragmatic breathing, progressive mus-cle relaxation and mindful meditation.

She is studying the use of a pain psy-chology class at Stanford for women under-going surgery for breast cancer called “My Surgical Success” designed to help patients develop a personalized pain-managment plan to control the anxi-ety associated with anticipating surgical

“it turns out that a lot of chronic pain patients are re-ling surgery, and pre-surgical ‘catastrophizing’ is a major risk fac-tor for having a lot of pain,” Darnall said.

“We hope that by optimizing patients’ psychology — and giving them skills to calm their own nervous system — they will have less pain after surgery, need fewer opioids and recover quicker.”

Laurence Baker, PhD, professor of health research and policy, is also a co-au-thor of the paper.

The research was funded by a grant from the Foundation for Anesthesi Ed-ucation and Research and the Anesthesia Quality Institute.

Stanford’s Department of Anesthesiolog also supported the work.

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nerve cells connecting the eye to the brain, said Huberman. “When the cells’ axons are severed, it’s like pulling the vision plug right out of the outlet,” he added.

Axons in eye don’t regenerate

When axons in the brain and spinal cord of a normal adult human, the axons retained their own GPS systems,” said Huberman.

Restored vision incomplete

However, even mice whose behavior showed restored vision on some tests, including the one described above, failed other tests that probably required finer visual discrimination, said Huberman. He noted that the investigators could prove that axons from two specific retinal ganglion cell types that successfully extended back to and establish former contact with their target structures, as well as find ways to engage and assess most or all of the roughly 30 subtypes of retinal ganglion cells.

“‘We’re working on that now,’ Huberman said.

The study was conducted in collaboration with researchers at UCSF, Harvard University and Utah State University.

Funding for the study was provided by the National Eye Institute and the Glaucoma Research Foundation.

Stanford’s Department of Neurobiology also supported the work.

Retinal ganglion cells are the only nerve cells connecting the eye to the visual system. They are involved in not only what we typically think of as vision, but also circadian rhythms and mood.

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A new study by researchers at Stanford and Johns Hopkins universities puts to rest any lingering doubts about whether eating canned food increases exposure to a chemical linked to diabetes, cardiovascular disease and other health effects.

Researchers at Stanford and Johns Hopkins University have found that canned food contains higher levels of the compound bisphenol A, or BPA, compared to other food packaging.

The study, published online June 29 in Environmental Research, highlights the importance of reducing exposure to BPA, which is known to disrupt hormone function and has been linked to a variety of health problems, including diabetes, heart disease and cancer.

"This is a really important finding," said Jennifer Hartle, PhD, postdoctoral scholar at the Stanford Prevention Research Center at the School of Medicine.

Previous research has focused on analyzing levels of BPA in various types of food packaging and measuring BPA exposure within groups of fewer than 75 people. Evaluating BPA concentrations and BPA levels in urine of people who recently consumed canned food, the new analysis assessed thousands of people of various ages and geographic and socioeconomic backgrounds.

**Urinary BPA concentrations**

Hartle and her colleagues found that canned food was associated with higher urinary BPA concentrations, and the more canned food consumed, the higher the BPA. The result confirms canned food’s outsized influence on exposure to BPA. The researchers also found that particular kinds of canned food were associated with higher urinary BPA concentrations. The worst offenders (in descending order): canned soup, canned pasta, and canned vegetables and fruit.

A previous study led by Hartle found that children, who are especially susceptible to hormone disruption from BPA, are at risk from school meals that often contain canned foods and other packaging.

This upick in packaging is a result of schools’ efforts to streamline food preparation and meet federal nutrition standards while keeping costs low.

In 2015, as part of the Stanford Woods Institute for the Environment’s Rising Environmental Leaders Program, Hartle met with members of Congress who are working on regulating BPA in food packaging.

"It was hard to keep up with the other kids," he said. "I had little appetite and often couldn’t keep my food down. When he was a high school freshman, Arredondo’s dysphagia began to show its unpredictable side. He felt very weak, had little appetite and often couldn’t keep his food down.

After a series of tests, it was determined that the disease was affecting a very important muscle: his heart.

"With muscular dystrophy, you get a diastolic cardiomyopathy, a weakness of the heart muscle that is in direct parallel to the skeletal muscle," Rosenthal said.

Arredondo was referred to Children’s Hospital Oakland to Lucile Packard Children’s Hospital Stanford, the only pediatric heart transplant center in Northern California.

"It’s a referral his family is very grateful for," said Arredondo’s mother. "The doctors and nurses love their work. They worry not just about the patient, but the family, too. No matter your background they treat you good."

**Ventricular assist device program**

Mending poorly working hearts is nothing new for Packard Children’s, for 15 years, the program has been using medications and VADs to keep children’s hearts functioning while they await a transplant. "In 2010, we started using a VAD called the HeartMate II, which is totally implantable in the body and has wires on the outside that are easier to care for," nurse practitioner Aileen Lin, RN, said. "Most places weren’t trying this in kids yet. At the time it was a huge push in the field."

In Arredondo’s case, the pressure in his lungs was too high to allow for an immediate heart transplant, so the care team decided that a VAD would allow the lungs to recover and the pressure to fall so that he could undergo heart transplant later.

"In addition to providing medical care, a significant part of the VAD program is dedicated to educating patients and their families about the device, setting patients on a path to outpatient life."

California has listed BPA as a female reproductive toxicant, and the U.S. Food and Drug Administration has restricted its use in some products. However, the FDA is still working to “answer key questions and clarify uncertainties about BPA,” according to the agency’s website.

The FDA no longer allows BPA to be used in baby bottles, sippy cups and liquid infant formula canned linings, and many food and beverage companies are moving away from the use of BPA, Hartle said. “However, we do not know if synthetic BPA replacements are safe,” she said.

The researchers suggest that federal regulators expand testing beyond BPA to other chemicals used as BPA replacements in food packaging, none of which are included in national monitoring studies.

Co-authors of the study include Ana Navas-Acien of Johns Hopkins and Columbia universities, and Robert Law-rence of Johns Hopkins. 