A device allows scientists to noninvasively capture vast amounts of information about Parkinson's disease brain-firing patterns.

By Tracie White

A new study led by a School of Medicine researcher shows that decreased estrogen levels after menopause are largely unrelated to changes in cognitive ability and mood.

The study did find, however, a possible link between levels of another hormone — progesterone — and cognition among younger postmenopausal women.

Estrogen, the main sex hormone for women, plays a crucial role in a woman's reproductive cycle and overall cognition. Then, the researchers assessed them for depression and measured their levels of estradiol, estrone, progesterone and testosterone.

The study did find, however, a possible link between levels of another hormone — progesterone — and cognition among younger postmenopausal women.

Estrogen, the main sex hormone for women, plays a crucial role in a woman's reproductive cycle and overall health. After menopause, the depletion of ovarian follicles leads to a permanent reduction in a woman's levels of estradiol (the predominant estrogen before menopause), estrone (the predominant estrogen after) and progesterone, another hormone involved in the menstrual cycle. Several studies have examined the association between hormone concentrations and cognition, but results have been inconsistent.

Some researchers have speculated that the effect of estrogen on cognitive aging might differ depending on whether the hormones affect women differently based on their age and how much time has elapsed since they reached menopause.

In the current study, Henderson and his colleagues analyzed data on 643 healthy postmenopausal women who were part of the ongoing Early Versus Late Intervention Trial With Estradiol. The women, none of whom were on hormone therapy, ranged in age from 41 to 84. They were sorted into two categories: those who had gone into menopause less than six years previously, and those who had gone into menopause more than 10 years previously. The researchers gave the women a series of neuropsychological tests to gauge their memory and overall cognition. Then, the researchers assessed them for depression and measured their levels of estradiol, estrone, progesterone and testosterone.

They viewed the availability of hormone levels as an opportunity to test one aspect of the critical-window hypothesis — especially since...
Size, connectivity of brain region linked to anxiety level in kids

By Louis Bergeron

Prolonged stress and anxiety during childhood is a risk factor for developing anxiety disorders and depression later in life. Now, School of Medicine researchers have shown that by measuring the size and connectivity of a part of the brain associated with processing emotion — the amygdala — they can predict the degree of anxiety a young child is experiencing in daily life.

They found that the larger the amygdala and the stronger its connections with other parts of the brain involved in perception and regulation of emotion, the greater the amount of anxiety a child was experiencing.

The findings do not mean that a young child with an enlarged and highly connected amygdala will necessarily go on to develop an anxiety disorder, said Vinos Menon, PhD, professor of psychiatry and behavioral sciences and senior author of the study, which was published online Nov. 20 in Biological Psychiatry.

“We are not at a point where we can use these findings to predict the likelihood of a child developing mood and anxiety disorders as an adult, but it is an important step in the identification of young children at risk for clinical anxiety,” Menon said.

Participants in the study were 76 children ages 7 to 9. “For the cognitive emotional assessments to be reliable, 7 years old is about as young as a child can be,” said Menon, who is a member of the Child Health Research Institute at Stanford. “But the changes to the amygdala may have started earlier.”

The parents of the children in the study filled out the Childhood Behavior Checklist, a standard measure of a child’s general cognitive, social and emotional well-being. All the children in the study were typically developing, with no history of neurological or psychiatric disorders, and were not using medication. And none of the children in the study were experiencing so much anxiety in their daily lives that they could be considered clinically anxious.

The researchers compared the results of the assessment with the size and connectivity data of each child’s brain to draw their conclusions.

“Anxiety is a common emotional reaction to stress. It normally helps us cope with difficult situations. But sustained anxiety can lead to disabling conditions such as phobias, post-traumatic stress disorder and generalized anxiety disorder.”

Studies of adults suffering from anxiety disorders have shown that they possess enlarged, highly connected amygdalae. Studies of laboratory animals placed in an environment causing chronic stress have determined that the animals’ amygdalae grew additional synapses and that synaptic connectivity increased in response to the resulting persistent anxiety.

The amygdala is an evolutionarily primitive part of the brain located deep in the temporal lobe. It comprises several subregions that are involved in different aspects of perceiving, learning and regulating emotions.

The basolateral amygdala, a subregion important for processing emotion-related sensory information and communicating it to the neocortex — the evolutionarily newer part of the brain — is specifically affected in anxiety disorders such as phobia, post-traumatic stress disorder and generalized anxiety disorder.

“The amygdala is an evolutionarily primitive part of the brain located deep in the temporal lobe.”

Roughly one in 7,000 children are born each year with TSC, a genetic birth defect that is inherited in about one-third of cases. TSC causes nonmalignant tumors to grow in vital organs, including the brain, eyes, heart, kidney and lungs. The side effects can vary widely, but patients often have seizures, developmental delay, intellectual disability and autism.

Brenda Porter, MD, associate professor of neurology and neurological director of Packard Children’s TSC clinic. Prior to her arrival at Stanford in late 2012, Porter spent 15 years at Children’s Hospital of Philadelphia, where she served as the pediatric director of its TSC clinic.

“It’s a very challenging disease,” Porter said. “But you can really change outcomes in a child’s life if you get them early. We now have very specific therapies we can offer.”

Early diagnosis and intervention critical element in the care and quality of life for children. For these findings to provide robustness, the condition often causes seizures, which can cause brain damage if not treated early. Intensive drug therapies and medical technologies are effective in treating the disease and controlling seizures.

Molly Britt, 1, of Fremont, Calif., was diagnosed with TSC at 18 months old and was having seizures, improved quickly and dramatically under the care of Porter, who prescribed medication to control the seizures and one to treat infantile spasms.

