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THE NEW DEAN

Christian Larsen has been a college student, medical student, clinician, and faculty member, all at Emory. Now he takes on the deanship of the medical school.

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(Not the) Dean's Message

In our backyard, a home-grown talent

This space usually is reserved for a few words from the dean, but as this issue marks a transition in leadership of the School of Medicine, please allow me to borrow it to introduce our new dean, Dr. Christian Larsen. I take considerable pride in the fact that Dr. Larsen (Chris) is an alumnus of Emory. He graduated from Emory College in 1980 and from the medical school in 1984, and he completed postgraduate training at Emory, and also at Stanford and Oxford, in surgery and transplantation.

I am proud too that Chris decided to pursue his career at Emory. He joined the faculty in 1991 and became founding director of the Emory Transplant Center in 2001 and chair of surgery in 2009. During his time here, he has earned great respect not just for remarkable accomplishments (see article on page 12) but also for his collaborative spirit and ability to lead by example.

Because he has seen Emory from so many perspectives—as student, resident, teacher, researcher, surgeon, and administrator—no one knows more about the school's strengths, challenges, and potential in all its missions than Chris Larsen does. Nor is anyone better suited to help shape the school's culture to meet present and future needs.

At Emory and at other academic medical centers throughout the country, we are facing unprecedented change that will significantly affect all of our missions. We are facing financial constraints and changes in national policy that will impact the new discoveries needed to improve health as well as training for the next generation of health professionals. For our medical school to thrive, we need a visionary leader who can approach this new environment with creativity and in an integrated fashion, one who has the courage to do more with less by focusing on areas where we can have the most impact, one who can bring together teams of professionals to solve these big challenges.

That person is Chris Larsen, our new dean of medicine, vice president of health center integration in the Woodruff Health Sciences Center, and chair of the board of the Emory Clinic. With his passion and dedication to service, he epitomizes the principles of our benefactor Mr. Robert W. Woodruff. He is the right leader for this time.

S. Wright Caughman
Executive Vice President for Health Affairs
CEO, Woodruff Health Sciences Center
Chairman, Emory Healthcare

In Brief

$8.3M grant for Autism Center of Excellence links Atlanta partners

A new Autism Center of Excellence (ACE), funded by an $8.3 million grant from the National Institutes of Health (NIH), will create a comprehensive research effort among the Marcus Autism Center at Children's Healthcare of Atlanta, the medical school's Department of Pediatrics, and Yerkes National Primate Research Center at Emory. The ACE is one of only three such centers nationwide and brings together more than 25 researchers and physicians in eight laboratories in the three Atlanta institutions, along with collaborators at Florida State University.

The ACE will study risk and resilience for autism in infants and toddlers and develop new screening programs in early infancy. The ACE also will create new community-based health care for infants and toddlers with autism spectrum disorders (ASD).

The first two ACE research projects will focus on social visual engagement and social vocal engagement in ASD, building on earlier research first conducted by ACE director and Georgia Research Alliance scholar Ami Klin and collaborators Warren Jones and Gordon Ramsay, both of Emory's Department of Pediatrics. Eye-tracking studies of social engagement and biological motion in adolescents, toddlers, and infants have already uncovered factors that are predictive of ASD in the first six months of life.

Recent work with social visual engagement compared typical infants and infants at risk for ASD. Marcus Autism Center will follow these infants from birth with new tests of social visual and vocal engagement measured through "growth charts" comparing normal social engagement and deviations in the first year of life.

Another research project, at Yerkes Research Center, will study behavior in rhesus macaques, connecting eye-tracking behavioral studies of social visual engagement and growth charts of social engagement along with genetics, behavioral, and brain imaging studies in nonhuman primates.

Who gets **CPR?**

Residents living in high-income white and high-income integrated neighborhoods were more likely to receive bystander CPR during an out-of-hospital cardiac arrest than arrest victims in low-income black neighborhoods, according to a publication in the Oct. 25 issue of the *New England Journal of Medicine.* Arrest victims in low-income white, low-income integrated, and high-income black neighborhoods were also less likely to receive bystander CPR.

In an effort to look at future CPR training processes, researchers from Emory University, the University of Colorado, and several other institutions wanted to better understand the effects of different neighborhoods on the probability of receiving bystander CPR in out-of-hospital cardiac arrests. More than 300,000 out-of-hospital cardiac arrests occur in the United States each year.

Using surveillance data submitted from 29 U.S. sites to the Cardiac Arrest Registry to Enhance Survival (CARES), the researchers looked at data from 2005 through 2009. Out of 14,225 usable cardiac arrests registered in CARES, bystander CPR was provided to 4,068 patients.

The CARES program was developed by Emory's Department of Emergency Medicine and has been funded by the Centers for Disease Control for the past eight years.

In Brief

Overcoming **'original sin'**

Scientists studying flu vaccines have identified ways to overcome an obstacle called "original antigenic sin," which can impair immune responses to new flu strains.

Original antigenic sin (OAS) occurs when the immune system encounters one viral strain and then a related new one, but can only respond by making antibodies against the first strain, resulting in a less effective defense.

Researchers at the Emory Vaccine Center have demonstrated in experiments with mice that OAS can be overcome by using a vaccine additive or by repeated immunization with the second viral strain.

The findings could be important in vaccination of people with weaker immune systems, such as those with chronic infections, young children, or the elderly.

The influenza virus has become so widespread because it can infect a wide range of hosts, such as pigs and birds, and because its genome is flexible, says Joshy Jacob, an Emory microbiologist.

"Original antigenic sin is really a reflection of the agility of the influenza virus," he says. "OAS becomes a factor when the new circulating strain is a 'drifted' version of what came before. The old antibodies can't neutralize the new virus, and that helps the new virus survive."

Jacob and colleagues demonstrated that combining the immunization with a vaccine additive allows mice to respond better to the live virus. The adjuvant is a squalene oil-in-water emulsion. Squalene is a vaccine additive licensed in European countries since the 1990s but is not approved for use in the United States.

"It appears that the adjuvant is making the immune responses to the first viral strain broader, so that a wider range of antibody-producing cells are able to respond to the second strain," Jacob says.

Two Emory hospitals awarded **top 10 status** by University HealthSystem Consortium

The University HealthSystem Consortium (UHC), an alliance of 119 academic medical centers and 291 of their affiliated hospitals, ranked Emory University Hospital (combined with Emory University Orthopaedics & Spine Hospital) second and Emory University Hospital Midtown sixth in the 2012 UHC Quality Leadership Awards. This is the first time UHC has had two hospitals from one health care system rank in the national top 10. The UHC rankings are traditionally looked upon as providing the best, most non-biased national quality measurement system available for teaching hospitals.

"The main reason these rankings are important is that they are indicative of our significant improvements in achieving high survival rates, infection rate reductions, substantial reduction of ventilator-acquired pneumonia, and many other quality, safety, efficiency, and patient service indicators," says John Fox, president and CEO of Emory Healthcare.

Immune system compensates for 'leaky gut' in IBD susceptibility

New research could clarify how inflammatory bowel diseases (IBDs) develop.

"Our study results suggest that when there is a chronically leaky intestine, defects in the immune system need to be present for the development of IBD," says Emory pathologist Charles Parkos. "Breakdown of the intestinal barrier can occur as a result of intestinal infections or stress. The normal response involves several components of the immune system that help to heal the injury while controlling invading bacteria. When this normal response is defective and there is a leaky barrier, the risk of developing IBD is increased."

JAM-A deficient mice have a "leaky gut," meaning that chemicals and bacteria can cross more easily from the insides of the intestines to the rest of the body.

Parkos and his colleague, pediatrics researcher Tim Denning, have been studying mice that are deficient in a protein called JAM-A (junctional adhesion molecule A). JAM-A is an important regulator of the epithelial barrier in the intestine. Denning describes JAM-A and other "tight junction" molecules as forming a seal between epithelial cells like a zipper, which keeps bacteria away from the rest of the body.

JAM-A deficient mice have a "leaky gut," meaning that chemicals and bacteria can cross more easily from the insides of the intestines to the rest of the body. Passage of bacteria across the intestinal wall and into the body can cause inflammation and disease. JAM-A deficient mice have more bacteria in the liver and lymph nodes and are more susceptible than regular mice to a chemical treatment (DSS) that induces colitis.

"This is a situation that may be analogous to first degree relatives of people with Crohn's disease," Parkos says. "Some of these people have increased intestinal permeability, which suggests that they are more susceptible to developing disease, but they don't get sick. Gut permeability also transiently increases in normal people based on what we eat and drink, yet disease doesn't occur. We think that immune compensation is what protects the body under these conditions."

