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WHAT'S INSIDE

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Christian Griffith, an ultra-marathoner from Atlanta, regularly competes in 50- to 100-mile races around the world, but a microscopic parasite nearly brought him down.

Can you identify this deadly amoeba?



Embracing complexity

Where do you go when no one can figure out what's wrong with you?

The Emory Special Diagnostic Services clinic is one of a handful of clinics in the country dedicated to working with patients harboring complex, vexing, and undiagnosed illnesses.

These medical mysteries are tackled by a broad team of experts, from pathologists to neurologists to geneticists, acting as “disease detectives.”



CHRISTIAN LARSEN
Dean, Emory School of Medicine
President, Emory Healthcare
Physicians Group

While Special Diagnostic Services was initially envisioned as a “rare disease clinic,” in practice most of the cases the team encounters are not rare at all, but common illnesses and conditions with atypical symptoms.

By the time patients arrive at the clinic, they have often been through several doctors and are discouraged. These complex cases can confound even the most experienced physicians. Clyde Partin, Emory’s own “Dr. House” who directs the special diagnostic team, calls the process “jousting with diagnostic demons.”

Part of what makes the clinic special is that, instead of traveling from one specialist to another over the course of months or even years, patients can come to one place where

the focus is on them. “Our team devotes as much time as necessary to determine the source of the problem, although a conclusive diagnosis might remain elusive,” says Partin.

Clues emerge from spending time with the patients: asking detailed questions, listening closely, and observing carefully. Modern technology, such as advanced imaging and genomics, can augment the medical history and physical exam, but should never take its place. Asking about patients’ professions, families, where they grew up, what type of stress they have in their lives and how they handle it, is often as illuminating as any CT scan.

While brainstorming with colleagues can lead to creative problem solving, this isn’t something that happens only at Special Diagnostic Services.

Doctors and researchers across our enterprise are solving similar problems daily. They are uncovering rare genetic diseases, ferreting out tropical parasites, researching infectious diseases, helping athletes return to the field, and responding to unexpected trauma (such as pine tree impalement, as featured in this issue’s cover story) in heroic fashion.

Our patients, after all, aren’t “curious medical cases” to be solved but people with loved ones and busy lives to return to.

It is up to us to bring our collective knowledge, professional skills, and medical expertise to bear to help them do just that.



Download our iPad app (search under **Emory Health magazines**). Bonus features are online at emorymedicinemagazine.emory.edu.

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When a pine tree fell on Sylvia Ennis's car as she was driving to work, it was the beginning of a three-year medical journey involving a care team of dozens.

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The Emory Special Diagnostic Services clinic takes on the most challenging and complex cases—and strives to give patients answers about what they have and how to treat it.

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Two of the Stinchcomb's four children have an extremely rare disorder. Emory geneticists were able to give the family a diagnosis and to connect them with others dealing with NGLY1 deficiency.

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“In spite of enormous technological advances, there remains a multitude of patients who suffer the torment of undiagnosed or misdiagnosed disease.” 22

Letters

I am married to a Chastain descendant from Jasper, GA. I recently came across the article “Blessing from a Curse” (*Emory Medicine*, Winter 2016) and was intrigued by the correlation of the Chastain lineage and Alzheimer’s risk. My husband’s family, namely his grandfather and his grandfather’s male siblings, have been affected by Alzheimer’s, with many of them being deceased now from complications. Their children, however, are approaching older age and I would like more information about the Emory testing.

My grandmother, who was a Pierce from Ellijay, also had Alzheimer’s and its effects are felt far and wide, from the family that becomes caretakers and mere strangers to their loved one. It is a heartbreaking illness to say the least, and I witnessed first-hand as an adolescent its devastation. My grandmother’s brother and sister also were diagnosed and passed from complications of Alzheimer’s. If you can provide me with any information about possibly being involved in testing, or if I can provide any kind of family data to Emory on my husband and/or his family’s behalf, I am happy to do so.

Erika Chastain

Jasper, Georgia

I read with interest your “Blessing from a Curse” article (*Emory Medicine*, Winter 2016). My

mother-in-law’s mother, Sarah Isabel Mary Nettie Jane, was a Chastain from near Clayton, Georgia, born in Scaly Mountain, Tennessee, I think. Is she on your Chastain family tree?

Elizabeth Blalock

Emory University School of Medicine, Class of 1970
Waimanalo, Hawaii

EDITOR’S REPLY: We are happy to forward the names of anyone who would like to be involved in the ongoing studies to the Emory Alzheimer’s Disease Research Center.

On a recent trip to Atlanta, and my first visit to Emory University,

I stumbled upon the Winter 2016 *Emory Medicine* publication. When exploring new areas I typically pick up as much local reading material as I can, as I’ve found it is one great way to better understand a community. I read *Emory Medicine* in its entirety and thoroughly enjoyed my time doing so. I was interested to learn about former President Jimmy Carter, in collaboration with his cancer team from Emory, fighting diligently and doing well in his bout with cancer. Since the printing of the publication, President Carter announced that he had a miraculous turnaround and that a recent MRI has not found any cancer at all. The hope is that more and more people receive similar news. Additionally, the cover story, “Invisible Wounds of War” was very compelling. Reading about the support and services Emory provides to many veterans with health issues returning from conflict is encouraging and much needed. I’m looking forward to keeping up with *Emory Medicine* online.

Mike Calevski

Cleveland, Ohio

We like to hear from you. Send us your comments, questions, suggestions, and castigations.

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Find the Winter 2016 issue and more online emorymedicinemagazine.emory.edu

People are talking



“The notion that you can block inflammation and relieve some of the symptoms of depression is really just the tip of the iceberg.”—Dr. Andrew

Miller, Emory psychiatrist, in *STAT* news.



“Women may live 30 to 40 percent of their lives after menopause, and there are preventive measures to optimize their health.”—Dr. Mary

Dolan, on recently becoming one of eight certified menopause practitioners in Georgia.



“The biggest thing I try to tell parents is, ‘You don’t want your child to have to see me.’”—Dr. Lisa Flowers,

who specializes in precancerous conditions and HPV, responds to news that rates are dropping due to vaccinations, on WSB-TV.

Best diet? Just what you'd think—healthy whole foods

Emory Heart and Vascular Center cardiologist Laurence Sperling, president of the American Society for Preventive Cardiology, and a panel of nutrition experts have ranked some of the country's most popular diets. The *U.S. News & World Report's* Best Diets 2016 rankings took into consideration short- and long-term weight loss, ease of following, nutrition, safety, and performance as a diabetes and heart diet.

The DASH diet was named Best Diet Overall, while the new MIND diet came in at second overall, tying with the TLC diet.

"The MIND diet is a healthy, sensible plan supported by science," says Sperling. "It takes two proven diets—DASH and Mediterranean—and promotes foods in each that specifically affect brain health." These foods include green leafy vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine. The MIND diet recommends avoiding foods from five unhealthy groups: red meats, butter and stick margarine, cheeses, pastries and sweets, and fried or fast food.

Sperling offers three key things to remember:

1
Find a diet you can maintain. The more restrictive a diet, the less likely a person can adhere to it long-term. While fad diets or diets very low in fat or very low in carbs have short-term potential benefits, they are difficult to follow over time.

2
Make your diet part of a larger, healthier lifestyle. The word "diet" comes from the Latin word "dieta," which really means a way of life, not just a way of eating. Healthy, well-proportioned eating, walking or physical activity on most days of the week, keeping an ideal body weight—maintaining these behaviors is key throughout your life.

3
Balanced diets focus on healthy fats and healthy proteins. Fruits, vegetables, and low-fat dairy are good choices, as are lots of fish, nuts, seeds, and legumes. Unprocessed carbohydrates can be included in small portions. Then, sparingly, things like sweets, alcohol, and meats.



GETTING OLDER EVERY DAY

Emory is looking for 100,000 adults in Atlanta to take part in a study of something we're all doing, like it or not: aging. The Emory Healthy Aging Study is an online study that aims to learn about aging and age-related diseases such as cardiovascular disease, Alzheimer's disease, cancer, and diabetes. Anyone 18 and older may participate, and the time commitment is minimal—participants are asked to periodically complete an online health history questionnaire and various memory tests. Select individuals will be invited to participate in other, more involved studies. To learn more about the Emory Healthy Aging Study, go to healthyaging.emory.edu. ■

For more information on Best Diets 2016, go to health.usnews.com/best-diet.

You Be the Doctor

CHRISTIAN GRIFFITH, 44, IS AN ULTRA-MARATHONER FROM ATLANTA WHO REGULARLY COMPETES IN 50- TO 100-MILE RACES AROUND THE WORLD. So the Georgia

marathoner, at a more standard 26 miles, should have been a breeze. But he felt horrible afterward, with severe stomach pain, headache, and a low-grade fever.

The next day, Griffith experienced chest pain and had trouble breathing. He feared he was having a heart attack and went to the ER. Doctors made an initial diagnosis of pleurisy, an inflammation of the lining that surrounds the lungs often caused by the flu, and prescribed ibuprofen, but he got no better.

He started having night sweats and his temperature rose to 104. Griffith went to Emory Saint Joseph's Hospital, which ran a battery of tests.