“She lost about two months’ time. She would sit there and lay there when other kids were starting to play with toys,” said Molly’s mother, Brianna Britt. “As soon as the medications stopped the spasms, I got my baby back. It was immediate.”

Molly, who developed come to a near halt during the two months she was having seizures, improved quickly and dramatically under the care of Porter, who prescribed medication to control the seizures and one to treat infantile spasms.

“With a lot of genetic diseases I can’t offer the families much, but these kids you can,” Porter said. “We are beginning to get a handle on this.”

By Diana Walsh

The Tuberous Sclerosis Complex Clinic at Lucile Packard Children’s Hospital has earned a specialty designation from the Tuberous Sclerosis Alliance.

The designation acknowledges that the clinic has an outstanding team of specialists with expertise in treating children with the often complex and challenging effects of TSC and referred her to Porter and the clinic.

“Our goal is to find ways to better treat children in the future without creating more harm,” Menon said.

Molly’s amygdala, a subregion involved in processing emotion-related sensory information and communicating to the neocortex — the evolutionarily newer part of the brain — is specifically where Shaozheng Qin, PhD, a postdoctoral scholar and lead author of the study, detected the enlargement.

Qin used magnetic resonance imaging to measure the size of the various subregions of the amygdalae and functional MRI to measure the connectivity of these regions to other areas of the brain.

Menon said they were surprised that alterations to the structure and connectivity of the amygdala were so significant in the children with higher levels of anxiety, given both the young age of the children and the fact that their anxiety levels were too low to be considered clinical.

The study was funded by the National Institutes of Health, the Netherlands Organization for Scientific Research, Stanford’s Child Health Research Institute and the Lucile Packard Foundation for Children’s Health.

“The researchers identified four functional neurocortical systems that were affected.”

One of the systems deals with perception, another with attention and vigilance, a third with reward and motivation, and the fourth with the detection of salient emotional stimuli and regulation of emotional responses.

“The researchers identified four functional neurocortical systems that were affected.”

“In four of these core systems are impacted by childhood anxiety,” Qin said.

Menon said they were surprised that alterations to the structure and connectivity of the amygdala were so significant in the children with higher levels of anxiety, given both the young age of the children and the fact that their anxiety levels were too low to be considered clinical.

The study provides important new insights into the developmental origins of anxiety, he added. Understanding the influence of childhood anxiety on specific amygdala circuits, as identified in the study, could aid in the early identification and treatment of children at risk for anxiety disorders.

The study was funded by the National Institutes of Health, the Netherlands Organisation for Scientific Research, Stanford’s Child Health Research Institute and the Lucile Packard Foundation for Children’s Health. The Department of Psychiatry and Behavioral Sciences also supported the work.

Please also contact him to receive an e-mail version of Inside Stanford Medicine.

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu.
Common brain cell prunes neural circuits, study finds

By Bruce Goldman

School of Medicine neuroscientists have discovered a new role played by a common but mysterious class of brain cells. Their findings, published online Nov. 24 in the journal Nature, could help explain how astrocytes, because of their star-like shape, actively refine nerve-cell circuits by selectively eliminating synapses — contact points between neurons. The researchers discovered that astrocytes, convoy impulses to another — much as a sculptor chisels away excess bone to create an anatomical form. “This was an entirely unknown function of astrocytes,” said Ben Barres, MD, PhD, a postdoctoral scholar in Barres’ lab. More than one-third of all the cells in the human brain are astrocytes, but until quite recently, their role in the brain has remained obscure. The study was performed on brain tissue from mice, but it is likely to apply to people as well, Barres said. The discovery adds to a growing body of evidence that substantial remodeling is possible throughout the adult brain and that astrocytes are master sculptors of its constantly evolving synaptic architecture. The findings also raise the possibility that astrocytes’ participation in the wholesale destruction of synapses that erupts in neurodegenerative disorders, such as Alzheimer’s and Parkinson’s disease. “Astrocytes are in the driver’s seat when it comes to synaptic formation, function and elimination,” Barres said. In previous studies, he and his colleagues have shown that in old age or the wholesale destruction of synapses which in other cell types have been known as a “natural” part of the aging process. “The genes for two separate biochemical pathways were active in astrocytes. If that process is altered by phagocytosis, the trash-collection process by which specialized cells in the body engulf and dispose of waste materials, including bacteria; debris from wounds; and so forth. At the leading edge of the two pathways were two phagocytic receptors, MERKTK and MEGF10, which in other cell types have been shown to bind to particular proteins on targeted cells and mediate both engulfment, ingestion and digestion of the targets. The researchers first demonstrated that both MERKTK and MEGF10, along with their corresponding toll-like receptors, are present in living astrocytes in the mouse brain. In unpublished work, they have since confirmed this using human astrocytes.) Next, they showed that mouse astrocytes in a lab dish eagerly gobble up synapses and disabled LGN neurons in the retina severely impaired neuronal activity. Other tests showed that astrocytes’ ability to engorge themselves on synapses; knocking out both receptors in the retina completely eliminated the synapse-pruning activity by about 90 percent. To see if this happens in real life, Chung, Barres and their associates turned to a familiar experimental model: a brain area called the lateral geniculate nucleus, which is a key component of the brain’s vision-processing system. The LGN receives inputs from neurons just a couple of steps downstream from the photoreceptors in the retina. In early development, neurons to the LGN are innervated by inputs from both eyes. But at a critical point in development, a highly selective synaptic pruning process kicks in, resulting in each neuron in the LGN being contacted precisely by only a single eye. This pruning process in the LGN is dependent on the transmission of waves of spontaneous neuronal impulses originating in the retina. The Barres team also has previously shown that an intervention which had entered the critical period for synaptic pruning in the LGN, the investigators found that of other phagocytic cell types is known to do, it could reduce the aging brain’s capacity to adapt to new experiences, he said. “Maybe you need the astrocytes to gobble up old synapses to make room for new ones.” If so, it may be possible someday to design drugs to keep astrocytes’ phagocytic process from slowing, Barres added. Such drugs might prevent the accumulation in aging brains of past-their-prime synapses, which are vulnerable to degeneration in Alzheimer’s, Parkinson’s and other neurodegenerative disease characterized by massive synapse loss. Other Stanford co-authors were Stephen Smith, PhD, professor of molecular and cellular physiology; postdoctoral scholars Laura Clarke, PhD, and Gordon Wang, PhD; life science research assistant Chandrani Chakraborty; former Stanford undergraduate Julia Joung; and former graduate student Lynette Foo, PhD. The study was funded by the National Institute of Neurological Disorders and Stroke, the McKnight Foundation and the Damon Runyon Cancer Research Foundations. The Department of Neurobiology, also supported the work.