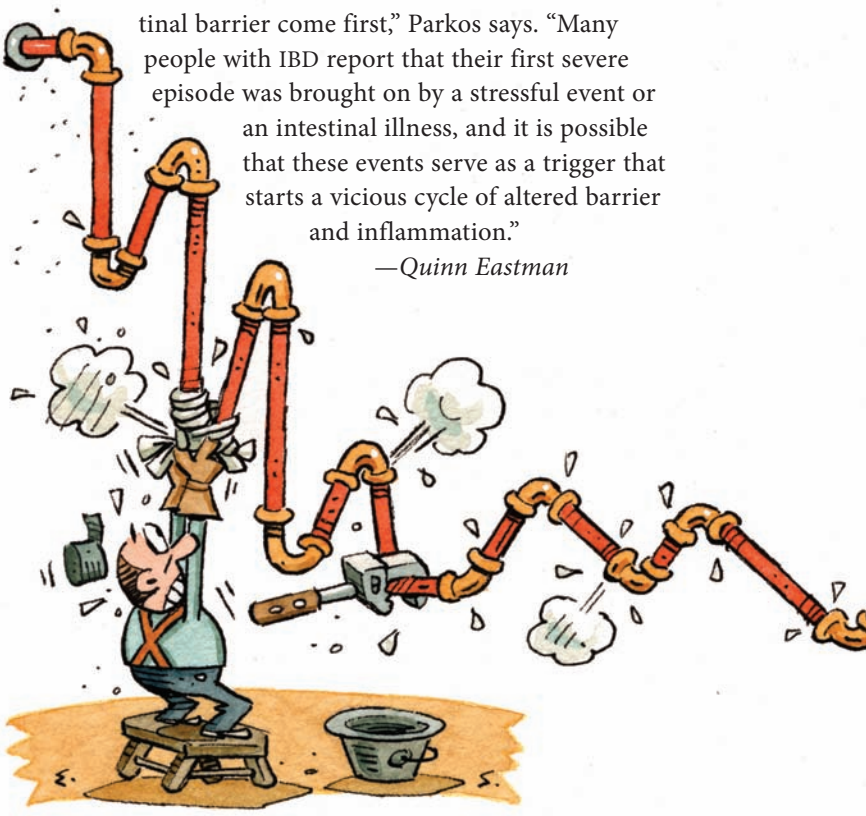
The researchers wanted to dissect which types of immune cells were responsible for this effect so they treated JAM-A deficient mice with antibodies that depleted certain types of immune cells. They found that CD4+ T immune cells are needed to produce signals that encourage production of the antibody IgA, which limits incursions by bacteria in the intestine.

"In normal mice, immune cells such as CD4+ T cells and IgA-producing B cells do not play a big role in DSS-triggered colitis," Denning says. "But if the mice have a preexisting leak, the immune system plays an important role."

While defects in the production of IgA alone do not result in colitis, the presence of a chronically leaky gut along with an IgA deficiency results in increased susceptibility to abnormal intestinal inflammation. During intestinal inflammation, the amount of JAM-A in the epithelium can decrease, further weakening the intestinal barrier.

"There is a 'chicken or the egg' question with respect to whether inflammation or alterations in the intestinal barrier come first," Parkos says. "Many people with IBD report that their first severe episode was brought on by a stressful event or an intestinal illness, and it is possible that these events serve as a trigger that starts a vicious cycle of altered barrier and inflammation."

—Quinn Eastman



In Brief

New lead on drugs against Parkinson's disease

Emory scientists have identified a compound that boosts the survival of neurons threatened by Parkinson's disease. The compound, bis-3-cognitin, could be a starting point for finding drugs that delay Parkinson's disease progression.

In mice, bis-3-cognitin could protect neurons from damaging toxins and from developing motor problems when it was given together with the toxin.

Zixu Mao, an Emory pharmacology researcher, and his colleagues had been studying MEF2D, a protein vital for the survival of neurons. Mao's previous research had shown that MEF2D is altered in the neurons of people with Parkinson's disease. The MEF2D protein is sensitive to cellular changes, such as oxidative stress, which can lead to neuron damage in Parkinson's.

"For years, we had been talking about looking for drugs that enhance MEF2D," Mao says. "The challenge was how to set up a screening system."

Bis-3-cognitin appears to have been a good catch. Cognitins are a family of compounds derived from tacrine, the first drug approved by the FDA to treat the symptoms of Alzheimer's disease. Tacrine was eventually discontinued because of liver toxicity and other side effects.

Bis-3-cognitin could protect cells in culture by increasing MEF2D levels. It also protected against the toxin MPTP, which kills neurons.

"We think MEF2D is not the only target of bis-3-cognitin," Mao says. "It is a potent antioxidant, but MEF2D is required for the neuroprotective activity—we found that if you knock down MEF2D in cell lines, the protective effects are much weaker."

He adds that bis-3-cognitin also appears to avoid the acute toxicity problems of tacrine.

Study clarifies **benefits of coronary stents**

Who should get stents to keep once-clogged coronary arteries open? Someone who is having a heart attack certainly should, and the life-prolonging benefits have been demonstrated in several studies. But results have been more ambiguous for patients who have stable angina.

An Emory study by Kreton Mavromatis, director of cardiac catheterization at the Atlanta VA Medical Center, showed patients with stable angina who received stents along with medical therapy were less likely to be hospitalized than those receiving only medical therapy, 4% versus 13%, respectively.

Researchers used a technique called fractional flow reserve (FFR) to decide if someone with stable angina should receive a stent or medical therapy with drugs such as aspirin and statins.

In the study, researchers used a technique called fractional flow reserve (FFR) to decide if someone with stable angina should receive a stent or medical therapy with drugs such as aspirin and statins. Conventionally, X-ray coronary angiography is used to assess the need for a stent. FFR involves introducing a pressure sensor via guidewire into the coronary artery, to measure how much blood flow is being blocked.

Some cardiologists have criticized the results, noting that the benefits of stenting didn't reduce deaths and heart attacks.

"It is important to recognize that reducing symptoms of angina and the chance of hospitalization is a tremendous benefit to patients," Mavromatis says. "I think FFR will play a bigger role in evaluating and treating coronary artery disease, as it can direct stenting much more precisely than angiography toward clinically important coronary artery disease, improving outcomes and saving money."

The FFR procedure costs several hundred dollars but is significantly less expensive than a coronary stent. Habib Samady, director of interventional cardiology at Emory, also has been an advocate for the use of FFR to select who would benefit from a coronary stent.

"At Emory, we are sometimes asked to reevaluate patients who have been slated for coronary artery bypass surgery at another hospital where recommendations are made based on angiography alone," says Samady. "When we evaluate these cases using FFR, we are sometimes able to recommend courses of treatment that involve fewer stents or even medical therapy. Occasionally, based on FFR data, we send our patients for an endoscopic or 'minimally invasive' bypass and stent the remaining narrowings."

A large, multi-center study called ISCHEMIA is starting that will address the coronary stent versus medical therapy issue in a more definitive way. Both Emory and the Atlanta VA Medical Center are participating.

New gene for Alzheimer's risk identified

Researchers have identified a genetic variation that may indicate an increased risk for late-onset Alzheimer's disease.

The finding is a result of a collaboration between deCODE genetics in Iceland and Emory Alzheimer's researchers. They read the entire genomes of 2,261 Icelanders.

The new variant increases risk by about a factor of three, an effect that is similar in scope to that of the most common genetic risk factor for Alzheimer's, ApoE E4. However, the new variant, called TREM2, is rarer: it is found in one in every 160 people in Iceland, compared with more than 17% of the Icelandic population for ApoE E4, a percentage that is higher in other countries. People who carry the variation and do develop Alzheimer's disease do so roughly three years earlier than non-carriers. Although rare, the variant is important because it adds to a growing list of genes linked to Alzheimer's disease, and it provides clues to causal mechanisms.

"First, the results demonstrate that certain rare genetic variants can have a strong influence on Alzheimer's disease risk for individuals carrying those variants," says Allan Levey, director of Emory's Alzheimer's Disease Research Center and chair of neurology. "Second, since the TREM2 gene is expressed in microglia and other immune cells where it triggers production of inflammatory cytokines, the finding provides growing evidence that chronic inflammation is relevant for the development of the disease, and that modulating TREM2 signaling and microglial function is a potential therapeutic strategy."

Targeting inflammation to **treat depression**

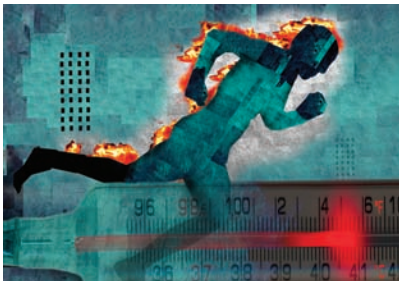
Researchers at Emory have found that a medication that inhibits inflammation may offer promise for people with difficult-to-treat depression.

Prior studies have suggested that depressed people with evidence of high inflammation are less likely to respond to anti-depressant medications and psychotherapy. This study was designed to see whether blocking inflammation would be a useful treatment for people with difficult-to-treat depression or only those with high levels of inflammation.

The study employed infliximab, used to treat autoimmune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Infliximab blocks tumor necrosis factor, a key molecule in inflammation that has been shown to be elevated in some depressed people.

Study participants all had major depression and were moderately resistant to conventional antidepressant treatment. Each participant was assigned either to infliximab or to a non-active placebo treatment.

When investigators looked at the results for the group as a whole, no significant differences were found in the improvement of depression symptoms between the drug and placebo groups. However, when the subjects with high inflammation were examined separately, they exhibited a much better response to infliximab than to the placebo. Inflammation in this study was measured using a simple blood test that is readily available and measures C-reactive protein.