Infectious disease physician Mitchell Blass was called in to consult and discovered that Griffith's left lower abdomen was tender. Blass ordered a CT scan of the area, which showed a mass on his liver as large as a softball.

"It was the largest I've seen in my career and was potentially life-threatening for him," says Blass, a 1992 alumnus of Emory's School of Medicine who completed his residency and fellowship in infectious disease at Emory.

Doctors treated Griffith with broad-spectrum antibiotics, but the mass continued to grow at an alarming rate. The next morning, a follow-up X-ray showed the mass had increased from 8 cm to 14 cm.

Any ideas, careful reader, what the mysterious mass might be? Well, its rapid growth was Blass's first clue that the growth was probably an abscess or infection caused by a parasite: in this case, *Entamoeba histolytica*, the second deadliest parasite in the world next to malaria. About 100,000 people die each year from these parasitic protozoa, which exist in water, soil, and food.

The infection can be asymptomatic (many who have the parasite don't even realize it) or can lead to amoebic dysentery or a liver abscess, as in Griffith's case. His mass, in fact, was in imminent danger of rupturing, so doctors performed emergency surgery. As a catheter drained fluid from his liver, his fever broke.

Griffith believes he got the parasite, which thrives in tropical climates, during a race in Nicaragua.

He and Blass were featured on a recent episode of the Animal Planet television program *Monsters Inside Me*, a series that tells the real-life dramas of people infected by unusual parasites and the doctors that save their lives.

"The experience taught me to follow what I believe to be my own path in life," says Griffith. "No fear. No regrets."

To watch the *Monsters Inside Me* episode: liveforaliving.com/living-blog/christian-griffith-monsters-inside-me



Lung cancer surgery effective even on high-risk patients

Emory cardiothoracic surgeon **Manu Sancheti** wanted to test the notion that patients considered high-risk with early stage lung cancer should be treated only with nonsurgical therapies. So he compared clinical outcomes of high-risk patients with those of standard-risk patients after lung cancer surgery.

The study, which ran in the *Annals of Thoracic Surgery*, concluded that surgical lung resection can be a safe and effective treatment even for high-risk patients with early stage lung cancer.

Previous research suggested that high-risk patients—60 and older, long-term smokers, with other health problems—were more likely to have complications or die after lung surgery. This led to one in five patients with stage I non-small-cell lung cancer being deemed inoperable or high-risk for surgery.

Using Emory data from the Gen-

eral Thoracic Surgery Database of the Society of Thoracic Surgeons, the team identified 310 standard-risk and 180 high-risk patients who underwent surgical resection for early stage lung cancer at Emory from 2009 to 2013.

While average length of hospital stay was one day longer for high-risk patients (five days) compared with standard-risk patients (four days), there was little difference between the two groups in post-operative mortality

(2 percent for high-risk; 1 percent for standard-risk).



Researchers also found that the spread of cancer to the lymph nodes was discovered during surgery in about 20 percent of the high-risk patients—something that would not have been detected and treated with a non-surgical approach.

At three years post-surgery, 59 percent of high-risk and 76 percent of standard-risk patients were still alive. ■



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Volunteering for Clinical Trials Made Easy

Have you ever wanted to volunteer for a clinical trial? Or do you have an illness you feel might benefit from a new, experimental treatment?

A new Emory clinical trials website has easy-to-access information about nearly 1,000 trials currently seeking volunteers.

At **clinicaltrials.emory.edu**, potential participants can search for trials related to specific health conditions, browse topic areas such as cardiology, cancer, or the neurosciences, and view quick facts about each of the individual trials available at Emory.



Winship Cancer Institute researcher Shannon Matulis (left) with Deana Chiusano, who took part in a clinical trial that led to an effective treatment for her multiple myeloma.

Although many clinical trials are seeking patients who have a particular disease, others are seeking healthy volunteers.

Information about each trial includes its purpose, timing, inves-

tigators, process, and key eligibility criteria.

Potential volunteers can click on a link to reach the leader of each trial and send a message asking to participate or requesting more information.

The clinical trials website includes frequently asked questions, additional resources available at Emory, and National Institutes of Health information about clinical trials.

A link to the NIH database—clinicaltrials.gov—has more detailed information.

“Clinical trials are a key part of Emory’s research mission, which helps lead to the approval of new lifesaving medicines, medical devices, and treatment protocols,” says David Stephens, vice president for research in Emory’s Woodruff Health Sciences Center.

“As an academic medical center, Emory stands out in its ability to conduct numerous clinical trials sponsored by both the NIH and by industry.” ■

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Defending against Zika virus

THE ZIKA VIRUS, UNLIKE OTHER MOSQUITO-BORNE VIRUSES LIKE MALARIA, HAS BEEN RELATIVELY UNSTUDIED—UNTIL NOW. That is set to change since Zika, now spreading through Latin America and the Caribbean, has been associated with an alarming rise in babies born with abnormally small heads and brain defects—a condition called microcephaly. “This is a huge public

rash, joint pains, eye inflammation, and fever.

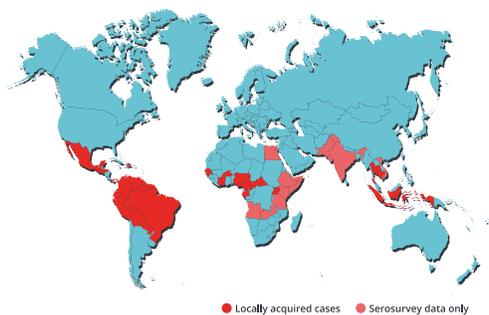
“Zika represents a horrifying illness for women who are pregnant, but for most people, it’s either asymptomatic or mild,” says Professor of Infectious Diseases Phyllis Kozarsky, co-director of Emory’s TravelWell clinic, who says the Aedes mosquito is, unfortunately, a very effective vector. “It’s not like they are just in the swamps, in the rice fields, in the rural areas. These mosquitoes thrive around people.”

Researchers from Emory’s School of Medicine are helping to determine exactly how the Zika virus harms the developing brain. Emory geneticist Peng Jin and colleagues were part of a rapidly assembled team, including scientists from Johns Hopkins and Florida State University, whose research showed the Zika virus can infect neural stem cells critical for brain development. The role of Jin’s lab was to analyze how the patterns of gene activity in neuronal cells were altered by Zika infection.

The Emory Vaccine Center has assembled a team of scientists to study the pathogenesis of the Zika virus and immune responses. “Our current work—growing Zika virus in the laboratory, studying its biology, and eventually working with Zika-infected blood samples—is critical in characterizing the virus for future vaccine development,” says Mehul Suthar, a virologist and assistant professor of pediatrics at Emory.

Also, Drug Innovation Ventures at Emory and Emory Institute for Drug Development have launched efforts, with early support from the Georgia Research Alliance, to identify and develop antivirals to treat Zika virus infection. ■

COUNTRIES WITH EVIDENCE OF ZIKA VIRUS TRANSMISSION



health emergency and horrible on many levels,” says Uriel Kitron, chair of Emory’s Department of Environmental Sciences and an expert in vector-borne diseases, which are transmitted by mosquitoes, ticks, or other organisms. “It appears that this virus may pass through a woman’s placenta and impact her unborn child. That’s about as scary as it gets.”

The Zika outbreak, which also has been linked to increases in the nerve disorder Guillain-Barré syndrome, began in Brazil last spring, with an estimated 500,000 to 1.5 million people infected. Symptoms of the virus may include a

UP TO
1.5
MILLION

**IN THE
WORLD
INFECTED**

ABOUT 1 IN 5 PEOPLE INFECTED
WITH ZIKA VIRUS BECOME ILL



MICROCEPHALY

Voles who console

What happens when a vole is upset? The vole equivalent of a hug.

Prairie voles show an empathy-based consoling response—grooming—when other voles are distressed, found researchers at Yerkes National Primate Research Center. This is the first time consolation behavior has been observed in rodents, which contradicts the belief that empathy is uniquely human.

“Scientists have been reluctant to attribute empathy to animals, often assuming selfish motives,” says study coauthor Frans de Waal, director of Yerkes’ Living Links Center. “These explanations have never worked well for consolation behavior, however, which is why this study is so important.” Coauthors Larry Young, division chief of Behavioral Neuroscience and Psychiatric Disorders at Yerkes, and graduate student James



Burkett demonstrated that oxytocin (a brain chemical responsible for maternal nurturing and social bonding) acts in a specific brain region of prairie voles, the same as in humans,

to promote consoling, which is demonstrated through calming contact directed at a distressed animal. While primates might hug, voles groom the distressed animal. The prairie voles’ consoling behavior was strongest toward familiar voles. ■

Hawks Nest

Emory Healthcare and the Atlanta Hawks plan to build a training and sports medicine center on Executive Park Drive in Brookhaven, which also will serve as the team's official headquarters and practice site. The team expects to break ground this summer on the 90,000-square-foot, privately funded facility.