For prawns, disease-carrying snails are detectable escargot

By Rob Jordan

A freshwater prawn may not appear intimidating at first glance — it’s a petite bottom-feeder that can fit in the palm of most people’s hand. But for prawns, snails, however, it might as well be Jack the Ripper. In fact, the prawn, which dines heavily on snails that carry a debilitating infection called schistosomiasis, could provide an environmentally safe option for controlling the spread of the disease, while creating a source of marketable, protein-rich food. Researchers at Stanford and the Stanford Woods Institute’s Environmental Venture Projects seed grant program are exploring this possibility by studying the effects of rearing prawns with no snail host snail cells, or Senegal. The broad potential of this project is validation of microglia both as a driver of pruning in early development, when the connections — the synapses — are highly selective synapses in development, a critical point in the prawn’s life to continually restructure our nervous system in response to experientially induced brain activity. If astrocytes’ synaptic pruning slows with aging, as that of other phagocytic cell types is known to do, it could reduce the aging brain’s capacity to adapt to new experiences, he said. “Maybe you need the astrocytes to gobble up old synapses to make room for new ones.” If so, it may be possible someday to design drugs to keep astrocytes’ phagocytic process from slowing, Barres added. Such drugs might prevent the accumulation in aging brains of past-their-prime synapses, which are vulnerable to degeneration in Alzheimer’s, Parkinson’s and other neurodegenerative disease characterized by massive synapse loss. Other Stanford co-authors were Stephen Smith, PhD, professor of molecular and cellular physiology; postdoctoral scholars Laura Clarke, PhD, and Gordon Wang, PhD; life science research assistant Chandrani Chakraborty; former Stanford undergraduate Julia Joung; and former graduate student Lynette Foo, PhD. The study was funded by the National Institute of Neurological Disorders and Stroke, the McKnight Foundation and the Damon Runyon Cancer Research Foundations. The Department of Neurobiology, also supported the work.

Common brain cell prunes neural circuits, study finds

By Bruce Goldman

School of Medicine neuroscientists have discovered a new role played by a common but mysterious class of brain cells. Their findings, published online Nov. 24 in the journal Nature, could help explain how astrocytes, because of their star-like shape, actively refine nerve-cell circuits by selectively eliminating synapses — contact points between neurons. The researchers discovered that astrocytes, convoy impulses to another — much as a sculptor chisels away excess bone to create an anatomical form. “This was an entirely unknown function of astrocytes,” said Ben Barres, MD, PhD, a postdoctoral scholar in Barres’ lab. More than one-third of all the cells in the human brain are astrocytes, but until quite recently, their role in the brain has remained obscure. The study was performed on brain tissue from mice, but it is likely to apply to people as well, Barres said. The discovery adds to a growing body of evidence that substantial remodeling is possible throughout the adult brain and that astrocytes are master sculptors of its constantly evolving synaptic architecture. The findings also raise the possibility that astrocytes’ participation in the wholesale destruction of synapses that erupts in neurodegenerative disorders, such as Alzheimer’s and Parkinson’s disease. “Astrocytes are in the driver’s seat when it comes to synaptic formation, function and elimination,” Barres said. In previous studies, he and his colleagues have shown that in old age or the wholesale destruction of synapses which in other cell types have been known as a “natural” part of the aging process. “The genes for two separate biochemical pathways were active in astrocytes. If that process is altered by phagocytosis, the trash-collection process by which specialized cells in the body engulf and dispose of waste materials, including bacteria; debris from wounds; and so forth. At the leading edge of the two pathways were two phagocytic receptors, MERKTK and MEGF10, which in other cell types have been shown to bind to particular proteins on targeted cells and mediate both engulfment, ingestion and digestion of the targets. The researchers first demonstrated that both MERKTK and MEGF10, along with their corresponding toll-like receptors, are present in living astrocytes in the mouse brain. In unpublished work, they have since confirmed this using human astrocytes.) Next, they showed that mouse astrocytes in a lab dish eagerly gobble up synapses and disabled LGN neurons in the retina severely impaired neuronal activity. Other tests showed that astrocytes’ ability to engorge themselves on synapses; knocking out both receptors in the retina completely eliminated the synapse-pruning activity by about 90 percent. To see if this happens in real life, Chung, Barres and their associates turned to a familiar experimental model: a brain area called the lateral geniculate nucleus, which is a key component of the brain’s vision-processing system. The LGN receives inputs from neurons just a couple of steps downstream from the photoreceptors in the retina. In early development, neurons to the LGN are innervated by inputs from both eyes. But at a critical point in development, a highly selective synaptic pruning process kicks in, resulting in each neuron in the LGN being contacted precisely by only a single eye. This pruning process in the LGN is dependent on the transmission of waves of spontaneous neuronal impulses originating in the retina. The Barres team also has previously shown that an intervention which had entered the critical period for synaptic pruning in the LGN, the investigators found that...
with family. But they knew it was just a first step, not an overnight cure, and that their help would be key to their daughter’s success.