"The prediction of an antidepressant response using a simple blood test is one of the holy grails in psychiatry," says Andrew Miller, senior author of the study and the Timmie Professor of Psychiatry and Behavioral Sciences. "This is especially important because the blood test not only measured what we think is the root cause of depression in these patients but also is the target of the drug."

How Emory doctors put the brakes on one woman's endless sleeping and found a new treatment for a widely misunderstood condition

Ending the big sleep

By Quinn Eastman • Illustration by Christiane Beauegard

Sleep was consuming Anna Sumner's life. The Atlanta attorney routinely slept 16 hours every day, and it never felt like quite enough. She needed multiple alarms to wake up and could sleep through a phone ringing or someone shaking her. When she came to Emory Sleep Center in 2005, she told doctors there that she "craved" sleep all the time.

"It came to the point when faced with a choice between sleeping and eating, I would rather sleep," she recalls. "But when I did sleep it was not restorative."

Sumner's care team had considered and ruled out common causes of sleepiness, such as sleep apnea and narcolepsy. The typical drugs of choice to combat sleepiness, prescription stimulants, didn't help. This was a type of sleep disorder that they did not know how to treat.

"It required a shift in thinking," says neurologist David Rye, who has led the effort to understand Sumner's mysterious condition. "Usually if people are having trouble staying awake, the conventional thought is that their brains are deficient in excitatory monoamines, like histamine or dopamine, and are in need of a jolt from these wake-promoting neurochemicals. In Anna's case, giving her extraordinary doses of stimulants was like trying to drive a car with the parking brake on. We needed to release the brake, rather than push the gas harder."

Sumner's condition would lead Rye and his team on one of the most demanding—and rewarding—scientific journeys they've had. In the end, they were able to put a name to her condition and track down the world's first treatment for it. But along the way, Rye discovered the scientific community wasn't as convinced as he was about his discovery.

The 'Sumner stupor'

Sumner says her sleep demands increased in high school. While she was studying at Princeton, her parents in Mississippi became more concerned because she'd spend much of her holidays at home asleep. During law school, a flexible schedule allowed her to conceal her sleep requirements. As an attorney, she says she never missed a critical legal appointment, although the strain became difficult to bear. Over the years, she kept a list of "things I slept through," like a friend's wedding she had traveled across the country for. She managed to keep a sense of humor about her situation, joking with her brothers about the "Sumner stupor."

When Sumner came to Emory's sleep clinic, Rye and his team diagnosed idiopathic hypersomnia and prescribed her stimulants, such as modafinil and amphetamines. These drugs proved beneficial for a while. However, the increasing doses needed to sustain the effect made Sumner feel "twitchy," elevated her blood pressure, and suppressed her appetite. And she began experiencing crashes. Unpredictably,

she would sleep for 30, even 57 hours at a stretch.

"That was the scary part," she says. "If I went to bed, I didn't know if I'd fall off the map and wake up two days later."

She took a leave of absence from her job, and her mother had to move in with her to wake her so she could eat.

"We had never had a patient quite like her before," says former Emory nursing sleep specialist Kathy Parker, who is now at the University of Rochester. "I thought to myself that she's going to sleep her life away if we don't do something."

Hey, GABA

Parker made a chart of all the signaling molecules in the brain, checking off each one as she and Rye tried different drugs to alter Sumner's brain chemistry. With the list of untried neurotransmitters growing very short, they decided to look at the brain chemical GABA (gamma-amino butyric acid), an amino acid that calms the nervous system for sleep. Sleep-promoting circuits in the brain are thought to use GABA. Barbiturates and benzodiazepines, such as Valium and Ambien, make neurons respond more strongly to GABA.

Parker enlisted anesthesiology researcher Andrew Jenkins, who has been studying since the 1990s how GABA affects brain cells, to look at Sumner's cerebrospinal fluid (CSF). He found a normal level of GABA in her CSF, but her CSF contained a substance with an amount of GABA-enhancing activity comparable to someone undergoing oral surgery or a colonoscopy who had received a strong sedative. (He did not find any synthetic benzodiazepines in her CSF.)

The mystery substance appeared to be working with her GABA to tamp down her brain's activity, like an ever-present sleeping pill. But neither Jenkins nor Rye could figure out what the substance was in her CSF.

"Sleep and anesthesia may share some features in common, but they're not the same thing," Jenkins says. "You don't wake up feeling satisfied after general anesthesia."

Jenkins wanted to see if the substance was similar to a benzodiazepine and tested it against flumazenil, an antidote kept on hand in emergency departments for benzodiazepine overdoses. When Jenkins added the flumazenil on top of Sumner's sample, it nearly reversed the effects. That led to the question: would it accomplish the same feat in Sumner?

The eye-opening moment

Flumazenil is known to provoke seizures in people going through benzodiazepine withdrawal, so the team decided to give Sumner the drug in Emory University Hospital's epilepsy unit over the course of two days in June 2007. Sumner occupied herself with "the world's most boring video game," a psychomotor vigilance test that measured her alertness by timing how fast she could react to numbers on a screen. The team monitored her vital signs and brain waves. When the dose reached two milligrams, she exclaimed, "I feel alive!"

"The best way to describe it is that my eyes opened, after being half-closed for so long. It was as if a force grabbed my eyelids and pulled them upwards," she says.

For the researchers gathered around, the moment was dramatic as well.

"In a matter of days, we went from a biophysical experiment in the lab to having a real impact on a patient's life," Jenkins says. "It was certainly one of the highest points in my career."

As exciting as the test result was, the drug's effect wore off after a few hours. Since flumazenil rapidly metabolizes if swallowed whole, it is usually given intravenously, but Sumner would need a formulation that was more convenient. Parker wanted to reformulate the drug, but it was only approved to counter overdoses, and there was little supply of the drug. It had not been manufactured since 2004.

Parker worked with the FDA to secure a compassionate-use exemption for Sumner and with drug patent holder Roche to tap the last flumazenil supply, held in Roche's laboratory in Switzerland. Parker also worked with a compounding pharmacy to develop a 6-milligram flumazenil lozenge for Sumner to put under the tongue throughout the day. Sumner discovered that having the level of flumazenil in her system swing too drastically made her nauseous or groggy. Along with the lozenges, a flumazenil-containing cream applied to her forearms before bedtime helped her wake up in the morning.

Sumner reported that this regimen finally worked, with few side effects. She could drive, something that didn't feel safe when sleep was such an overpowering urge. She could watch entire television shows for the first time in years. In short, she had her life back.

Finding others…and skepticism

His success with Sumner led Rye and his team to examine

CSF samples from other patients who had experienced daytime sleepiness. The sleepiness was severe enough that some had applied for disability and others needed leaves of absence from school or work. Sleep apnea and other conditions that cause daytime sleepiness had been ruled out.

"Even when they're ostensibly awake, these patients report that they feel as if they are walking around in a fog," Rye says. "They have the reaction times of someone who has stayed up all night, all the time."

Rye found enhanced GABA activity similar to that in Sumner in their CSF samples. He tested Sumner and six others in a clinical study on the effects flumazenil could have on their alertness, measured by a psychomotor vigilance test. Flumazenil improved reaction times and perceived alertness in all seven, although their responses were not uniform.

When Rye wrote up the results of his clinical study, his quest to get his paper published proved to be as long as finding a treatment for Sumner. A number of journals turned him down, citing skepticism about his results. The journals' goodwill had been tainted by a similar, but bogus, study in Italy in the 1990s.

The Italian neurologists reported that they had identified patients experiencing a "recurrent stupor" because their bodies produced benzodiazepine-like substances. It was later revealed that the Italian patients were being given the benzodiazepine drug Ativan covertly.

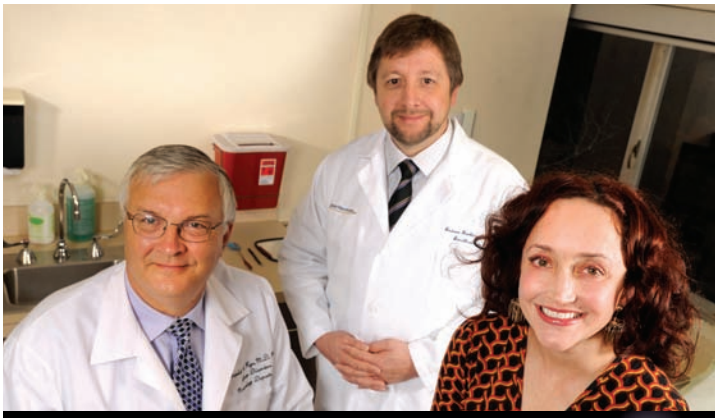
Rye's study was finally published in the Nov. 21, 2012, issue of *Science Translational Medicine*, but not before he and Jenkins went to great lengths to show that the unknown substance was not an artificial benzodiazepine drug taken by the patients. Using the latest technology, they scoured patients' CSF samples for benzodiazepines. They also showed that the sleep-inducing substance works in situations where benzodiazepines don't. In the lab they demonstrated that the substance still works upon GABA receptors that were mutated and rendered insensitive to synthetic benzodiazepines.