It will be the first training facility in the NBA to be co-located with a sports medicine center, allowing for



The Atlanta Hawks Basketball Club and Emory Healthcare are partnering on a training and sports medicine center (rendering above) that will offer the latest in preventive and rehabilitative treatments on site and is scheduled to open in late 2017.

expert and immediate treatment and access to equipment such as the 3 Tesla MRI scanner, which provides diagnoses for soft tissue and bone bruise injuries.

Emory will become the official sports medicine provider of the team, offering preventive and rehabilitative treatment and sports perfor-

mance training. Physicians from Emory's current Sports Medicine Center will relocate to Brookhaven, where they will see and treat patients.

"Emory Healthcare has built outstanding orthopaedics services over the past decade, and we are excited to continue to grow this area," says Jon Lewin, president,

CEO, and board chair of Emory Healthcare. "Delivering on-site care will enable us to provide faster care to Hawks players and will enhance our ability to conduct sports performance research and translate what we learn to all athletes, both professional and recreational." ■

THE BIG IDEA Inflammation the culprit?

Individuals with schizophrenia, bipolar disorder, or major depressive disorder appear to have similarly elevated patterns of blood cytokine levels, according to Emory researchers.

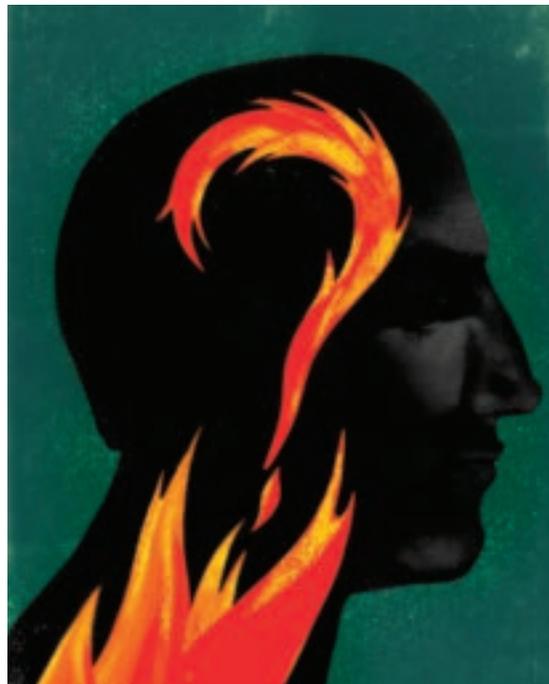
Cytokines are the key signaling molecules of the immune system. The results of the study, the first broad-based analysis of cytokines in all three disorders, were published online in *Molecular Psychiatry*. In reviewing 69 studies of acutely ill patients and 46 studies of chronically ill patients, researchers sought to better understand what was happening in the patients' immune systems.

"We know the immune system is important when looking at psychiatric disorders, but no one had really looked at this by comparing several disorders in one study, or by focusing on the phase of illness," says

David Goldsmith, chief resident for the research track in the Department of Psychiatry and Behavioral Sciences at Emory. The researchers found there were elevated levels of certain

cytokines in acute phases of all the disorders and some commonality in the chronic phase. For example, one inflammatory cytokine, interleukin-6, was found to be elevated in all three disorders in both acute and chronic phases of illness.

By comparing these levels across diseases, the researchers were able to determine that the immune system is likely involved in psychiatric disorders for some patients and that treatment options may need to be more personalized. "Ultimately these findings call for a need for more studies to determine exactly which individuals might benefit most from anti-inflammatory drugs," says Goldsmith. ■



Lewin named new Executive VP for Health Affairs



Jon Lewin's father was a general practitioner who often spent evenings delivering babies or making house calls for sick patients. "I thought everyone's father gave them their shots," says Lewin, who liked computers, technology, and science.

He worked as a scrub tech during college, built a CO2 laser for the Diebold lab at Brown University as an undergraduate, and began thinking about how medicine and technology were going to become ever more intertwined. "I am always attracted to the innovative edge, to whatever people at the time think is impossible," he says.

At Yale School of Medicine, Lewin focused on radiology and imaging. "When I left, they didn't even have an MRI at Yale. At Case Western, there were two, and it was fun stuff—physics, technology, and engineering." He took a fellowship in magnetic resonance research in West Germany in 1989, where he helped take a chunk out of the Berlin wall. Following his passions of radiology and advanced imaging technologies, he went on to Case Western and then Johns Hopkins, redesigning MRI technologies

along the way and collecting 25-plus patents. He also gained experience in administration, strategic planning, and health care integration. "We dealt with many of the same issues we're dealing with here at Emory," he says.

Now a few months into his role as a leader of both the Woodruff Health Sciences Center and Emory Healthcare, Lewin is excited about the possibilities. "This is an unbelievable organization in a lot of ways," he says, "As I've walked around, listening and observing, I have been continually reminded of the remarkable number of talented and dedicated individuals that make up the Emory health sciences community."

Transparency, integrity, and authenticity are core cultural values to him, he says, and patient welfare "should always come first. All patients and their families

should be treated like VIPs."

Lewin has adopted a new personal communications strategy: Tweeting. "With around 24,000 individuals contributing to

our clinical, educational, discovery, and community service missions," he says, "it's a daunting task to ensure that people get to know me, my aspirations for the institution, and my appreciation for all the great work being done here. Twitter is a wonderful mechanism for getting the word out."

He enjoys playing the saxophone and prefers "cool jazz" by the greats—Davis, Mulligan, Monk. His wife, Linda, is a pediatrician, daughter, Sarah, a science writer, and son, Ben, a computer science major at Tufts. "The thrill of finding creative solutions to complex problems is what interests me," Lewin says. "Whether the problem is research, clinical, or business, what matters is the level of complexity, and the challenge in figuring out the solution." ■

"I have never enjoyed the middle of an island of knowledge, but the periphery—off into the unknown."

CV HIGHLIGHTS

- Current executive vice president for health affairs, executive director of the Woodruff Health Sciences Center, and president, CEO, and chair of the Board of Directors of Emory Healthcare.
- Former senior vice president for integrated health care delivery and co-chair for strategic planning for Johns Hopkins Medicine; professor and chair of the Morgan Department of Radiology and Radiological Science.
- Bachelor's in chemistry, Brown (1981); medical degree, Yale (1985); internship in pediatrics, Yale-New Haven hospital; residency in diagnostic radiology at University Hospitals; neuroradiology fellowship at Cleveland Clinic.
- Fellow, International Society for Magnetic Resonance in Medicine and the American College of Radiology; president, Society of Chairs of Academic Radiology Departments; past president, American Roentgen Ray Society; past president, International Society for Strategic Studies in Radiology.
- Pioneer in interventional and intra-operative magnetic resonance imaging, with more than 25 patents. ■

‘Food deserts’ lead to host of health problems

Cardiologist Heval Mohamed Kelli found that Atlantans living in low-income areas distant from access to healthy foods—“food deserts” where the nearest supermarket was a mile or more away—were more likely to have hypertension or hyperlipidemia, smoke, be obese, and have higher levels of systemic inflammatory markers and stiffer arteries. Kelli’s research was conducted through the Emory Clinical Cardiovascular Research Institute, using information on 712 community participants from the META-Health study and 709 Emory and Georgia Tech employees from the Predictive Health study.

“Neighborhood characteristics that affect availability of healthy foods contribute to an increased risk of cardiovascular disease beyond their effects on traditional risk factors,” Kelli says. ■



Diabetes numbers quadruple worldwide

The number of people with diabetes around the globe has increased four-fold since 1980, according to new research. The comprehensive study, published in *The Lancet*, found that, after adjusting for the influence of aging, the proportion of men with diabetes has more than doubled—from 4.3 percent in 1980 to 9 percent in 2014. Diabetes among women during the same period rose from 5 percent to 7.9 percent. With the growth in the size of populations worldwide, this means that the absolute number of people with diabetes has almost quadrupled to 422 million adults, up from 108 million in 1980.

Emory researchers collaborated with the study leaders at Imperial College London, the Harvard T.H. Chan School of Public Health, and the World Health Organization to compile data from 751 surveys and 4.4 million adults.

“The growth and sheer number of people affected has major implications for health care, health expenditures, and health systems worldwide,” says Mohammed Ali, associate professor at Emory’s Global Diabetes Research Center and one of the study’s authors. “Diabetes is a chronic condition requiring lifelong care, attention to lifestyle choices, and adherence to medications, and these are challenging and costly to maintain.” ■

Unexpected Payoffs from a Bacterial Immune System

The tale of how a bacterial defense system against viruses became one of the most promising new platforms for genetic engineering and biotechnology also highlights the importance of basic research.

In 1987, researchers studying an enzyme that keeps intestinal bacteria like *Salmonella* out of the bloodstream discovered a curious set of segments of DNA containing short repetitions of base sequences, which they called CRISPR. Each repetition was followed by a “spacer DNA” segment from previous exposures

to a bacterial virus or plasmid, which gave the bacteria “immunity” to that virus by allowing it to recognize and target this foreign intruder. Researchers began to investigate how to harness CRISPR’s power to “edit” DNA in animals, plants, and even human cells. Emory microbiologist David Weiss has taken that a step further—to affecting RNA.