Lucile is one of about 17 other hearing-impaired toddlers from across Northern California — from San Luis to the Oregon border — to participate in a new “teletherapy” program called BabyTalk, a collaboration between the Department of Otolaryngology at the School of Medicine and the Jean Weingarten Peninsula Oral School for the Deaf in Redwood City. The program is designed to teach children under the age of 3 how to use their newly implanted cochlear devices to learn how to listen and speak, regardless of where they live or whether their families can pay for the therapy. Every Friday since her cochlear implants were activated, Lucile and her family members have been holding therapy sessions over an iPad from their home in Marin County to learn how to interpret the strange new sounds Lucile is hearing. And she’s been making progress.

“For getting an implant is the easy part,” said Nikolas Blevins, MD, the Larry and Sharon Malcolmson Professor and a cochlear implant surgeon. Blevins is part of the BabyTalk team, which also includes a Stanford audiologist and a social worker, in addition to the teachers like Nutini from the Weingarten School.

“The question is, what are you going to do with it once you’ve got it?” Blevins added. “Without follow-up education and therapy, it’s not a useful device. The patient will not develop speech.”

For Lucile’s mother and father, the decision to outfit their youngest daughter with a cochlear device came after hearing deterioration to the point that she was almost completely deaf in both ears. The couple first discovered that she had hearing loss shortly after her birth, and a gene test revealed that Lucile was born with a profound loss in one ear and mild loss in the other. Doctors couldn’t pinpoint a cause, but the hearing loss wasn’t severe enough then to warrant cochlear implants. Instead, she got hearing aids. But by 8 months, her hearing loss had progressed, and at 10 months her parents scheduled surgery.

But it can give a deaf person a useful representation of sounds and help him or her to understand speech. In order to do that, however, the implant-wearers need training.

This is where the BabyTalk program comes in. BabyTalk sets up virtual classrooms in the children’s homes in the monthly following implantation of the cochlear devices so that teachers can meet regularly to train families both on the mechanics of using the devices and on how to help their child.

The training is conducted over video calls on an iPad, which allows face-to-face communication between the teacher and the student and his or her family members. Participation in the program typically lasts until the child turns 3.

“My therapists are passionate about this,” said Kathleen Sussman, director of the Weingarten school, whose staff works with the children enrolled in BabyTalk. “They realize the isolation these families feel, and Lucile is quickly gaining ground. Her parents hope her language skills will eventually catch up to those of her 3-year-old sister, Siena, who is not hearing impaired.

“She’s giving us signs that she understands us, that she’s learning language,” Lizzie Ross said. “We think she’s going to do it. We do the exercises that we do during the week. We sing songs that elicited certain language. We work on the recognition of sight words. We have fun with her, which led to the notion, a lot of fun play stuff with her own toys — just what she would normally do on a daily basis.

“We knew it would be a hurdle. But for us, it’s been worth every minute of it. We’re just lucky that the opportunity was out there for her to hear and develop speech at a young age. It’s been a pretty amazing experience.”
School of Medicine investigators have successfully implanted and recorded data from a device that not only generates brain stimulation but also allows neuroscientists to noninvasively capture vast amounts of information about the patient’s brain-firing patterns to discern the “neural signatures” characterizing that patient’s symptoms, gain insights into the progression of the disease, and ultimately, it is hoped, develop algorithms that can predict symptoms in advance. “With this ‘brain radio’, we can study the brain’s signal patterns at the same time that we’re observing a patient’s precise movements — whether intended or not — with the goal of understanding just which brain rhythms correspond to which specific patterns of movement.”

In the past, brain-activity data has been downloaded from people with Parkinson’s disease while they’re lying on the operating table, but such data reflected only brain activity while patients were at rest. On Oct. 30, a surgical team led by Jasmin Hendersen, assistant professor of neurosurgery at the medical school who treats patients at Stanford Hospital & Clinics, implanted a device called a neurostimulator under the collar of Parkinson’s patient Frank Donobedian. Donobedian and hooked it up to two fine, insulated electrical filaments, or leads, in Donobedian’s brain. In a surgical procedure a week earlier, the team had threaded the leads into the patient’s brain so that they impinged on twin structures, one on each side of the brain, called the subthalamic nucleus. The subthalamic nucleus has been tied to symptoms of Parkinson’s disease such as tremor, difficulty in initiating movement and a tendency to ‘freeze’ in place mid-motion.

The neurostimulator is analogous to a pacemaker in cardiology; it transmits signals — at frequencies, amplitudes and durations programmed by a neurologist — to the leads, which then send currents of electricity that counteract the aberrant brain signals producing the physical symptoms. “Over time, the neurostimulator’s impulse-transmission pattern is optimized via a trial-and-error process involving extensive patient-neurologist interaction.”

When Donobedian and Henderson performed the same procedure on Oct. 30 unique wasn’t the surgery itself but rather the nature of the neurostimulator, the first of its type ever implanted in the United States. This new neurostimulator not only transmits signals to the subthalamic nucleus but can sense and store the subthalamic nucleus’ electrical output. (In August, a Parkinson’s patient in Germany received such a next-generation DBS device.) Both the currently marketed and new DBS devices are manufactured by Medtronic Inc.