The still unknown substance

Rye and Jenkins' next quest is developing new tests to look for the unknown sleep-inducing substance. What they have determined so far is that based on its size and sensitivity to certain enzymes, the substance could be a peptide, similar to the hormone oxytocin. While the substance is detectable in blood, its concentrations are much higher in CSF, suggesting that it is synthesized in the brain.

"I think the 'sleepy stuff' is something that is made by everyone's brain in some amount," Jenkins says. "Either Anna and other people like her make more of it, or what they make is more potent, which is the direction I'm leaning now."

If the substance is present in all of us, would flumazenil wake up sleep deprived healthy people? If so, could truck drivers, airplane pilots, and medical residents use it to stay awake? Presented with this idea, Rye threw cold water on it.



Neurologist David Rye, researcher Andrew Jenkins, and patient Anna Sumner.

"We are not the first to think that if you muck around with GABA, you can wake people up," he says. "The military tried out flumazenil on sleep-deprived recruits years ago and seems to have abandoned it."

Several studies with flumazenil indicate that for most people it has no stimulant effects, even if it has now been shown to restore alertness in a handful. Rye says this variability may have something to do with a patient's sensitivity to sleep deprivation, possibly genetic—his hypersomnia patients often have a close relative with similar experiences.

Although flumazenil has helped Sumner, it may not be a practical long-term treatment for others. The supply of the drug is limited. Sumner has about a year's supply left, and no manufacturers so far have expressed interest in taking up flumazenil.

Rye's other hypersomnia patients are taking the antibiotic clarithromycin. (Sumner says she will probably transition to this drug once her flumazenil runs out.) This drug came by way of Sumner herself. After contracting bronchitis in 2010 and taking clarithromycin, she found herself with insomnia. She called Emory, and soon thereafter, clarithromycin's effects on GABA were tested in the laboratory. The results were promising, and clarithromycin is now the focus of another clinical study, supervised by neurologist Lynn Marie Trotti.

Rye and Jenkins say they still have some work to do in convincing their peers that hypersomnia has genuine biology behind it, judging from an experience of Sumner's parents. They approached a prominent neurologist [not at Emory] and described their daughter's condition, only to be told that she was probably taking drugs recreationally. Some of Rye's other hypersomnia patients have received diagnoses of narcolepsy or depression, but hypersomnia may be more common than narcolepsy, he says.

"Looking back on it, it just demonstrates the good luck that I had to be dealing with doctors who listened to me," Sumner says. "I am grateful for their perseverance." **EM**

Christian Larsen is the new dean, and he's got big plans to integrate care, research, and education in the health sciences.

A NEW ROLE FOR A NEW TIME

By Rhonda Mullen

Christian Larsen was just a boy when he saw his first patient. He used to accompany his dad, a cardiac surgeon, on weekend rounds to check on patients recovering from coronary bypass surgery. When he got older, he'd enter data from his father's research studies into a big IBM mainframe, marking the beginning of a lifelong interest in science and technology.

Chris Larsen at his Emory medical school graduation with his father, a cardiac surgeon.

The elder Dr. Larsen was unusual for his time. In the 1970s, he already was breaking the mold of a stereotypical surgeon by emphasizing patient care provided by teams. He performed heart transplants and sought out Thomas Starzl, who performed the first successful human liver transplant in 1967, to learn about immunosuppression. (Chris Larsen remembers setting up a reel-to-reel projector in his family's living room so that they could watch a movie of one of his father's transplants.) While in private practice in Miami, the father Larsen developed a wound care program, and at one point, he even left surgery to pursue a PhD in biology at the University of Miami Medical Center. Larsen's first mentor, his dad, was willing to take some risks. So, it turns out, is his son.

The trajectory of Larsen's career in many ways resembles that of his father. Described by colleagues across the country as both surgeon extraordinaire and brilliant scientist, Larsen has brought teams of people from many disciplines to provide the complicated care needed for transplant patients, along with developing a new class of immunosuppressive drugs. After his many successes in both the clinical care and scientific arenas, it seems like destiny that Larsen would be chosen for his new role as dean of the Emory School of Medicine, vice president for health center integration at the Woodruff Health Sciences Center (WHSC), and chair of the Emory Clinic board.*

Additional titles that Larsen has held include the **Joseph Brown Whitehead Professor and **Chair of Surgery and the Carlos and Marguerite Mason Professor** in the medical school.*

But it wasn't always so clear to the boy who was fascinated by science and nature and grew up exploring the tide pools of Miami what he wanted to do. He thought he might study marine biology, which in his mind meant he could swim at the beach AND do science.

Then Emory happened. While Larsen doesn't remember any particular point of decision during his undergraduate studies, it became clear to him that he wanted to be a physician, maybe a pediatrician.

HIS "CHIEF OF STAFF" As an undergraduate at Emory, Larsen met Clotilde Allard Stanley, a psychology major who had had an international upbringing. Stanley's mother was Mexican, and her father—who died when she was 2—was French. Her mom later married an American, whose career with the Ford Foundation took his new family around the globe. A native Spanish speaker, Clotilde learned English at age 9.

The exotic beauty caught Larsen's eye at a freshman mixer, and the chemistry major spent the evening asking her a stream of questions about her high school in Karachi, her travels, and her family. Larsen later told a friend, "One day I'm going to marry her."

It took until their senior year for Larsen to persuade Stanley to go out with him. Up until then, she thought of him only as a friend, "a person to go to if you needed help with something like a flat tire or chemistry homework."

But Larsen's prediction of marrying her one day is indicative of how he works. When he sets his mind to something, he can figure out how to make it happen. They wed in 1981, a year after graduating from Emory College, when Larsen had one year of medical school at Emory under his belt.

The couple moved into an apartment, long since torn down, near Emory's campus on Clairmont Road across from Athens Pizza. Already in those early years of married life, Clotilde—Cloé to friends—became her husband's sounding board. As Larsen's mother was to his father, she was his rock, support, and sanity. "He's a good talker, and I'm a good listener," she says. By the time his career landed Chris Larsen as chair of surgery at Emory, she had listened so much that she adopted an unofficial title for herself—Larsen's "chief of staff."

As often happens, Larsen didn't stay with the specialty that he had planned to pursue at the beginning of medical school. Instead, he became more and more interested in surgery. He liked the opportunities that surgery presented to make an immediate difference in patients' health and what he describes as its "elegance and beauty." He began thinking of a career in congenital heart surgery, which would marry his interests in children and surgery.

But along the way, nephrologist David Lowance introduced transplantation into the mix. During his rotation with Lowance, Larsen noticed a striking difference between patients who had received a transplant and those on dialysis. "The restoration of health and vitality was evident in the transplant patients," he says.

That observation changed his course once again, and he applied for a residency in general surgery, snagging a coveted slot at Stanford. Larsen's life was about to change again.

ACROSS THE POND AND BACK W. Dean Warren, Emory's chair of surgery at the time, had given Larsen good advice during medical school: "If you're going to be a surgeon, you should really spend your time with the best teachers outside of surgery. Pick the best teachers in areas that will broaden you as a physician."

A year into Larsen's residency at Stanford, he got a chance to reconnect with his old mentor. At a conference in San Francisco, Warren asked, "How is everything going?" Larsen answered enthusiastically. He was great. He loved the training. But when Warren asked, "How's Cloé?," there was a long pause. The fact was, Larsen's work-life balance was almost nonexistent, and his wife, at home with baby Nicole, felt isolated. The dean saw an opening and invited the young surgeon back to complete his residency at Emory. The family started packing.

As a second-year resident, Larsen came under the tutelage of Emory's chief of transplant surgery John Whelchel in the operating room. He also stayed interested in the science behind the techniques that he was learning. When an opportunity came along to study in the lab of renowned transplant surgeon and immunologist Peter Morris at Oxford University, Warren (along with Whelchel and Lowance) once again enabled Larsen to pursue his passion.

The Larsens headed to England, now with two toddlers, for what was supposed to be a year of studies that turned into three.

A year later, Thomas Pearson, who had just finished his surgery residency at Emory, also arrived in Oxford to

HE THOUGHT HE MIGHT STUDY MARINE BIOLOGY, WHICH IN HIS MIND MEANT HE COULD SWIM AT THE BEACH *AND* DO SCIENCE.

Thomas Pearson and Larsen at the retirement party of Peter Morris at Oxford University. Larsen studied under Morris, a renowned transplant surgeon and immunologist, known widely as "The Professor."

Pearson and Larsen teamed up in covering their research and patient care services. One month, Larsen was in the lab and Pearson on clinical rotation. The next, they switched.

"He's a good talker, and I'm a good listener," says Clotilde (Cloé) Larsen of her husband.

Pearson and Larsen are avid runners and train together for events such as the ING marathon.

study immunology. The two surgeons were in staggered years in training in Atlanta and hadn't known each other before, but they soon grew to be fast friends. They rode bicycles to work in the mornings while they talked about ongoing projects in their respective labs. Their families had dinner together on Friday nights.

To this day, Larsen and Pearson continue to work together, run together, and socialize together—especially now that both families are empty nesters. As Larsen began as dean of medicine on January 15, Pearson, who is Livingston Professor of Surgery, assumed the position as executive director of the Emory Transplant Center.