Of the numerous types of CRISPR, Type II is the one that especially interests researchers such as Weiss. It requires only the action of RNA segments and one CRISPR associated protein, Cas9,

making it significantly easier to use than the other types, which require multiple proteins. “We found Cas9 in our screen way before we understood what it did,” says Weiss, associate professor of infectious disease and a researcher at Yerkes National Primate Research Center. “When we pursued it, we found it knocks down the expression of specific RNA.”

Like the search function in a word processing

program, Cas9 can be guided to specific locations within a complex genome by a short RNA search string.

“We can envision using Cas9-based technology to prevent viral infections in transgenic animals and plants,” Weiss says. “We could also re-engineer Cas9 to target RNA in human or other mammalian cells.” ■



New anti-rejection drug for kidney recipients shows better survival rates



Transplant surgeon and School of Medicine Dean Christian Larsen (left) and Emory Transplant Center Executive Director Thomas Pearson helped develop belatacept.

Kidney transplant recipients must take medications to prevent their immune systems from rejecting their new organs. But long-term use of calcineurin inhibitors (CNIs), the immunosuppressants most transplant patients have relied on for nearly 20 years, can damage the transplanted kidneys and lead to cardiovascular disease and diabetes.

A seven-year, multi-center study of kidney transplant recipients has shown for the first time that an alternative drug, belatacept, which controls the immune system and prevents graft rejection, has a significantly better record of patient and organ survival than CNIs.

Transplant surgeon Christian Larsen, dean of Emory School of Medicine, and Emory Transplant Center executive director Thomas Pearson played key roles in developing belatacept, which is produced by Bristol Myers Squibb and was approved by the FDA in 2011.

Results from the worldwide study, led by Larsen and UCSF kidney transplant surgeon Flavio Vincenti, were published in January in the *New England Journal of Medicine*.

The average life span of the recipient of a deceased donor kidney—the most common type—is eight to 12 years. The risk of death or loss of the transplanted kidney after seven years was about 13 percent for belatacept, compared with 22 percent for cyclosporine A.

“While the best uses of belatacept still need additional definition, these results indicate that using belatacept as standard of care has the potential to improve long-term outcomes,” says Larsen. ■



President Wagner retiring after 13 years

Come the end of August, James W. Wagner will retire as president of Emory.

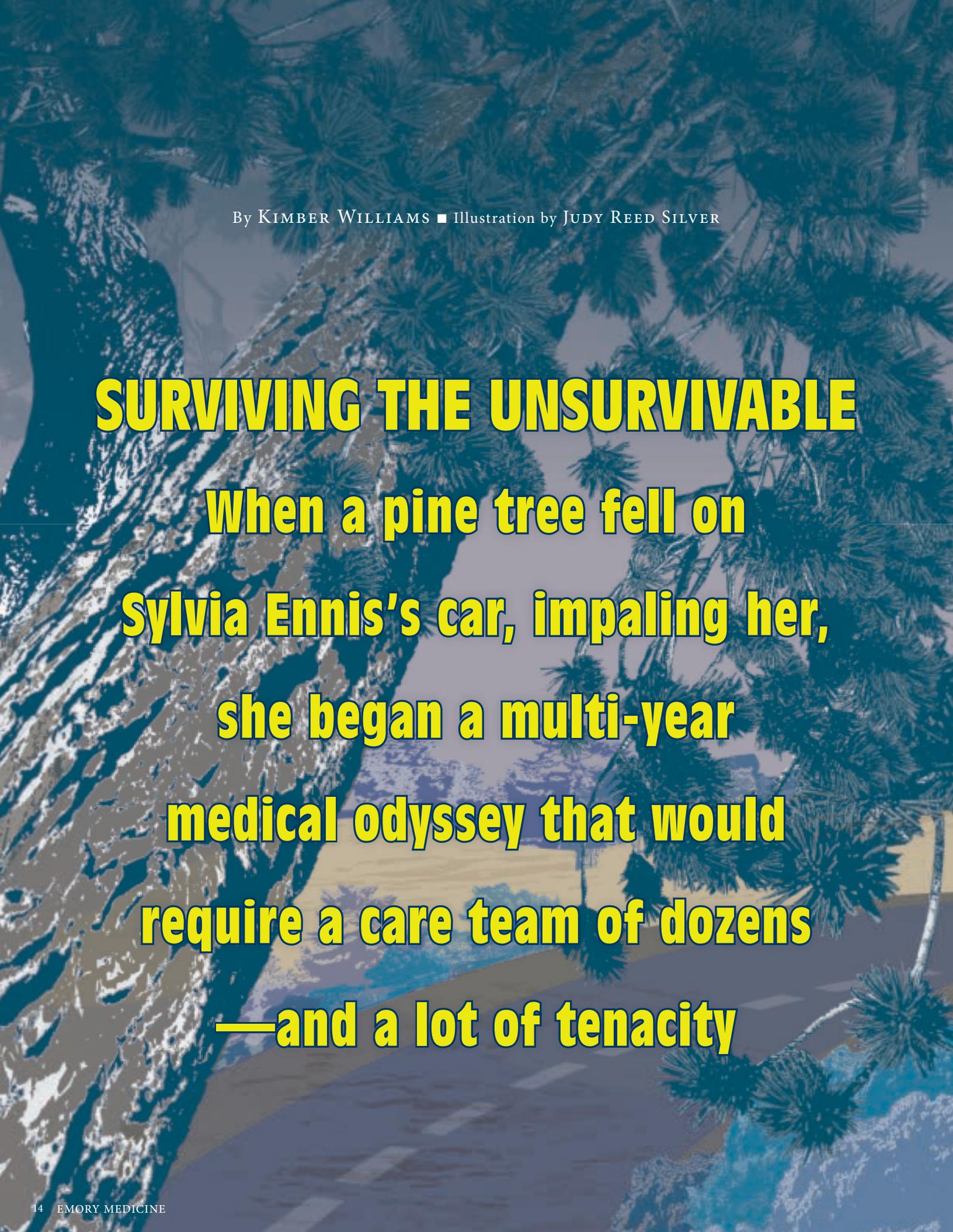
A national search is under way to fill the position he has held since 2003. During his presidency, Wagner set in motion a campus-wide initiative to develop a clear vision statement, resulting in a 10-year strategic plan to strengthen the university at all levels. He also led a \$1.7 billion fund-raising campaign, the largest university campaign in Georgia history. Wagner has worked to enhance the educational experience of students, grow

“The Emory [community] ... has demonstrated the power for positive transformation that is inherent in research universities.”

research, and foster more effective partnerships among universities, government, and industry.

He spoke often of Emory’s intent to have a positive impact on the world. One of many examples of this during his tenure was when Emory University Hospital accepted and successfully treated four patients with the Ebola virus. “Emory’s mission is to create, preserve, teach, and apply knowledge in the service of humanity. In that sense, the team making decisions about these special patients was acting on a deeply held and broadly understood commitment,” Wagner said. “In the end, our physicians, nurses, staff, and communications professionals not only earned the gratitude of patients and their families, they also demonstrated the power for positive transformation that is inherent in research universities.”

At a “block party” for Jim and Debbie Wagner on April 21 in Asbury Circle, Emory students, faculty, and staff gathered to eat hot dogs, chips, and ice cream beneath bobbing blue and white balloons while a band played. To join in the community-wide farewell, write a note to the Wagners at emory-university.wagner.sgizmo.com/s3/. ■



By KIMBER WILLIAMS ■ Illustration by JUDY REED SILVER

SURVIVING THE UNSURVIVABLE

**When a pine tree fell on
Sylvia Ennis's car, impaling her,
she began a multi-year
medical odyssey that would
require a care team of dozens
—and a lot of tenacity**

THE MORNING OF JAN. 2, 2013, DAWNED UNREMARKABLY ACROSS ATLANTA—COOL AND OVERCAST, WITH A LEADEN SKY THAT HINTED OF RAIN.

Weak winter light threaded through the treetops that tower over Clifton Road as Sylvia Ennis wound her way to work on a pleasant, woody route just south of the Emory campus, past vintage brick homes, tidy lawns, and dense foliage that changed with the seasons.

Normally, Ennis wouldn't have been heading back to campus so soon after the holidays. But it was the start day for a new hire, and they had arranged to meet at the Neonatology Division of the Department of Pediatrics at Emory School of Medicine, where Ennis was a clinical business manager.

As her Toyota Corolla spun along Clifton Road, Ennis mentally primed herself for the workweek. Wearing a new gray suit and earrings, a pretty blue blouse, and her favorite boots, she felt sharp and prepared, ready to meet the day. Despite the gloomy weather, her thoughts spooled happily among the tasks that lay ahead and the excitement of an upcoming trip, a long-awaited Caribbean cruise with friends in early February to celebrate her 50th birthday.

Altogether a routine morning—until, abruptly, it wasn't.

Ennis never heard the tree coming down, only its deafening arrival atop her sedan, an instantaneous explosion of crushed steel, shattered glass, and sudden, enveloping darkness.

The loblolly pine was more than 100 feet tall, a towering reminder of a time when dense woodland patches rose over much of North Georgia. Its trunk was so stout it would have

taken the arms of two people to encircle it.

Falling from the opposite side of the street, the tree landed diagonally upon Ennis's car, stretching from the left front bumper across the front passenger's seat, where it fully collapsed that side of the roof.