There is no evidence that DBS slows the progression of the underlying brain pathology of Parkinson’s disease, although it typically lessens patients lowering their medication dosages, which can alleviate side effects. (More than 100,000 first-generation DBS devices have been implanted worldwide — more than 600 of them by Henderson, in fact — with substantial overall success in providing relief from not only the symptoms of Parkinson’s disease, but also those of epilepsy, chronic pain and more.)

On Nov. 20, Donobedian, a 72-year-old retired schoolteacher from Seaside, Cali., came to Stanford for an appointment with Bronte-Stewart, who regularly sees patients a few weeks after their DBS devices have been implanted. Donobedian had deliberately skipped his routine Parkinson’s medications so Bronte-Stewart, who is also the John E. Cahill Family Professor, could more easily observe his symptoms and watch how they responded to different DBS frequencies and intensities. But in addition, the doctor and patient were embarking on the first of a series of groundbreaking sessions during which Bronte-Stewart would download data from Donobedian’s implanted device via a telemetric receiver and attempt to correlate his symptoms with his brain activity.

She hopes to identify the neural signatures of not only the resting state, but also of voluntary movement and task performance, as well as of the tremor itself, and to see directly how these neural signatures change in response to manipulations of DBS frequency and voltage output.

“For the past decade, we’ve been measuring our patients’ motor control by observing their tremor and voluntary movement, tweaking the amplitude or frequency of their DBS device, seeing whether that seems to improve their symptoms, and telling them to come back in three months and report on how things have improved,” she said. “Now, we can access our patient’s brain signals by waving a telemetric ‘wand’ over his chest while he sits, walks, speaks or performs a task. We can even retrieve brain data the device picked up earlier — say when the patient was at home sleeping. And we can begin to figure out which brain rhythms correspond to his movement-disorder symptoms.”

This second-generation version of an existing deep-brain-stimulation device. AnaVelasquez, far left, and Carlos Rodriguez, second from left, help Bronte-Stewart test and calibrate the device.

Section of Welch Road will close to traffic beginning today

Beginning today, a section of Welch Road between South Pasteur Drive and Campus Drive will be closed to traffic for approximately four months. This closure is due to the Stanford Energy System Innovations project’s ongoing utility construction to serve the Stanford campus and the hospitals. Access to the Stock Farm garage and parking lots will be available via Stock Farm Road; Alternative pedestrian pathways will be constructed to ensure access around the medical center during construction.

Access to the Lucas Center and School of Medicine will be maintained.

The Marguerite Shuttle Line MC-D will continue regular service between Stock Farm parking and the hospital Fountain Entrance. For more information on the Marguerite shuttle and available routes, please visit: http://transportation.stanford.edu/marguerite/MargueriteSched.html

Additional partial closures of Quarry Extension and Ruth Way will also take effect today to accommodate utility work. These closures are scheduled to remain in place until Feb. 28. Access to the Emergency Department will remain open at all times.

For more information about the partial road closures, please visit sesi.stanford.edu or sesiprojects@lists.stanford.edu.

Prawn continued from page 3

can countries began building dams in the 1980s. Hsieh, De Leo and Sokolow speculate this is due, at least in part, to the decline in prawn restocking, among other influencing factors. But their work continues to prove successful, they envision introducing prawns in other areas of Africa. If the prawns prove to be effective disease fighters, Hsieh, De Leo and Sokolow envision them as natural tools in optimizing drug treatment for schistosomiasis by minimizing environmental exposure that can lead to reinfection. "The ships turn to ecology for a solution where drug treatment, alone, has failed to deliver results in terms of sustainable disease reductions," Sokolow said.

The sustainability of prawns as a solution is a focus of research and rest on their tastiness. Local communities could be inspired to maintain prawn populations in order to market the delicacy domestically and, perhaps, internationally. rob jordain is a writer for the Stanford Woods Institute for the Environment.
“When a key piece of the puzzle is shown to be wrong, it’s of extreme importance to scientists.”

The new study was conducted to better understand how a part of the hearing process works by studying the machinery of the inner ear that converts sound waves into electrical signals.

"To me this is really a landmark study," said Ulrich Mueller, PhD, professor and chair of molecular and cellular neuroscience at the Scripps Research Institute in La Jolla, who was not involved with the study. "It really shifts our understanding. The hearing field has such precise models — models that everyone uses. When one of the models rumbles, it's monumental."

Humans are born with 30,000 cochlear and vestibular hair cells per ear. When a significant number of these cells are lost or damaged, hearing or balance disorders occur. Hair cell loss occurs for multiple reasons, including aging and damage to the ear from loud sounds. Damage or impairment to the process of adaptation may lead to the further loss of hair cells and, therefore, hearing. Unlike many other species, including birds, humans and other mammals are unable to spontaneously regenerate these hearing cells.

“As the U.S. population has aged and noise pollution has grown more severe, health experts now estimate that one in three adults over the age of 65 has developed at least some degree of hearing disability because of the destruction of these limited number of hair cells. ‘It’s by understanding just how the inner machinery of the ear works that scientists hope to eventually find ways to fix the parts that break,’ Ricci said. ‘So when a key piece of the puzzle is shown to be wrong, it’s of extreme importance to scientists working to cure hearing loss.’

Stanford postdoctoral scholar Thomas Effertz, PhD, is also an author of the study.

The research was funded by the National Institutes of Health and the German Academic Exchange Service.