"There is no way that Chris could be doing what he's doing without Tom's support," says Cloé Larsen. "They have each other's back."

When the surgeons finished their training, earning an MD and DPhil, they each had an offer to have a clinical practice and a research laboratory at Emory. Instead they decided to share both. One month Larsen covered the lab and Pearson, the clinical rotation, and the next month, they switched.

They brought complementary skills to the budding partnership. "We both work really hard," says Pearson. "But on ideas and strategy, he's the man. My contribution is, well, I'm the operations person."

Both felt it was important not only to restore health to seriously ill patients via transplant but also to find better long-term solutions to the immunosuppressant therapy that patients had to take ever after to keep their bodies from rejecting the donor organs.

Pearson remembers that they started their lab with an empty room and no funding. They wrote their first grant in 1991. "We had an idea that a particular pathway was important in organ rejection and if we blocked that

pathway, we could create tolerance," he says.

"Our research program was always rooted in trying to ask questions and understand biology in ways that would create new opportunities for treatment," Larsen says. "The clinical team knew we were not satisfied with the treatments we had today."

Within 10 years, Larsen and Pearson had built a comprehensive transplant center that integrated patient care and research. They were making progress on their understanding of immunity after transplantation. They had developed collaborations with scientists at the Yerkes National Primate Research Center and with other disciplines across the Emory campus. They had redesigned how clinical care was provided to transplant patients.

The effort was so impressive in such a short time that Oxford came calling. Morris, whom everyone called "The Professor," was retiring, and Larsen was offered the chance to take over his program. It gave him pause. There was the chance to enjoy the prestige of Oxford and to step into the big shoes of a mentor he respected. Pearson remembers standing in the rain outside the DeKalb Farmer's Market and taking Larsen's call about the offer. "You've got to come with me," Larsen told his colleague and friend. Cloé Larsen and his daughters were willing to go. Pearson, his wife, and two daughters were considering the move. Larsen had a running list of pluses and minuses on whether to go or stay. It tied both families in knots. Then one winter's day as he walked among the Japanese maples that he and Cloé had recently planted, Larsen made his decision. With Pearson, he had built a program in Atlanta and made relationships that were starting to grow and bear fruit. "In the end, I couldn't conceive of starting over or of making the advancements any place else," Larsen says. He stayed.

Larsen, Pearson, and faculty and staff of the Emory Transplant Center celebrate the publication of their paper on co-stimulation blockade in Nature.

Larsen takes the reins from former dean Thomas Lawley, who served as dean at Emory for 16 years and will remain on the faculty.

TEAM TRANSPLANT Larsen's decision turned out to be the right one for patients, his field, his own career, and Emory. It was here that he and Pearson built a truly interdisciplinary program that pulls together surgeons, nephrologists, nurse practitioners, infectious disease specialists, nutritionists, social workers, and pharmacists to improve the experience for patients. Here that they did the pivotal research that eventually led to FDA approval of a new immunosuppressant, belatacept, that causes less long-term damage to kidneys than cyclosporine. Much of that success goes back to Larsen's fundamental approach to everything he touches: building teams.

He has collaborated for more than a decade with Rafi Ahmed, director of the Emory Vaccine Center and a Georgia Research Alliance Eminent Scholar, on protective immunity. The NIH has repeatedly asked the two how they collaborate so well, to pass along the model to less amicable research teams.

Mandy Ford, a basic bench scientist who did her training in autoimmunity at Emory, has been a part of the transplant team effort for nine years and at

the university for 14. During that time, she's met frequently with Larsen to talk science, always feeling more inspired when she left his office than when she arrived. Now on the research faculty, she has stayed at Emory not only because she believes in the mission and the work but also because of her mentor. "People make life decisions about where they want to live, raise their family, and have their careers based on Chris Larsen," she says.

Andrew Adams, who also studied with Larsen as an MD/PhD student, returned to Emory as a transplant surgery fellow after a residency at Massachusetts General Hospital—in part because of Larsen. "He's a good person to emulate as a surgeon, scientist, and family man," says Adams, who helped start Emory's islet transplant program to cure diabetes. "There are a lot of good and smart mentors, but he really champions people. He is there to help you succeed, and there is no hint of being in it for his own good."

Larsen recruited another team member, Heather Hamby, for the transplant center's strategic planning effort. She came to know him as someone who respected and valued the perspectives of everyone on the team. However, she did discover a challenge in trying to keep up with him. "He is someone of enormous energy and someone who pushes," she says. "For example, when we ran out of space for the program in Emory Hospital, Dr. Larsen set his sites on the sixth floor of Clinic B. Never underestimate his ability to persuade and convince," she says. Larsen convinced the administration to let him take over the found space, and the Mason Trust donated the support for the renovation to keep the transplant program growing.

ACCEPT NO BARRIERS Larsen takes on his new roles at Emory at a time of acute challenges to health care, in particular to academic, tertiary medical centers that provide care for some of the sickest people in the country. Tremendous downward pressure is being exerted on the finances of medicine, and changes are afoot in the way medical centers and providers are reimbursed. The nation is facing a shortage of doctors, and while new slots are opening up for medical students, the number of residency positions are not keeping pace. Research opportunities have never been better in some respects, but the NIH most likely is facing a budget that will stabilize or decline.

In light of such challenges, why would Larsen want to take on the deanship? He laughs when asked, but his answer is serious. "It might be more comfortable to stay in my current roles, which are challenging enough. But I feel a broad desire to serve people, to share what we've learned in the transplant center and surgery to help Emory rise to meet the challenges of today's environment."

"HE RESPECTS NO BARRIERS, AND I MEAN THAT IN A GOOD WAY." –Wright Caughman

Larsen's new role also carries the title of vice president for health center integration, a function that Wright Caughman, Emory's executive vice president for health affairs, describes as looking holistically at the medical enterprise and working closely with Emory Healthcare. "The new environment requires creativity and courage and someone who can focus us on the areas where we can have the biggest impact," he says. "Chris embraces that. He's a good leader who instills confidence in others and coalesces what he learns to create a synergy in the teams he puts together. He respects no barriers, and I mean that in a good way."

Larsen also has the advantage of already knowing the challenges particular to Emory. But being "home-grown" from his undergraduate years all the way through his professional career could have had a downside. Sometimes trainees aren't taken as seriously when they transition at the same institution from resident to fellow or fellow to faculty member. When Larsen was named chair of surgery in 2009, some of the faculty in his department were his teachers in medical school. "I learned that that's okay," he says. "The relationships have been great, and people have been supportive."

As Larsen considered applying to succeed Tom Lawley, who had served for 16 years as dean of Emory's medical school, he turned as usual to his two sounding boards—his wife and "chief of staff" and the man who has had his back all these years, Tom Pearson.

Through more than 30 years of marriage, Cloé Larsen has come to know her husband as a hard worker with "a lot of drive, energy, and vision." She's fully on board with his new roles, even with the higher profile and the inevitable entertaining role that comes with being the wife of an Emory dean. "I'm all for it as long as I don't have to cook," she jokes, "and you can quote me on that."

Pearson believes that his best friend and collaborator is up to the challenge of these new jobs in this new time. "The amazing thing about Chris is that he is so incredibly competent in diverse arenas and can switch from one to another easily. He can go from discussing state-of-the-art bench immunology to analyzing complex financial spreadsheets, to showing great clinical judgment in the operating room. Being dean will be very challenging. I'm glad we have Chris to do it." **EM**

Walker enlisted anyone he could to help with the effort. Countless Emory faculty and students found themselves conducting workshops on health care policy and administration, analyzing health outcomes, and helping Georgians lobby for health care reform.

Photographer Uriel Sinai/Getty Images

Transforming medicine in another Georgia

By Dana Goldman

Six thousand miles away from Emory, internist Ken Walker 56Ox 58C 63M was in the "other" Georgia—the former Soviet territory—when the bombing started in August 2008. Tensions with another region had escalated, and Georgia had begun exchanging fire with the breakaway region of South Ossetia and Russia. Staying in Tbilisi, Georgia's capital city, Walker watched as hundreds of casualties streamed into Central Republican Hospital.

Photographer Vano Shlamov/Getty Images

Walker, deputy chief of medicine at Grady Hospital, would learn that the hard work of Emory physician faculty in Georgia had paid off. Only months before, 17 of Georgia's doctors had completed a mini-residency program in emergency medicine under the tutelage of Emory faculty. Until the group's graduation, the specialty of emergency medicine had been nonexistent in Georgia, a country of more than 4 million people. By the end of the Russo-Georgian conflict a few weeks later, the newly anointed emergency medicine doctors cared for hundreds of casualties with only a few deaths.

The H. Kenneth Walker Resident Education Fund was established to help residents travel to educational conferences, buy equipment, and conduct research. Joseph Overton Jr. 88C 92M helped establish the fund. "In hindsight, Walker's tugging and pushing of the residents helped us all reach the next level. Hopefully this fund will help continue his teaching excellence," Overton says. For more information on the fund, please contact Alicia Kanjira at 404-727-3989.