Through a haze, Ennis struggled to absorb a landscape

suddenly turned bizarre and nonsensical. She saw the damage around her before she fully understood it, and felt her senses awaken in staggered waves. The tree's trunk had landed inches to her left, trapping her in the only part of the car that hadn't been flattened. Peering through a fractured windshield Ennis could make out a wall of dark, mossy bark and a dense tangle of pine needles and branches, which enveloped her like a prickly cocoon.

Glancing down, what she saw didn't make sense—a tree limb the size of a fence post protruded from her abdomen. A good six inches in diameter, the jagged branch had speared through the windshield and the steering wheel before striking Ennis. Oddly, she didn't see a drop of blood.

Shivering and in shock, she knew only that she was cold, conscious,

breathing, alive. Her thoughts immediately flashed to her son, Dayvon, and grandson, Nasir. Ennis realized she wasn't going to live through the day. There was no surviving this. Closing her eyes, she prayed that they would be able to find peace without her.

Through a jumble of pine needles and dark branches, a man's face appeared at her window. Ennis didn't understand. Am I already in heaven? Is this an angel?

"Are you okay? Can I call somebody?" the passerby shouted.



Sylvia Ennis went through more than 15 surgeries over three years after being impaled by a pine tree branch.

AT 8:47 A.M., THE CALL CAME TO DEKALB COUNTY FIRE AND RESCUE STATION ONE.

Tree on vehicle. Possible entrapment. 1183 Clifton Road.

Seven minutes later, Engine One arrived to find the road completely blocked by a toppled pine. Upended, the tree's exposed root system stretched skyward, taller than a person. "We'd had rain the night before. It was as if the ground just gave out," recalls firefighter and paramedic Matt Robison, among the first responders at the scene. "Basically, the tree had swallowed the car."

Complicating the rescue, the tree had snapped a power pole. Electrical lines snaked atop Ennis's car; no one knew if they were hot. As some responders began crawling between branches toward the vehicle, others grabbed chainsaws.

Captain Jeff Goins was already in the field that morning, wrapping up an earlier call with Station One's HazMat team a few blocks away when they heard the call and responded. Two employees from Georgia Power also happened to be in the area and rushed to the scene to confirm that the downed line was dead—critical information that saved precious time, notes Goins, who began directing extrication even as other units arrived.

Reaching Ennis, rescue workers found her stunned but conscious, quietly studying the five-foot branch that had speared through her windshield and appeared to be jammed up against her abdomen, effectively pinning her to the seat. It wasn't until Station One HazMat team member Samuel Payton Owens slid behind the driver's seat that he fully realized what they were seeing. The branch had passed right through Ennis—entering her lower left abdomen, exiting her right buttock, and coming to rest on the floor of the backseat.

Owens asked Ennis for her name, and how she was feeling. "A tree just fell on my car," she reported calmly.

"This is going to sound crazy," he told her, "but you have a tree limb all the way through your body, and we're going to take care of you."

For fire and rescue crews, reports of impalements aren't uncommon. "You'll occasionally see a pencil, a knife, a fencepost—things usually resulting from people being ejected from a car, jumping from a building, or running from the police," Goins says. "This was different."

As a frenzy of brush-cutting growled to life outside the car, Owens sat in the backseat with his arms wrapped around Ennis, an embrace intended to comfort and stabilize her.

Before Ennis could be removed, two cuts had to be made: One outside, to separate the branch from the tree trunk, and another inside the car, between Ennis and the steering wheel, to shorten the branch and permit extrication. She would need to be moved with the branch still within her.

"Impalements typically act as a cork," Goins says. "When that tree went in, it just stopped the bleeding—the tree took up all the space. Blood is going to circulate everywhere else.

The minute you pull the tree limb, she's bleeding out."

With the car doors and the roof removed, the team moved to assess Ennis's vital signs, which, surprisingly, were fairly stable.

Grabbing a Sawzall reciprocating saw, HazMat team member Carey Patton stood on the hood of the car and began cutting the branch from the tree trunk. But the vibrations caused Ennis to moan softly, the only sound of distress she ever made, Owens recalls. They immediately switched to a smoother-running chainsaw.

Work inside the vehicle was trickier. First, they wedged cribbing—large plastic blocks—between Ennis and the steering wheel. If the chainsaw slipped, or the branch gave way, it would offer support and protection. Using a sheet to shield Ennis from flying sawdust, rescue workers began trimming the branch just inches from her face.

It was delicate work. The airbag, which had not deployed, could go off at any moment.

For first responders, the goal of most trauma calls is straightforward: plug holes, start fluids, and get your patient on a surgeon's table, fast. Since the tree branch had to remain in place, EMT Jeanine Fannell worked around it to insert an IV line in Ennis's arm and begin pushing fluids, a routine protocol that would have a big payoff down the line.

Ennis was eased from the car, branch intact, and carefully placed on her side onto a transfer board. In the ambulance, blankets were wedged against her to secure her position.

By 9:18 a.m., she was on her way to Grady Hospital's Marcus Trauma Center, among the busiest Level 1 trauma centers in the country.

AT GRADY, TRAUMA SURGEON OMAR DANNER WAS COMPLETING MORNING ROUNDS WITH NURSE PRACTITIONER LEXI FREDERICK WHEN HE RECEIVED A PAGE FROM THE DISPATCH CENTER DESCRIBING SOMEONE IN ACUTE SHOCK: A 49-YEAR-OLD WOMAN IMPALED BY A TREE. TACHYCARDIC HEART RATE. FALLING BLOOD PRESSURE...

They both thought it had to be a trauma drill.

Reporting to the trauma bay, Danner found an ocean of blue and green scrubs—emergency medicine and surgical trauma team members, all awaiting Ennis.

When the EMTs rolled her in, Ennis lay on her side, the tree branch protruding from her torso almost as if she had been harpooned, thought Danner.

Her blood pressure was plummeting. When trauma nurses attempted to draw blood, there was nothing to extract—a sign of near-total circulatory collapse. Attaching a unit of blood to the existing field IV, they sped toward Trauma Room One, an operating room reserved for the most critically injured patients.



CARE TEAM | Trauma surgeon Omar Danner was the first doctor to encounter Sylvia Ennis in Grady's trauma bay after the accident; Chief of Urology Jeff Carney would ultimately reconstruct her ureter, reconnecting it to her bladder.

Without a detectable blood pressure, Ennis was clearly in extremis—deep shock—and likely about to die. The call went out for all hands on deck.

Danner, associate professor at Morehouse School of Medicine, recalls thinking that this was the moment when all of his years of medical school and residencies and emergency room experience would be put to the test.

News of the case, which resembled an episode of “Untold Stories from the ER,” traveled fast, from cardiovascular and orthopedic specialists to neurology, urology, anesthesiology, and emergency nursing staff.

Sheryl Gabram, Grady surgeon-in-chief and professor of surgery at Emory, and surgeon Ed Childs, chair and professor for trauma and critical care at Morehouse, were also notified of the unusual case, along with former Grady trauma medical director and fellow trauma surgeon Jeffrey Nichols.

“Needless to say, by the time we got there, she had an audience,” Danner says.

Level 1 trauma care is a team endeavor, each patient’s treatment a complicated choreography requiring many hands, from first responders to surgical specialists to critical care nurses.

“Because of the uniqueness of the injury, there was no routine protocol, no best-practices handbook on removing tree branches,” Danner says.

Two beds were shoved together to accommodate both the patient and the protruding branch, and Ennis was intubated and sedated. Ravi Rajani, assistant professor of vascular surgery at Emory and director of vascular and endovascular surgery at Grady, ordered an X-ray of the arteries of her pelvis and abdomen.

The arteriogram showed vessels that were somehow intact, Danner says.

“We were relieved, to say the least,” he says. “There was hope.”

Her major blood vessels were spared. Had they been badly damaged, it would have changed everything. With improving hemodynamics due to the transfusion, focus turned to removing the branch and assessing her internal injuries.

Ennis’s abdomen was prepped for surgery and a sterile plastic drape was placed over the branch. As the team opened her with a midline incision from her xiphoid process to her pelvis, it became evident that the internal damage was extensive.



CARE TEAM | Plastic surgeon Angela Cheng had seen impalements before, but nothing quite like the one suffered by Ennis, which required her abdominal skin to be substantially expanded to cover the gaping wound left by the branch.

The tree limb had breached the abdominal wall and plunged through her pelvis, where it remained firmly lodged. The abdominal muscle and surrounding connective tissue across her lower left side “were basically obliterated,” Danner says.

With Donna Keen, one of Grady’s most experienced trauma nurses and operating room team leader, on hand, the team was ready to try to remove the limb. Using surgical pads for traction, Danner directed chief resident Trey Walker to grasp the branch and pull on his count.

One. Two. Three...

Heaving and hoisting, twisting and turning, Walker pulled the branch forcefully from Ennis’s body, and Danner and Childs hurriedly packed the wound cavity with surgical pads to help control blood flow.

“Do we have blood pressure?” Walker asked.

With a nod from Emory anesthesiologist Gary Margolis, the dressings were removed and Danner began cataloging internal injuries.