The Department of Otolaryngology-Head & Neck Surgery also supported the study, which is part of the Stanford Initiative to Cure Hearing Loss (http://hearingloss.cure.stanford.edu), a large-scale research effort to find biological cures for deafness.

Visiting Russian doctors train on use of simulations at CAPE

A Russian delegation recently visited the Center for Advanced Pediatric and Perinatal Education, known as CAPE, at Stanford to learn how it uses simulations to prepare health-care professionals for managing emergencies in the delivery room.

The delegation comprised five obstetricians, two neonatologists and a neonatology student from the Pirogov Russian National Research Medical University; one anesthesiologist from the N.V. Skilosvoskogo Research Institute of Emergency Medicine; and two medical education specialists from Arirbis, a continuing medical education center in Moscow.

The group attended the four-day simulation instructor program at CAPE.

“We learned a new way to teach, which we might not only use in simulation but also in our faculty practice,” said Marina Osanova, general director of Arirbis.

CAPE, which is affiliated with Lucile Packard Children’s Hospital and the School of Medicine, replicates a modern American hospital environment. It uses life-like mannequins, complete with beating hearts, pumping lungs and auditory cues (provided by staff members working in a separate control room) to generate a high degree of realism during the simulated clinical crises.

The Russians took part in simulated birthing scenarios in which problems developed for the mother or her newborn, or both.

Program instructors were physicians and simulation specialists from CAPE, led by Packard Children’s neonatologist Louis Halamek, MD, professor of neonatal and developmental medicine and the center’s founding director.

“With simulation-based training, it’s all about interactivity of the trainees,” said CAPE business manager Barbara Beebe.

Effective interacting with nonphysician members of the health-care team was one of the biggest challenges for the Russian physicians. Because they work in a hospital culture that is more hierarchical than that of the United States, skills such as teamwork and communication receive less emphasis.

“In the U.S., we’ve been evolving toward a multidisciplinary team model, with doctors, nurses and other team members functioning as equals as they’re dealing with a crisis,” Halamek said. “Exposure to the American style of professional interaction was an important part of the Russian doctors’ experience here.”

This was not lost on the team from Russia. “We need to change our culture to promote better communication between physicians and nurses,” said Marina Degtyareva, MD, head of neonatology at Pirogov.

After every simulation, instructors debriefed the trainees, asking questions about how the scenario unfolded — what worked, what didn’t and what could be changed for the better.

Not all the Russians were fluent in English, so CAPE employed several local health-care professionals who were fluent in Russian: A Stanford-trained neonatologist, a local nurse midwife and a Stanford emergency-medicine nurse. They participated in the scenarios, facilitating communication during the simulated clinical scenarios and the debriefings. In addition, a professional interpreter provided instantaneous translation during the entire program.

Members of the delegation plan to use what they learned at CAPE to promote the use of simulation to train health-care professionals in Russia. “Well-run simulation-based training reflects a systemic understanding of how many different parts work together to improve patient care,” Degtyareva said.

As one of the foremost simulation-based training and research centers in the fetal, neonatal, pediatric and obstetric sciences, CAPE has received increasing interest in its programs, Halamek said.

“We have our own unique approach, which is modeled after that taken by many other high-risk industries,” said Halamek, who was inspired to create CAPE by the rigorous training required of NASA astronauts.

“Those international programs provide an opportunity to disseminate our approach to hands-on, simulation-based training to health-care professionals around the world and also to gain insights and learn new strategies from them,” said Halamek.

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This was not lost on the team from Russia. “We need to change our culture to promote better communication between physicians and nurses,” said Marina Degtyareva, MD, head of neonatology at Pirogov.

After every simulation, instructors debriefed the trainees, asking questions about how the scenario unfolded — what worked, what didn’t and what could be changed for the better.

Not all the Russians were fluent in English, so CAPE employed several local health-care professionals who were fluent in Russian: A Stanford-trained neonatologist, a local nurse midwife and a Stanford emergency-medicine nurse. They participated in the scenarios, facilitating communication during the simulated clinical scenarios and the debriefings. In addition, a professional interpreter provided instantaneous translation during the entire program.

Members of the delegation plan to use what they learned at CAPE to promote the use of simulation to train health-care professionals in Russia. “Well-run simulation-based training reflects a systemic understanding of how many different parts work together to improve patient care,” Degtyareva said.

As one of the foremost simulation-based training and research centers in the fetal, neonatal, pediatric and obstetric sciences, CAPE has received increasing interest in its programs, Halamek said.

“We have our own unique approach, which is modeled after that taken by many other high-risk industries,” said Halamek, who was inspired to create CAPE by the rigorous training required of NASA astronauts.

“Those international programs provide an opportunity to disseminate our approach to hands-on, simulation-based training to health-care professionals around the world and also to gain insights and learn new strategies from them,” said Halamek.
Virus may act as signal of weak immune system, according to scientists

By Tom Abate

More than 260,000 Americans are alive today thanks to transplant operations that have replaced their failing kidneys, hearts, lungs or livers with healthy organs do-nated by volunteers or accident victims. But treatment doesn’t end with surgery. Transplant recipients follow strict drug regimens designed to sup-press their immune systems just enough to prevent re-jection of the donated organ, but not so much as to leave them prone to infection.

Until now, maintaining this delicate balance has been something of a medical guessing game. But in a study published Nov. 21 in Cell, Stanford scientists report the discovery of what may be a barometer of immune sys-tem strength: a little-known virus that proliferates as the medications suppress the immune system.

The work was led by senior author Stephen Quake, PhD, the Lee Otteson Pro-fessor in the School of Engineering and professor of bioengineering and of applied physics.