Georgia's new specialty of emergency medicine proved its usefulness. And Walker's project, which he named Partners for International Development (PfID), gained more momentum in its quest to transform health care in a developing country nine time zones away.

'Where's Tbilisi?'

The story of how Emory came to have a presence in Georgia goes back more than 20 years. It was 1992, less than a year after the fall of the Soviet Union, when a former Emory medical dean made a late-afternoon phone call to Walker.

"Do you want to go to Tbilisi?" the dean asked Walker with little preamble.

"Sure," Walker said. "Where's Tbilisi?"

The newly independent Georgia and its capital city, Tbilisi, were struggling economically amid social unrest. Despite a glut of doctors, health care was deteriorating, with basic supplies like thermometers available only sporadically. Nurses with only a high school level of education worked more like assistants than professionals in their own right.

Concerned that the health care of millions would spiral downward, the U.S. State Department created a program to match American hospitals and medical schools with their counterparts in the former Soviet Union. Soon Walker and other Emory doctors from Grady Hospital and from Morehouse School of Medicine were flying to Georgia.

"Our charge was to identify one particular hospital and help it. We visited individual hospitals and medical schools. They had about 27 institutes—the institute of surgery, of trauma, of internal medicine," Walker says.

At the end of the trip, Walker made a decision: "I decided that the partnership needed to be with the country rather than with an individual hospital."

Photo by Chris Hondros

Over the next decade, Walker enlisted anyone he could to help with the effort. Countless Emory faculty and students from throughout health sciences found themselves conducting workshops on health care policy and administration, analyzing health outcomes, and helping Georgians lobby for health care reform. When faculty members saw that Georgian medical libraries were stocked with outdated resource guides in Russian, they developed a multimedia library equipped with computers and high-speed internet and a generator to ensure usability during daily electricity outages.

During the academic year, Georgian students received training in Emory's schools of medicine, nursing, and public health. In the summers, Emory medical, nursing, and public health students traveled to Georgia to conduct research studies. One Emory student analyzed the placenta blood of Georgia newborns and discovered significant thyroid deficiencies in more than 60% of the babies. The problem hadn't existed in Soviet times, and Emory doctors soon discovered why.

"It turned out that in the Soviet Union there was a salt factory that produced iodized salt," says Walker. "When the Soviet Union imploded, the factory rusted and stopped." Iodized salt stimulates thyroid functioning. Once the problem was discovered, Emory worked with Georgian public health officials to find a new supply.

Teaching the teacher

For the past four years, Emory and PfID have held a mini-residency program in emergency medicine for doctors and training programs for practicing nurses with funding from the U.S. Agency for International Development, George Soros's Open Society Foundations, the B. Wardlaw foundation, and others. Doctors and nurses train at a learning center in Tbilisi established by PfID in 2009 that is furnished with modern medical simulation equipment and now employs 30 Georgians. So far, 17 emergency medicine physicians and thousands of nurses have been trained by PfID.

The train-the-trainer philosophy is central to PfID's plan. "The approach that Emory has taken in Georgia has been heavily oriented on education," says Archil Undilashvili, a native Georgian who serves as PfID's director of programs and director of research programs in Emory's Department of

Medicine. "Starting with full-time involvement, we gradually shift down and put our local colleagues in charge, although we keep in systematic contact with them. Because what we saw is that we can make much longer-term changes if we base our work on education rather than just doing point-and-shoot temporary work."

Walker adds, "The principle that's been so important to us is to educate the people of Georgia so that from then on they could educate their own people, and education by itself will open whole new professional opportunities."

The emergency medicine residency is popular with doctors, who recognize the specialty as a way to get a leg up in a country with an abundance of physicians. Says Ketevan Stvilia, the Georgian point person for PfID, "They are very happy because they are able to practice something different. Demand for them is very high. Now large hospitals are opening emergency departments, and they are the heads of these departments."

Over the past year or so, no fewer than 75 new small hospitals have been built around the country. "All of them have emergency departments, but they don't have the personnel to practice emergency medicine," says Stvilia. For that reason, a large health insurance company in Georgia recently contracted with PfID to provide the residency program to its doctors in rural areas around the country.

New curricula

PfID is currently piloting a new curriculum at Tbilisi State Medical University, following Emory's lead on a number of fronts: exposing medical students to clinical work early on, emphasizing the importance of communication skills, and exploring the role of the doctor-patient relationship, says project leader Gordon Churchward, the medical school's assistant dean for medical education. Each lesson interweaves themes familiar to students at Emory, such as leadership, scholarship, and societal responsibility.

Emory oncologist Mary Jo Lechowicz was part of a group that flew to Georgia this past fall. For seven days she met with faculty and students to support curriculum development for the country's medical schools. There, Lechowicz came to appreciate some of the challenges that come with a cross-cultural collaboration. "One of the students asked us, 'How many times a day do you lie?' because in their culture the patient doesn't always know the diagnosis," she says. "It's a totally different way of processing the doctor-patient relationship."

PfID's new learning center opened in 2012 and has approximately 24,000 square feet of space.

PfID, along with Emory's Nell Hodgson Woodruff School of Nursing, started the country's first-ever continuing education program for nurses in 2009. Until then, nurses were given little respect or responsibility. Walker explains, "Nurses were trained after the ninth or 10th grade of high school. There was not very much of a clinical component to their education," he says. As such, this left doctors to do what's typically considered the job of nurses in most developed countries.

PfID trained eight local nurses and eight local physicians to serve as local nursing faculty, collaborating to create intensive curricula to enhance nursing skills and knowledge. "We have about 50% didactic work, and then the rest is split between simulations and clinical sessions," reports Undilashvili. "We've worked with Georgian nurses on simple hand-washing practices, taking care of bedsores, how to clean the patient and equipment, and how to be a nursing leader and create a successful nursing service and structure."

Since 2009, more than 3,200 nurses around the country have taken the intensive training, including Georgia's first lady, Sandra Roelofs. "All the health care providers now are asking nurses to take our courses," says Stvilia. "They do not hire a new nurse if she does not have our certificate. There's a huge demand in regions with new hospitals."

Georgians helping Georgians

Georgians have taken notice of Emory's role in improving their country's development. Through the partnership, more Georgians have come to Emory for degrees than to any other university in the United States. Some, including Undilashvili, have joined Emory's faculty and staff.

And so when Georgians decided a few years ago to create a national training center for health care workers, they modeled it after PfID's own new learning center and asked the nonprofit to establish courses and curriculum. "Emory's name is very big here," says Stvilia. "That's why they decided to have Emory in charge of this new national training center because of the good reputation and confidence that Emory can do it." Georgia wants all its physicians, about 21,000 in all, to take part in training there; a new contract between the Georgia government and Emory was signed in September. If PfID continues on its path, the two Georgias will have more in common in terms of health care and health outcomes. **EM**

The healing hormone

Donald Stein finds further **vindication** in his long-held belief that progesterone is more than just a female hormone

By Martha Nolan McKenzie

If Don Stein were the kind of man who listened to what others said, he would have shut down his lab years ago. The Emory neuroscientist spent more than two decades investigating progesterone as a treatment for traumatic brain injury (TBI)—a pursuit that was unappreciated at best and maligned at worst. A naturally occurring hormone was too simple a solution to too complex a problem, according to the prevailing wisdom.

Today Stein stands if not on the threshold of vindication, at least within the general neighborhood. After better-than-hoped-for results from the first human trial, progesterone is being tested in two nationwide phase 3 trials and also internationally in more than 20 countries. And Stein is now expanding his scope to test whether progesterone can work its magic in other conditions, such as stroke, pediatric TBI, and brain tumors.

"I've spent most of my professional career pursuing this line of work," says Stein, Asa Candler Professor of Emergency Medicine and director of the department's Brain Research Laboratory. "Seeing our work in worldwide clinical trial is exciting, but what would really be gratifying would be to know that the work we did actually ended up helping a lot of people to live more healthy and fulfilling lives."

A positive outcome from the trial could mean just that. Researchers have tried unsuccessfully for decades to develop an acute treatment for TBI.

"The graveyard for drugs and promising therapies for TBI is extensive," says David Wright, associate professor in emergency medicine. "There have been many attempts, but zero have made it past a phase 3 clinical trial in something that is epidemic in this country."

All those failures stemmed from looking at the problem the wrong way, contends Stein. "One of the main reasons every single drug has failed is the persistent approach to target one gene, one pathway, one receptor, thinking you are going to find a magic bullet to treat a very, very complex disorder," says Stein.

Indeed, with TBI the initial injury is just the beginning. Even a very localized trauma results in a cascading release of inflammatory factors that cause swelling, tissue breakdown, and programmed cell death. "When you have a brain injury, you have a systemic disease," says Stein. "Every organ in the body is affected. So if you are just treating one spot in the brain or one pathway, you're going to fail."

Progesterone, on the other hand, works at multiple genes, multiple pathways, and multiple receptors. Not only is it able to stem the devastating inflammatory cascade, it actually helps repair the damage. "If you tear down a building, are you just going to leave the rubble?" says Stein. "No, you're going to clear it away and rebuild. That's where progesterone shines. It's a developmental hormone that is involved through the entire gestation of the fetus. So here you have an agent that not only blocks all these toxic events, but it also stimulates regenerative repair."