Scooping up Ennis’s small intestine with his gloved hands, he found that it had been torn into multiple pieces. He

clamped the remaining ends together to control contamination, meticulously removing bark and debriding dead tissue; later, her small bowel would have to be resected.

Ennis’s colon was intact but badly bruised, turning black and blue before their eyes. Compressed by the branch, her bladder had burst—the entire top of it was missing—and would have to be repaired.

The ureter on the right side of her body, a tube about the diameter of a pencil, had been ripped away from her bladder and was severely crushed.

For Jeff Carney, Grady’s chief of urology and assistant professor at Emory, detached ureters are fairly routine, often the result of gunshot wounds or stabbings. But he had never encountered anything like this.

“At Grady, you never know what’s coming in the door. But this was a once-in-a-lifetime trauma,” says Carney, who would later learn that the accident had occurred less than 200 yards from his own home on Clifton Road.

Since the medical team was unaware that Ennis had previously undergone a hysterectomy, there was initial confusion over the whereabouts of her uterus. Had it been obliterated

by the branch? Pushed out the back of her body along with her seatbelt? Within moments, however, they located the telltale scars signaling that it had been surgically removed.

In all, Ennis had injuries to her ureter, colon and small intestine, stomach muscles and soft tissues, and right buttock. Though her pelvis was fractured, Emory orthopedist Chris Sadlack concluded that it could be managed without surgery.

Despite the deep, dirty wound (her medical team would spend weeks flushing out bits of wood and debris), there was good news. Aside from her small intestine, Ennis was emerging with no major vascular injuries and no life-threatening organ damage.

Danner placed a temporary closure on Ennis's abdomen that would serve as something of a swinging door over the coming weeks, opening and closing for ongoing treatments. The exit wound in her right buttock would be sutured shut.

Finally, Ennis was taken to the ICU for a CT scan and what Danner describes as "aggressive resuscitation" throughout the night. With multiple surgeries anticipated, she would be kept in a medically induced coma for nearly three weeks and would battle sepsis, ventilator-associated pneumonia, and allergic reactions to several antibiotics.

During the month of January, Ennis returned to an operating room nearly a dozen times, where her wound was repeatedly washed out, her bladder and ureter repaired, and her small bowel assessed.

From the start, Danner knew that Ennis would need considerable reconstructive surgery on the jagged hole in her abdominal wall, a focus of her ongoing care. There was so much damage, it was hard to predict how things would turn out.

PLASTIC AND RECONSTRUCTIVE SURGEON ANGELA CHENG HAD SEEN HER FAIR SHARE OF IMPALEMENTS DURING HER TIME AT MEMORIAL HERMANN HOSPITAL IN HOUSTON—PATIENTS GORED BY BULLS AND STABBED WITH SAMURAI SWORDS, RANCHERS RUN THROUGH BY FENCE POSTS.

But Ennis's impalement, an utterly random act of nature, hit home for Cheng, now an assistant professor of surgery at Emory, in a way previous cases hadn't.

"A lot of us work at Emory and drive on Clifton Road," Cheng says. "That could have been me."

When Cheng was brought in for a consult the morning after Ennis arrived at Grady, the priority was clear: Stabilize her and address the most critical injuries.

Cheng's involvement would come later, but her treatment plan would arise from three initial questions: What's missing? How do we replace or reconstruct it? When is the best—and safest—time to do that?

It was clear that Ennis's abdominal muscle was completely blown out. Though her pelvic fracture would not require

surgery, her crushed ureter would eventually need to be reconnected.

It could have been worse. Being impaled by a large, blunt branch, as opposed to a thin, sharp implement, had shoved critical organs aside rather than pierce them.

Due to the multiple resuscitations, Cheng knew that Ennis's abdomen would be profoundly swollen and distended—the result of receiving massive amounts of blood and fluids, which is typical for trauma patients.

Two weeks after the accident, Cheng operated on Ennis, sewing about \$50,000 of Strattice, a biological mesh derived from pigskin, in place across her open abdomen. The mesh essentially served as an internal pair of Spanx—stabilizing her abdomen, holding organs in place, and supporting her breathing. "It's like a piece of leather used to fortify tissue or close hernias," Cheng says.

Closing the gaping wound left by the branch would take time.

Three weeks after the accident, Ennis was taken off the ventilator. Waking from her coma, she opened her eyes to see the face of her son, Dayvon. He looks like he's just had a haircut, she thought, as nurses began to talk with her, assessing possible memory loss or brain damage. At first, Ennis was deeply disoriented. She could name the president, but was uncharacteristically furious about already having been operated on at least 10 times. Her right leg was ablaze with pain. She didn't understand.

"I couldn't do anything," she recalls. "I couldn't walk, I couldn't move, I had to learn everything all over again."

Her family helped piece everything back together for her. Ennis learned that she'd lost a massive amount of blood and had very likely cheated death.

As the swelling in her abdomen receded, Ennis's skin gradually loosened. But Cheng knew that despite a small skin graft, there wasn't going to be enough abdominal skin to cover the wound. She decided to use tissue expanders—essentially, balloons filled with salt water. "Luckily, our abdominal skin is designed for lots of stretching," Cheng says.

The balloons also helped encourage regrowth of skin cells. After the skin on Ennis's stomach expanded an additional 25 to 30 centimeters, Cheng performed another operation to remove the expanders and close the wound. Ongoing physical therapy focused on strengthening Ennis's abdominal wall.

"For the patient, it's not a lot of fun," says Cheng. "But Sylvia had a lot going for her. She was very healthy, no pre-existing medical problems, no heart disease or diabetes, a good wound healer, educated and compliant and very motivated.

"And always a fantastic attitude—even when she could only wear big, ugly mumus, she made it fun."

Word of Ennis's accident spread quickly at Emory, leaving friends, co-workers, and colleagues in stunned disbelief.

Then they sprang into action, ferrying food to Ennis's



CARE TEAM | Neurologist Michael Silver is helping Ennis manage her lingering nerve pain, especially in her leg.

extended family, camped out in the waiting room, placing her name on church prayer chains, and coming to visit by the dozens, establishing a fund to help with medical bills.

“We knew it was almost unheard of, to recover from an injury like that,” says David Carlton, director for the Division of Neonatology in Emory’s Department of Pediatrics, where Ennis had worked. “But Sylvia is a very engaging individual who wants to do things the right way. When she’s in, she’s all in. Maybe that’s a quality that allows you to prevail.”

Cards of support arrived by the dozens: People she had known while serving on Emory’s Employee Council, the children of colleagues, physicians and administrators, close friends and acquaintances drawn in by her quick smile and caring ways.

For Ennis, these points of connection made all the difference. “If it wasn’t for the Emory community, I don’t know if I would have wanted to live,” she says.

After two months at Grady, Ennis was transferred to a long-term acute care facility in Emory University Hospital Midtown for four more months of rehabilitation. When she was cleared

for her first brief trip home, her sister, Janet Mitchell, “did a happy dance around my room,” Ennis recalls, laughing.

After 18 months of intensive therapy, she was upright and moving with a walker. But during the first 22 months of her recovery, she would spend just 30 days outside of a hospital. The ongoing surgical treatments seemed to unfold like chapters in a long, complicated novel. No. 11 was a skin graft. No. 12 was an ileostomy reversal. She lost track after 15 surgeries.

More than a year after the accident, Cheng and Carney teamed up for a co-surgery. Cheng wanted to perform final repairs on Ennis’s ruptured stomach muscles; Carney was determined to reattach her crushed ureter, freeing her from life with a nephrostomy bag.

When Carney had first seen Ennis’s injuries in the trauma room, he decided the repair of her ureter could be postponed. Because of the force of the trauma, between four to five inches of the tiny conduit was missing. Waiting could help Carney pinpoint what tissues were irreparably damaged and what he had left to work with.

To allow Ennis’s right kidney to drain in the meantime,

Carney had inserted a nephrostomy tube directly into the organ, diverting urine into an external bag. Now, because of her shortened ureter, Carney would have to rearrange Ennis's internal plumbing, repositioning her bladder and right kidney to accommodate her truncated ureter. After a year, multiple abdominal surgeries had resulted in a profound build-up of scar tissue. "It was really difficult," he recalls. "It was as if her bladder was encased in gristle."

Readjusting Ennis's organs and reattaching the shortened ureter took three to four hours and was one of his tougher cases. "To be honest, we just barely had enough of the ureter to reach her bladder," Carney says. "If I'd had another inch missing I'm not sure I would have been able to put it back together. It was close." In time, her kidneys, bladder, and ureter began functioning normally again, as did her intestinal tract.

"Her success was a team effort, a great partnering between Emory and Morehouse," reflects Carney. "To be a part of her story was easily one of the biggest thrills of my life."

As her treatment continued, Emory neurologist Michael Silver was drawn into Ennis's case. It had been two years since the accident, but the pain in her right leg was getting worse.

"When the branch went through her and came out her buttock, it hit all of these nerves adjacent to the spinal cord traveling to her right leg," he says. "Nerves that have been damaged typically go numb at first, but as they 'wake up' it can turn into chronic pain."