Quake and a team of collaborators, including transplant specialists from the School of Medicine, isolated specific DNA fragments from the blood of 96 heart and lung transplant patients for the study.

These fragments came from the blood plasma, red and white cells were extracted, leaving behind proteins and free-floating DNA. The free-floating DNA was from dead cells — the biological version of flotsam and jetsam.

Quake is a pioneer in genomics and was one of the first scientists to use genome sequencing to identify and quantify this free-floating DNA for diagnostic purposes.

One notable application of this technique relates to pregnancy. By studying fragments of cell-free DNA from maternal plasma, Quake has developed tests that can ascertain whether a woman is carrying a fetus with an extra copy of chromosome 21, which causes Down’s syndrome. Additionally, cell-free DNA analysis of frag-ments from cancerous cells has been used to assess dis-ease progression.

Cell-free DNA provides an amazing window into human health, and the applications are multiplying well beyond its traditional areas of cancer and prenatal diag-nostics,” Quake said.

In the new study, Quake’s team used these techniques to study the immune systems of transplant patients. They knew that these patients would begin taking powerful immunosuppressant drugs immediately after sur-gery. They reasoned that these drugs would affect the microbiome, which is the sum total of all the bacteria, viruses and fungi that inhabit the body.

Although we may not notice these microorganisms unless they cause illness, they help us digest food, excrete waste, make our feet itch or just float around with no discernable effect. In fact, the nonhuman cells that make up the microbiome “outnumber human cells in our bodies at least 10 to 1 one,” said lead author Iwijn De Vlaminck, PhD, a postdoctoral scholar in Quake’s lab.

The goal of the study was, essentially, to use cell-free DNA analysis to perform a census of the mi-crobiome. The hypothesis was that a systematic analy-sis of the nature and number of these microorganisms would reveal something about the interplay between the immune system and these nonhuman guests.

Initially we didn’t expect to find anything, we didn’t know how the immunosuppressive medications would affect the numbers,” De Vlaminck said.

The scientists collected plasma samples from each patient. From each sample, they extracted fragments of nonhuman DNA. They used genetic sequencing techniques to compare the fragments to a library of genetic sequences previously compiled by scientists all around the world. In this way, the team created a snapshot of the various types of bacteria, viruses and fungi in each patient’s microbiome.

The scientists wanted to understand how the microbiome in each patient re-sponded to immunosuppressant medica-tions over time. So they took these plasma samples from each patient about seven times over a two-year period. Each time, they ran a genomic analysis of nonhuman DNA fragments in the plasma. This al-lowed the scientists to sample the composi-tion of each patient’s microbiome, in a statistical version of time-lapse photography.

The scientists also studied the entire data set of 656 snapshots of all 96 patients as they looked for differ-ences or similarities among patients.

Through this process, one stunning and unmistak-able finding in the microbiome category was known as the anellovirus exploded into prominence as the immunosuppressive drugs kicked in, going from very low levels immediately after surgery to dominating the microbiome over time.

“IT looks like the anellovirus takes advantage of the lack of immune system surveillance,” De Vlaminck said. Why or how is unknown. In fact, scientists know very little about the anellovirus. Since it was first iden-tified as the cause of any disease. Since it was first iden-tified as the cause of any disease.

“nearly all scientists have looked for its genetic finger-prints. But this common bug has not yet been identi-fied as the cause of any disease.

But the Stanford team did find previous studies involving patients infected with HIV in which levels of anellovirus rose as those unfortunate patients progressed toward AIDS and the full-blown collapse of their im-mune systems. These two data points — the increased prevalence of anellovirus mentioned above and the large number of transplan-t patients in the Stanford study, and the prior findings from AIDS research — provided strong hints that rising lev-els of anellovirus are a sign of an immune system in dis-angle and found out that the answer was not true. Twenty patients suffered moderate or severe episodes of organ rejection during the two years of the experiment. In these 20 patients, levels of anellovirus were sig-nificantly lower … at almost every point in time,” the au-thors write, adding that “the lower viral load observed for rejecting patients is thus indicative of a higher level of immunocompetence.”

Put another way, lower levels of anellovirus suggest a stronger immune system and an elevated risk of organ rejection, while higher levels signal a weaker immune system with a corresponding shift in risk toward vulnerability to infection.

“These findings suggest an effective tool to individu-alize the monitoring and, ultimately, the treatment of rejection. Low levels of anellovirus may allow for the safely lower the doses of immunosuppressive drugs pa-tients receive, thereby avoiding devastating side effects,” the authors write.

This research was supported by the National Insti-tutes of Health and the Howard Hughes Medical Institute.

Steven Quake was the co-senior author of the paper. Another Stanford co-authors were Calvin Strehl and Britka Kohli, clinical research coordinators; research nurse Helen Luikart; Norma Neff, PhD, genomics core director; technician Jennifer Okaman; former postdoc teacher Thomas Snyder, PhD; and David Comstock, MD, the Anne T. and Robert M. Bass Professor in Pedi-atric Pulmonary Medicine; Mark Nicolls, MD, associ-ate professor of medicine; David Well, MD, professor of medicine; and Daniel Bernstein, MD, professor of pediatric cardiology.

The Department of Bioengineering, which is jointly operated by the School of Engineering and School of Medicine, also supported the work.

Tom Abate is the associate director of communications for the School of Engineering.

Estrogen continued from page 1

we had two fairly large samples of women,” Henderson said.

Henderson said he and his col-leagues had hypothesized that lower levels of estradiol would be positively associated with memory performance in women who had experienced menopause more than a year prior. In an examination of multiple sex hor-mones in the same population, however, neither group needed to safely lower the doses of immunosuppressive drugs pa-tients receive, thereby avoiding devastating side effects.”