Progesterone certainly took a step toward proving its worth in the small 100-patient phase 2 trial. Stein and his team were merely hoping to demonstrate that the high dose of the hormone used was safe, so they could proceed to a larger trial. Any evidence of efficacy would be gravy. They got gravy.

For years Donald Stein persisted in his research despite many naysayers, who are now quiet.

"Much to our surprise, we saw a 50% reduction in death in the treatment group, which was just over the top," says Wright. "And in a certain subgroup, we also saw functional improvement. That shifted the whole curve from keeping people alive to actually making them better."

For Stein, applying these positive findings to other conditions only makes sense. "Everything we do has to do with brain injury," he says. "Whether it's from a head trauma, a stroke, or a tumor, it's still an injury to the brain."

In collaboration with the Pediatric Emergency Care Applied Research Network (PECARN) and the University of Michigan, his lab is looking into the effect of progesterone on younger TBI victims. "There is currently very little that can be done for children with severe brain injuries—that's a wide open field," says Stein. "But we need to make sure if we are working with a powerful developmental hormone it's going to be as safe and effective in kids and not produce any untoward effects. This work is still in very preliminary stages."

Much further along is Stein's research using progesterone to treat stroke victims. When rats were given progesterone after having an induced stroke, they experienced about 70% less brain damage than rats in the control group and had 50% to 60% greater functional recovery. "We did gait scans to check the use of all limbs, a maze to test memory, a grip analysis to test grip, and many other functional assessments," says Fahim Atif, a researcher in Stein's lab. "In all areas, the progesterone rats performed significantly better than the control rats."

In the laboratory, researchers also are investigating the timing of progesterone administration, treating animals up to 24 hours after their stroke. "The only FDA-approved drug for stroke has a very narrow window—it must be given within 3-1/2 hours of the stroke," says Atif. "As a result, less than 5% of the stroke population gets it. And even those 5% are at risk for serious side effects, such as brain hemorrhage. If progesterone proved effective even after a 24-hour delay—as it has in animal models with TBI—it could provide a much safer treat-

ment for many, many more people than is currently available."

Stein and his team of research scientists hope to wrap up the preclinical work and move the stroke study into human trials in the near future. "Progesterone promises to have an even more profound influence on stroke than it has on TBI," says Stein.

Stein's lab is having even more success in improving outcomes in animal models of trauma and stroke when progesterone is combined with vitamin D. "Vitamin D is actually a hormone, like progesterone, and it acts on many different biochemical pathways, like progesterone," says Stein. "We started working with vitamin D hormone at the urging of Mahlon DeLong, the former chair of neurology here at Emory. It turns out that both the very young and the elderly often suffer from vitamin D deficiency and this can impair the processes of healing after traumatic brain injury or stroke. When used in combination, the two hormones work better than either does alone. In a study we just published, there was significantly less brain damage and more functional recovery in stroke-induced rats that got progesterone and vitamin D in combination than in rats that got progesterone or vitamin D alone."

Another area of research was stumbled upon serendipitously. When working on a project to develop a synthetic version of progesterone that might be more effective in treating brain injury than the native form of the hormone, Atif happened to use tumor cells in his testing. As a part of the screening process, he found that high doses of progesterone were toxic to the cells. "At first I was sure I did something wrong, so I repeated about 10 more times and got the same result each time," says Atif. Subsequent research confirmed his findings. Mice treated with high-dose progesterone had a 50% reduction in neuroblastoma tumor size after only eight days. The hormone induced cell death and inhibited vascular growth. "We published this work last year in the journal *Molecular Medicine,* and we are very encouraged by the findings," says Atif. "Especially since every chemotherapy drug has severe side effects and progesterone appears to have none. It specifically kills the cancer cells but is absolutely safe for healthy, normal cells. We are now testing it with other types of brain tumors, such as glioblastoma and astrocytoma."

"Everything we do has to do with brain injury, whether it's from a head trauma, a stroke, or a tumor, it's still an injury to the brain."
–Don Stein

Finally, Stein's lab is working with the Department of Chemistry and the laboratory group of Dennis Liotta, the Samuel Candler Dobbs Professor of Chemistry, to modify progesterone to make it viable for use in the field, particularly in combat situations. "In a military situation, if you can help it, you don't want to have to start an IV and keep it going," says Stein. "You want something that you can get in quickly and easily, that can be used in all conditions, from -40 degrees to 120 degrees, that is highly stable so you don't need to replace it every two weeks, and that lasts in the system until you can get the injured person to a hospital. And that's what we're trying to develop."

It's hard to overstate the impact Stein's work will have if the phase 3 trial shows progesterone's efficacy in treating TBI. "Others have said if this works, it will dramatically change emergency care and treatment of brain injury, and that it could become standard of care around the world," says Stein. "But the real beauty is that progesterone is really cheap, it's easy to administer, and it doesn't require high technology. So you can't get away with charging vast amounts of money for it, and there's no reason it couldn't be available all over the world." **EM**

Class Notes | alumni news

Oliver Thomas Guertsen to Leslie Choy-Hee 91Ox 93C 97M 01MR

Wesley Donald to Clay Chappell 04M 11FM and Tresa Chappell 98Ox 00C 04M

Janet Witte 01M 02PH to John Hopkins

Kelly Healy 00C 05M

1980s

Gulshan Harjee 82M 85MR received the 2012 Jack Raines Humanitarian Award from the Medical Association of Georgia. She has conducted health fairs for the uninsured for the past seven years and established scholarship programs for high school and college students. She is president of First Medical Care in Decatur, Ga.

Thomas Pearson 82M 88MR was appointed executive director of the Emory Transplant Center. He is surgical director of the kidney and pancreas transplant program at Emory Healthcare and the Livingston Professor of Surgery in the medical school.

Mark Furman 83C 87M 12B was named a consultant at the Spencer Stuart executive search firm in Boston.

1990s

Scott Swygert 92M was named chief quality officer and chief medical information officer for Lakeland Regional Health Systems in Lakeland, Fla.

BORN: Oliver Thomas Guertsen on April 24, 2012, to **Leslie Choy-Hee 91Ox 93C 97M 01MR** and her husband, Kevin. She is an obstetric hospitalist at Wellstar Cobb Hospital.

2000s

MARRIED: Janet Witte 01M 02PH to John Hopkins in February 2011. She is a psychiatrist in private practice and conducts depression research at Massachusetts General Hospital.

BORN: Wesley Donald to **Clay Chappell 04M 11FM** and **Tresa Chappell 98Ox 00C 04M** on Nov. 9, 2012. He is an interventional cardiologist in Athens, Ga., and she is a pediatrician.

Kelly Healy 00C 05M 06MR 10MR was named an assistant professor of urology at Thomas Jefferson University in Philadelphia.

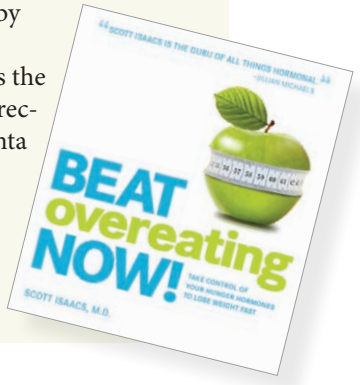
BORN: Rani Paige to **Padmashree Chaudhury Woodham 01C 05M 09MR** and her husband, Daron, on Oct. 23, 2012. Woodham recently joined Mercer University and the Medical Center of Central Georgia in Macon, Ga., as the director of maternal-fetal medicine.

Shveta Shah 02C 07B 07M and **Dinesh Shah 00C 07G 07M** have returned to Atlanta, and both are at the Gwinnett Clinic in Johns Creek, Ga. Shveta is an internist, and Dinesh is a neurologist. The couple has two young children.

A new prescription for diet

Scott Isaacs 89C 93M 98MR

Scott Isaacs 89C 93M 98MR, of Atlanta, recently had his book, *Beat Overeating Now! Take Control of Your Hunger Hormones to Lose Weight Fast*, published by Fairwinds Press. He is the medical director of Atlanta Endocrine Associates.



Class Notes | alumni news

Padmashree Chaudhury Woodham 01C 05M 09MR

Shveta Shah 02C 07B 07M

Dinesh Shah 00C 07G 07M

Lauren Hall 03C 08M 11MR

Lauren Hall 03C 08M 11MR is a Global Health Corps pediatrician in Swaziland with the Baylor International Pediatric AIDS Initiative at Texas Children's Hospital.

Residency Notes

Naureen Adam (anesthesiology) has joined the Atlanta office of Interventional Spine & Pain Management.

Jennifer Cranny (radiology) was named the on-site medical director at East Cooper Medical Center in Mount Pleasant, S.C.

Paul Fedalen (surgery-cardiovascular) recently joined Bayhealth Cardiovascular Surgical Associates in Dover, Del.

Susan Jones (internal medicine) has joined the Memorial Medical Group, the largest physician group in southwest Louisiana.

Kerry Ressler (psychiatry) was elected to the Institute of Medicine. He is on the medical faculty at Emory.

Richard Weil (pediatrics) was reappointed to the Georgia Composite Medical Board by Gov. Nathan Deal. He is chief of pediatrics at Piedmont Hospital.