Her nerves had been badly traumatized. In fact, the tree had come extremely close to hitting Ennis's spinal cord. "She was inches away from being completely paraplegic," says Silver.

To mitigate the pain of her neuropathy, he prescribed gabapentin—a medicine originally developed to treat epilepsy and seizures that can also be used to "tone down the signal in the nerves." He also prescribed tramadol, a pain reliever to help her sleep, and nortriptyline, a tricyclic antidepressant used to control the brain's reaction to pain.

Her next stop will be the Emory Center for Pain Management, where she'll be treated with a spinal cord stimulator, a device that uses an electrical current to stimulate spinal nerves at such a high frequency they can't read pain.

Of all the injuries Ennis sustained, pain and fatigue may be the primary lingering effects. "To some degree, I suspect that she will deal with the numbness, weakness, and pain for the rest of her life," Silver says.

It is a battle that Ennis accepts. "No matter how much pain that I still feel every day, I rejoice in that pain, because I am blessed to feel anything," Ennis says. "It could have just as easily gone the other way."

Cheng is still working with Ennis, transferring fat cells to make sitting more comfortable for her. Watching Ennis's progress, she says, reminds her of why she went into plastic surgery.

"In trauma surgery, you save people's lives," she says. "In

reconstructive surgery, I like to think I'm giving them their quality of life back, the ability to return to as-close-to-normal as possible."

ENNIS REFUSES TO BE DEFINED BY THE HORRENDOUS ACCIDENT, THE WINDING ROADMAP OF SURGICAL SCARS, THE YEARS OF REHABILITATION AND PHYSICAL THERAPY.

She talks readily about her gratitude and hopes for healing. She says she's blessed to be alive to see her 2-year-old granddaughter, McKenzie, who was born during the ordeal.

Still, even though much of what she carries forward is invisible, Ennis is changed. She's never revisited the scene of the accident and can't bring herself to drive that section of Clifton Road.

When a nearby tree branch fell into the street during a recent drive, "I thought I was going to have a heart attack," she says.

Ennis thought seriously about having every tree in her yard cut down, instead settling for the removal of only one dying specimen. To this day, if a news story comes on television about falling trees, she changes the channel.

She hasn't returned to her job at Emory and knows that may never be possible. Just sitting remains a challenge. There are small cognitive stumbles, such as when she pays a bill twice or forgets to write down a phone number. For someone who used to be the "go-to" person in her department—and a bit of a perfectionist—that's frustrating.

"I know I've suffered post-traumatic stress disorder. I'm not afraid to say that, to talk about it," she says. "Cognitive things have happened. Just understanding the impact a trauma like this can have on you has been a learning experience."

In December, Ennis closed the loop on something that was supposed to happen three years ago, joining her sister, Janet, former co-worker, Rosa White, and Rosa's husband on her long-delayed Caribbean cruise.

There were lazy moments in the tropical sunshine, good food, and generous amounts of laughter. But there was also a walker and fatigue and lingering discomfort. It was not the trip she had once envisioned—something she accepts as a fact.

As she wrestles with the frustration of her own limitations, Ennis' eyes have opened to the barriers people with physical disabilities face, trying to navigate through daily tasks. She is thinking of going back to school to become a psychotherapist.

Looking back on her ordeal, Ennis harbors only one regret. She is haunted by the face at her car window. That anonymous man who called for the help that would save her.

You see, Ennis never caught his name.

And she would very much like to say, "Thank you." ■

DIAGNOSTIC DEMONS

TAKING ON THE MOST CONFOUNDING CASES

By MARY LOFTUS

Emory Special Diagnostic Services, first patient, Sept. 30, 2013: *A 65-year-old man being evaluated for a renal transplant was referred by the transplant team for a workup. The reason for the referral was unusual lesions on his CT scan, multiple*

pulmonary nodules, and abdominal lymphadenopathy. Biopsy result was sarcoidosis, a poorly understood disease.

Nearly three years after seeing their first patient, the Emory Special Diagnostic Services team is sitting around a long table in a conference room on the first floor of the Emory Clinic, discussing challenging cases.

“It’s what inspires us, what we love,” says Special Diagnostic Services director Clyde Partin.

The team, consisting of five doctors and one nurse navigator, holds these roundtables routinely. “It’s always helpful to have more than one brain considering a patient’s case,” says Tom Jarrett, an internist at Emory Clinic. “We go in open-minded to all possibilities.”

Emory Special Diagnostic Services, part of the Paul W. Seavey Comprehensive Internal Medicine Clinic, is one of a handful of such clinics around the country, dedicated to patients with complex, undiagnosed illnesses. The team has seen more than 200 patients since opening, about half of whom received diagnoses. “What people really want is an answer,” says Partin, who is sometimes called “Emory’s Dr. House” for his diagnostic acumen, a moniker that, while tongue-in-cheek, is not far off the mark.

CASE STUDY 1: A photo of a middle-aged school teacher showed up on Dr. Clyde Partin’s cell phone. The patient was requesting a consult. “Swollen face” was the complaint. Her neck was erythematous with a red rash, Partin observed, and she appeared tired. Upon her arrival at the special diagnostic clinic, Partin encountered a 45-year-old woman, slightly overweight. She showed him a different photo of herself taken at a party, her face thin and youthful, just five months previous. She told him that she was exhausted, had gained twenty pounds, and could hardly climb up steps. Her past medical history included migraine headaches, which were worsening, and neck and back pain—for which she had had epidural steroid shots, 10 shots in the past 13 months. Diagnosis: excessive exogenous steroids, producing Cushing syndrome and steroid myopathy.



CASE STUDY 2: Drew Crenshaw was 18 when he started having severe ankle pain. An X-ray showed the college freshman had minor stress fractures in both feet. Casts were placed on his feet, and Crenshaw was wheelchair-bound for six months. He withdrew from college in Florida and retreated to his home. But the pain continued even after the casts were removed, and then he developed pain in all of his joints. “Some days, the pain was so bad I could not even get out of bed,” says Crenshaw. “My shoulders, knees, elbows, fingers and ankles were all affected. Everything hurt.” After multiple visits to doctors and health care facilities in several states, Crenshaw ended up at Emory’s Special Diagnostic clinic, where doctors determined that he had a severe case of gout, a condition often characterized by recurrent attacks of severe inflammatory arthritis. “With a diagnosis confirmed, the team ordered specific medications for Drew while getting all of his biochemical levels back in balance,” says Debra Cohen, nurse navigator.

To prepare for the Special Diagnostic clinic’s opening, Partin and his team of Rollins Distinguished Clinicians reviewed diagnoses of *House MD* scripts from the long-running Fox series and analyzed Lisa Sanders’s “Diagnosis” and “Think Like a Doctor” columns from *The New York Times*, many of which served as the basis for *House* episodes. They also reviewed the *New England Journal of Medicine*’s first 200 case conferences from the 1920s as well as 200 modern cases from 2005 to 2007.

“It may not have been the most scientific approach, but we were curious about what sort of diagnoses were persistently perplexing,” Partin says.

His own preparations included reading up on commonly missed diagnoses in outpatient settings, although he found the literature on this to be sparse and more focused on inpatient diagnoses.

“The subtle distinctions between missed diagnoses versus misdiagnoses can be vexing,” he says. “Atypical presentations of common diseases are much more likely than typical presentations of rare disease.”

In other words, the medical adage, “When you hear hoofbeats, think horses, not zebras,” holds true even for diagnostic clinics.

For each referred patient, the team requests existing medical records, imaging, and letters from previous doctors; takes a thorough medical and family history; and conducts a comprehensive physical examination, often with a variety of tests, new imaging, and tissue biopsies. Depending on the findings, Emory specialists from neurology to genetics are consulted.

“A lot of times, we know what it’s not, but not what it is,” says clinic internist Sharon Bergquist. Some of the seemingly mysterious cases brought before them

are “just oversights from disjointed evaluations,” she adds. “We take a second look to make sure that all elements of the patient’s history are taken into consideration.”

Often, even before coming to the clinic, the patients have seen multiple doctors and researched all of the horrible diseases that could possibly be related to their symptoms, courtesy of Google.

But symptoms, as Partin is fond of saying, do not a diagnosis make.

Unlike the patient cases handpicked for TV medical dramas, which are almost always neatly wrapped up by the end of the hour, “in the trenches of diagnostic clinics, answers waltz out of the closet less than half the time,” he says. “That is one of the unfortunate realities

Diagnostic Overload

- Practicing physicians draw on a store of at least 2 million facts
- Google can access > 3 billion articles
- Physicians process about 236 bits of data during an ICU visit
- WHO lists 12,420 distinct disease categories
- About 7,000 rare diseases exist; about 400 have prescribed treatments

of seeing the most difficult cases. There has to be a realistic willingness to accept failure.”

The most common of the clinic’s 100-plus diagnoses so far were neurologic (17), followed by circulatory, digestive, and musculoskeletal. There were nine mental health diagnoses. Eight patients died.

The clinic’s team—including Partin, Jarrett, Bergquist, David Roberts, and Jonathan Masor, along with nurse-navigator Debra Cohen—have developed their own intriguing case files, some of which can be read in the regular “You Be the Doctor” column in this magazine.