This research was supported by the National Insti-tutes of Health and the Robert E. and May R. Wright Foundation. The Department of Neurology and Neurological Sciences also supported the work.

By Victor Henderson

Other hormone levels were unrelated to verbal memory, executive function or overall cognition, or to mood, the researchers found, with one exception: Higher progesterone lev-els in younger postmenopausal women were positively associated with better memory and global cognition.

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Henderson’s collaborators are at the Uni-verse Medical Center, including se-nior author Wendy Mack, PhD, professor of biostatistics.

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Workshop helps oncology physicians improve communication skills

By Michael Claeys

One of hardest parts of a doctor’s job — delivering bad news to patients and their loved ones — is rarely addressed in medical school.

Now, a new workshop offers Stanford medical trainees communication instruction to help them handle challenging oncology and end-of-life discussions with clarity and compassion. They even get to practice difficult conversations with real people: trained actors who portray cancer patients and their family members, and provide a range of real-world responses to the news.

The School of Medicine launched the Karen K. Anderson Lecture Series in 2011. Faculty and trainees can attend a two-and-a-half-day program called “Challenging Conversations in Oncology.” It was designed to help cancer clinicians of all specialties learn to communicate more effectively with their patients.

“Facilitators with expertise in both cancer and communication led a series of talks and small group exercises in which the trainees interacted with the simulated patients and families. The sessions served to enhance participants’ awareness of ways to build a rapport and establish trust with patients and families, and develop individualized strategies for delivering the difficult news to them.”

“The importance of these programs in physician-patient communications cannot be overemphasized,” said Jonathan Berek, MD, director of the Stanford Women’s Cancer Center and professor and chair of obstetrics and gynecology, who organized the first workshop. “The skills required to deal with complex interactions with patients facing life-threatening illnesses can be taught and refined, and this workshop was designed to substantially enhance the finesse with which our oncology fellows-in-training deal with these complicated issues in a compassionate and positive manner.”

Twelve oncology fellows, representing medical, gynecologic, pediatric, radiation and surgical oncology, as well as palliative care medicine, participated in the intensives. The participants’ goal was to improve their ability to conduct serious conversations with cancer patients and families about difficult news related to the disease, end-of-life care and referral to hospice. Participants learned coping and adaptive communication strategies to tailor information to patients’ needs, as well as counseling strategies to become more comfortable with emotions in patients and in themselves. Instruction on cultural awareness and sensitivity was also included, as were strategies for preserving their emotional well-being in the face of cancer-patient deaths.

“I learned that it is important to stop and let patients express their feelings. It helps in fostering a more meaningful relationship and may aid in their care,” one participant wrote in a post-workshop evaluation.

“I will take time to let them cry or be silent,” another wrote.

Berek, who is also the Laurie Kraus Lacob Professor, and the other faculty instructors hope the lessons learned are incorporated in practice and will help improve the experience of each cancer patient with whom the participants interact in the future.

Other faculty who taught at the workshop included DavidSpeigel, MD, the Jack, Lulu, and Sam Willson Professor in Medicine and professor and associate chair of the Department of Radiation Oncology (Palliative Care) Program and clinical assistant professor of medicine; and Lidia Schapira, MD, an associate professor of medicine at Harvard Medical School.

The course was supported by the Karen K. Anderegg and William D. Rutherford Fund for Cancer End-of-Life Care, the Stanford Women’s Cancer Center, the Stanford Cancer Institute and the Stanford Hospital and Clinic.

Berek plans to repeat the oncology workshop each year and is exploring other types of sessions in patient-communication training for doctors, including for those who work in intensive care units. Announcements about future workshops for improving doctor-patient communication skills will be forthcoming, Berek said.

Michael Claeys is senior communications manager at the Stanford Cancer Institute.

$12.5 million for studies of environmental factors in child, fetal health

Gary Shaw, DPh, professor and associate chair of pediatrics at Stanford, has received three research grants totaling approximately $12.5 million.

The largest grant is for about $7.5 million from the National Institute of Environmental Health Sciences and the U.S. Environmental Protection Agency. The grant establishes the Berkeley/Stanford Center for Environmental Health and will fund four studies on which Shaw will collaborate with investigators from Stanford, UC-Berkeley and Cal State Fresno. The studies are “Exposures to Air Pollutants, Modifying Genes and Risk of Birth Defects and Preterm Birth,” “Mechanisms of Polycyclic Aromatic Hydrocarbon-Linked Immunopathogenesis in Atopy” (led by Kari Nadeau, MD, PhD, associate professor of pediatrics); “Obesity/Glucose Dysregulation,” and “Trans Exposures in Uterus.”

Shaw and Suzan Carmichael, PhD, associate professor of pediatrics, are co-principal investigators on a grant of about $3.5 million from the Centers for Disease Control to study causes and preventive of birth defects. Shaw also received about $1.5 million from the Eunice Kennedy Shriver National Institute of Child Health and Human Development to support a population-based epidemiologic study on a range of pesticide compounds for their potential influence on preterm birth.

William Cregers memorial to be Dec. 20

A memorial for William Cregers, MD, professor emeritus of medicine, is scheduled for 4 to 8 p.m., Dec. 20 at the Stanford Faculty Club. All are welcome to attend.

Cregers was 95. He was 91.

In lieu of flowers, the family prefers donations to Project Hope, KDFC Radio or the Stanford Cancer Institute.

Questions about the event may be directed to Phil Cregers at comcast.net.