Nanette Wenger (cardiology) was named a master of the American Association of Cardiovascular and Pulmonary Rehabilitation. She is on the medical faculty at Emory.

Deaths

1940s

Herbert Arnold 43C 45M 49MR, of Tuscaloosa, Ala., on Nov. 27, 2012. He was 90. He is survived by his wife of 66 years, Nell, three children, five grandchildren, and two great-grandchildren.

1950s

Duncan Farris 49C 51M 55MR, of Gainesville, Ga., on Oct. 7, 2012. He practiced obstetrics and gynecology for 23 years in Waycross, Ga. He is survived by his wife, Rachel, three children, five grandchildren, and a great-granddaughter.

Ted Staton 50C 53M 57MR, of Decatur, Ga., on Sept. 17, 2012. He was a urological surgeon.

Davis Boling 49C 54M 56MR, of Tampa, Fla., on Aug. 5, 2012, of cancer. He met his wife of 57 years, Marjorie, at Emory, where she served as the administrative assistant to the dean of the medical school. They moved to Tampa, where he was an orthopaedic surgeon for 40 years. In addition to his wife, he is also survived by five children and 12 grandchildren.

Prentis Huff 49Ox 50C 52G 55M 60MR, of Atlanta, on July 1, 2012. He is survived by his wife, Dorothy, two daughters, and five grandchildren.

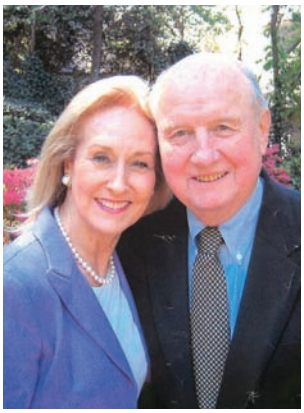
Lawrence Brannon 53C 56M 57MR, of Atlanta, on Nov. 22, 2012. He practiced psychiatry for 45 years and specialized in alcohol and drug addiction. He is survived by five children, 15 grandchildren, and five great-grandchildren.

Earle Toler 52C 56M, of East Point, Ga., on Aug. 4, 2012. He is survived by his wife, Jackie, and two children.

Charles Finney 56C 59M 60MR 80B, of Albany, Ga., on Aug. 11, 2012. He was an ophthalmologist before starting a pecan farm. He also owned two radio stations in Albany. He is survived by his wife, Charlie, four children, eight grandchildren, and two great-grandchildren.

Deaths | alumni news

Davis Boling 49C 54M 56MR



William Weatherly 55C 59M 66MR

Margaret Ann Gangarosa 74C 82M 86MR

Bernard Hochberg 59M, of Tampa, Fla., on Oct. 14, 2012. He was 77. He was born in Sokolow, Poland, and at the onset of WWII, his family fled to Russia. They were forcibly relocated to Siberia and then to Uzbekistan. After the war, they reunited with family in France and stayed in Paris for several years before being allowed to immigrate to the United States. They arrived in 1949 aboard the ocean liner Mauretania. Hochberg continued to celebrate his personal holiday, "Mauretania Day," each year. In 1970 he joined St. Joseph's Hospital as a urologist. He is survived by his wife, Moira, four sons, and five grandchildren.

William Weatherly 55C 59M 66MR, of Atlanta, on Aug. 5, 2012. He was 79. He was a psychiatrist for more than 40 years before retiring in 2009. He served as a clinical professor at Emory. He is survived by his wife, Jody, and four children.

1960s

Frank Pittman 60M 61MR, of Atlanta, on Nov. 24, 2012, of cancer. He was a psychiatrist in private practice, a clinic assistant professor at Emory, and a consultant at the Clayton County Mental Health Center. He is survived by his wife, Elizabeth, three children, and seven grandchildren. A prolific writer, Pittman wrote frequently about marriage and family relationships.

Martin Reeves 63M 69MR, of Suwanee, Ga., on June 22, 2012. He was 73. He is survived by his daughter and three grandchildren.

Frank Schuler 68M 73MR, of Newport News, Va., on Oct. 6, 2012. He practiced plastic surgery for more than 40 years. He is survived by his wife, Sandra, four children, and two grandchildren.

1970s

Render Nesmith 68C 73M, of Inglewood, Calif., on Feb. 23, 2012. He was 65.

1980s

Margaret Ann Gangarosa 74C 82M 86MR, of Brookville, Fla., on Oct. 25, 2012, of metastatic renal cancer. She was 59 and had served as a pathologist for 28 years. She was preceded in death by her husband, John Pullin. She is survived by her parents and three brothers.

Residency Deaths

John Gilligan (ophthalmology) of Alexandria, Va., on April 10, 2012. He was preceded in death by his wife, Barbara, and his oldest son, John, and is survived by four children and six grandchildren.

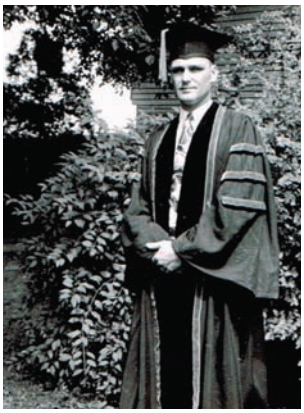
William Holloway (surgery), of Greenwood, S.C., on Sept. 11, 2012. He was 74. He was a vascular surgeon and opened the first accredited vascular center in South Carolina, the Carolina Vascular Institute at Self Regional Medical Center.

George Long (obstetrics and gynecology), of Atlanta, on Nov. 15, 2012. Long had idolized his father, a doctor who was the grand-nephew of physician Crawford W. Long, and had always said that he knew even as a small boy that he would follow in his father's footsteps and become a doctor. Seven days after his own father's funeral service, Long died of a suspected heart attack. He was 56. He is survived by his wife, Debbie, and three children.

Isabel Ochsner (emergency medicine), of New Orleans, on Nov. 6, 2012, of pancreatic cancer. She was 56. She is survived by three sisters.

Mason Robertson (internal medicine), of Augusta, Ga., on July 20, 2012. He moved to Savannah, Ga., in 1958 and practiced there for 25 years. He and his wife, Mary, were active in desegregation efforts in Savannah, participating in lunch counter sit-ins. His medical practice also was desegregated at a

Deaths | alumni news



Mason Robertson

Warren Sarrell

time when many were not. In 1987 he received the NAACP Freedom Award. He also helped establish the first sickle cell anemia clinic in Savannah. He retired in 1984 due to the effects of Parkinson's disease. In 2008, he and his late wife received the W. W. Law Award from the Economic Opportunity Authority of Savannah for their civil rights efforts. He was preceded in death by his wife, Mary, and is survived by three children and five grandchildren.

Warren Sarrell (cardiology) of Anniston, Ala., on Sept. 27, 2012, of bone marrow cancer. He was 87. He was instrumental in establishing the Sarrell Dental Clinic, which now has 14 facilities across Alabama and is the main provider of dental care for children on Medicaid. He is survived by his wife, Lela, six children, and 14 grandchildren.

Stanley Shapiro (surgery-otolaryngology), of Sandy Springs, Ga., on Nov. 18, 2012. He practiced at Wellstar Cobb Hospital and Wellstar Douglas Hospital for 40 years. He is survived by his wife, Alice, and two children.

Faculty Deaths

Hugh Randall 69Ox 71C 75M 79MR, of Crossville, Tenn., on July 1, 2012. He was 63. He joined the Emory gynecology/obstetrics faculty in 1979 and served at Grady. He also served on the faculties of New York University and Lincoln Memorial-DeBusk College of Osteopathic Medicine. He is survived by his wife, Sandra, and two daughters.

Have a plan.

Kamal Mansour 68MR began his career in 1966 as chief resident in cardiothoracic surgery at Emory University Hospital. An international pioneer of lifesaving techniques, he has shared his passion for medicine with thousands of students, faculty members, and patients for 47 years now. His residents dubbed him “the Tasmanian devil” for his speed in surgery and “the professor” for his devotion to teaching. Now Mansour is making an endless contribution to thoracic surgery at Emory: He and his wife, Cleo, have established the Kamal A. Mansour Professorship through a provision in their wills.

Plan to say thank you.

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CONGRATULATIONS TO OUR INAUGURAL CLASS

1st Row (l-r): Kalpana Rengarajan, Emory University; Dave Williams, Georgia Tech; Wendy Wright, Emory University, Emory Healthcare and Children's Healthcare of Atlanta; Jo-Ann House, Emory Transplant Center; Shaneesa Ashford, Emory University; Gukseop Yun; Yael Levy, *The Times of Israel;* L'Bertrice Hopson, P.E.N. Television Inc.; Thanicia Childs, Emory University. **2nd Row:** Tye Tavaras; Cindy Mayz, Emory University; Amy Mansfield, Kilpatrick Townsend; Paula Scotman, Emory University; Tarik Johnson; Pam Terry, Emory University; Cyndi Romero, Enercon Services. **Top Row:** John Kosky, Emory University; Octavian Blaga, Tenet; Ed Moseley, Emory University; Mariam Iobidze; John Holmes; Patricia Olinger, Emory University; Steve Nelson; and Adrianne Grubic, CNN.