Physicians who specialize in such difficult-to-diagnose cases are sometimes called “disease detectives”—modern, medical Sherlock Holmeses. In fact, one of the defining books in the field is the late *New Yorker* writer Berton Roueche’s 1947 nonfiction collection, *The Medical Detectives*, based in large part on his “Annals of Medicine” column.



Sharon Bergquist, assistant professor of medicine, internist.



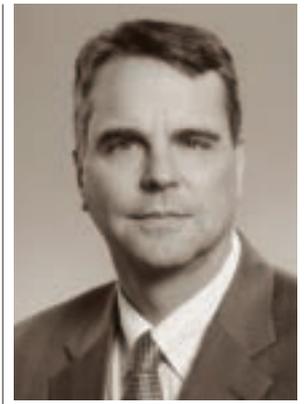
Debra Cohen, nurse navigator.



Thomas Jarrett, assistant professor of medicine, internist.



Jonathan Masor, associate professor of medicine, internist.



David Roberts, Charles F. Evans Professor of Medicine, internist.

But Partin sees other less obvious comparisons as well, such as the Magliozzi brothers, Tom and Ray, of *Car Talk* radio fame. “They were a brilliant example of deductive reasoning leading to a solid diagnosis time after time,” he says.

And so, the perfect diagnostician: part intuitive clinician, part mythical detective, part auto mechanic.

The generous time and resources that often must be devoted to complex patient cases may seem antithetical to the current emphasis on productivity related to the economic squeeze on health care providers. Indeed, many special diagnostic clinics—like Emory’s, which is funded largely through a grant from the O. Wayne Rollins Foundation—must rely on private philanthropy.

“The special diagnostic clinic was developed to meet what we thought was an unmet national need,” says Doug Morris, former director of the Emory Clinic and a driving force behind the diagnostic clinic. “In spite of enormous technological advances, there remains a multitude of patients who suffer the torment of undiagnosed or misdiagnosed disease.”

While the special diagnostic team is largely made up of internal medicine and primary care physicians—generalists, who take a comprehensive view—there’s a reason such clinics are often housed in academic medical centers: a host of specialists are needed to consult on cases, including neurologists, pathologists, geneticists, gastroenterologists, cardiologists, infectious disease doctors, rheumatologists, and psychiatrists. “There’s a great tension between what is psychosomatic and what is organic,” says Partin, who recently attended an international conference on rare diseases and undiagnosed illnesses in Vienna, and

toured Freud’s home and office.

Modern diagnostic clinics rely on advanced imaging, pathology lab results (“The issue is tissue,” Partin often says), and, more and more frequently, genetic testing, allowing doctors to investigate the possibility that a puzzling illness or set of symptoms is caused by an inherited condition or genetic mutation.

Partin believes that computer analysis and genome sequencing will play larger roles in difficult diagnoses in the future.

But the knowledge and intuition of experienced doctors and specialists, above and beyond their tools and technologies, cannot be overstated. Of the Emory Special Diagnostic clinic’s resolved cases, 17 were diagnosed through biochemical/lab results, 21 through pathology, 12 through radiology, 2 through response to treatment—and 58 through “clinical acumen.”

Even when a diagnosis is made, however, it can be hard to determine the best point at which to stop the inquiry. Partin prefers to seek out root causes. “The best thing you can do is keep asking yourself why. Something as simple as a patient with abdominal pain, is it due to pancreatitis? Why do they have pancreatitis? The gallstones. Why do they have gallstones?” says Partin. “You can go to the nth degree, and sometimes you will strike gold and sometimes you will hit a metaphysical dead end.”

A year after a patient visits the clinic, the staff contacts them to check on the validity of the diagnosis. Emory’s diagnostic clinic has had many gratifying successes—patients whose illnesses were identified and then properly treated. The team has diagnosed Lyme disease, post-polio syndrome, anemia, West Nile virus, sleep apnea, endometriosis, depression, neurodegenerative diseases, conversion

CASE STUDY 3: The 59-year-old female patient was experiencing shortness of breath, especially after physical effort like climbing steps. She had fatigue and left pleuritic-type chest pain, as well as tachycardia. She had been a smoker but quit in 1983. Her stress echocardiogram was normal, as was a chest CT scan and bronchoscopy. When the doctors asked if she snored, the answer was a resounding yes. Diagnosis? Moderately severe sleep apnea. With the use of a CPAP, she experienced complete resolution of her symptoms.

disorders, and dozens of other common and rare conditions.

Claiming victory with a definitive diagnosis, however, remains a tricky business. “Are we 100-percent right? There is a murky middle ground that makes us feel like our feet are firmly planted in mid-air,” Partin says. “So any case we do unequivocally solve is a cherished triumph.” ■



In Time to Help Jessie:

Two sisters, a shared rare disorder

THROUGH WHOLE EXOME SEQUENCING AND THE WORK OF EMORY GENETICISTS, A NORTH GEORGIA COUPLE LEARNED THAT TWO OF THEIR DAUGHTERS HAVE AN EXTREMELY RARE, NEWLY DISCOVERED GENETIC DISORDER—NGLY1 DEFICIENCY.

By QUINN EASTMAN

For most of her life, 19-year-old Jordan Stinchcomb's parents thought she had cerebral palsy. Jordan was born by emergency Cesarean section with the umbilical cord wrapped around her neck, and had to be resuscitated. Her parents assumed that lack of blood flow and oxygen at birth had damaged her brain, causing her inability to walk and speak.

Pam and Tony Stinchcomb, who live in Hoschton, Georgia, had two more children, Jenna and Jake, who were born without similar difficulties. Then when Jordan was 13, her youngest sister Jessie was born, after an almost perfect pregnancy.

"We knew something was not right," says Pam, a physical therapist. "She cried for the first six months and would scream if we put her on her stomach."

Jessie missed early milestones such as being able to roll over or sit up by herself. At around six months of age, she started wheezing because of an airway restriction. Her parents thought they saw hints that Jessie was experiencing seizures, which Jordan had started having at age 11. They decided to seek help and an explanation.

Neurologists they consulted suspected Jessie had a congenital condition: perhaps Rett syndrome, a neurodevelopmental disorder that mainly affects girls, or a mitochondrial disorder. A muscle biopsy and other invasive procedures were performed. Months went by, while tests for known diseases came back negative.

When the Stinchcombs were referred to Emory, they encountered a delay when a respected geneticist who specialized in rare disorders, Paul Fernhoff, associate professor of human genetics and pediatrics and the medical director of human genetics at Emory University Hospital, died unexpectedly.

When medical geneticist Michael Gambello arrived at Emory from Houston in 2012, he recommended that the family proceed with whole exome sequencing for Jessie. It wasn't a

difficult decision. At that time, whole exome sequencing was emerging as a powerful technique for finding the mutations that might be responsible for a disease that looks like an inherited condition, when tests for known genetic disorders have not proven helpful.

Several weeks later, the Emory Genetics Laboratory, under the direction of Madhuri Hegde, found something, but it needed additional confirmation. Gambello asked whether Jordan's DNA could also be tested.

Pam and Tony were surprised, since they had thought Jordan's condition was caused by the circumstances of her birth.

"It made sense 19 years ago," Pam says. "Until Jessie was born, we never had a need to look for anything else."

Gambello told the Stinchcombs about the sequencing results, but he was able to tell them little about the disease or Jessie's prognosis.

Pam Stinchcomb recalls the conversation going something like this:

"We've learned that your daughter has N-glycanase-1 deficiency. It's only been identified recently."

"What is that?"

"We really don't know. There is another patient reported in the medical literature, who has symptoms almost identical to Jessie."

The disorder was not something doctors were familiar with, even geneticists who deal with rare diseases.

"At that point, there was one publication out there describing a single patient with NGLY1 deficiency," Gambello says. "It could have been wrong. But we had two affected siblings, and the parents were carriers."

N-glycanase 1 is an enzyme—part of a complex apparatus that processes proteins—that cell biologists have studied for years in the laboratory. However, it was highly unusual for doctors to see not one, but two living patients in the same

family who appeared to lack this enzyme.

Coincidentally, shortly after talking with the Stinchcombs, Gambello received an email from a genetic counselor he had worked with in Houston, seeking advice for another family with a child with NGLY1 deficiency.

From this communication, he and the Stinchcombs learned about several other children around the world with the same genetic deficiency, whose cases had not yet been published in medical journals.

Several of the affected families share the same exact genetic mutation in the NGLY1 genes, even though the families do not appear to be related, beyond sharing European ancestry. This may indicate a “founder effect” reaching back many generations.

Having felt isolated and alone, the families were hungry for information from the medical community and from each other.

It’s hard enough for your child to have a chronic or debilitating condition, let alone one that doctors are stumped by.

One of the fathers, Matt Might, a computer scientist at the University of Utah, wanted to find other families dealing with the same challenges.

After an odyssey of diagnostic missteps led to the identification of

NGLY1 deficiency in his son, Bertrand, Might wrote the essay “Hunting down my son’s killer” on his personal website.

“Aside from severe jaundice, Bertrand was normal at birth,” Might writes. “For two months, he developed normally. At three months, his development slowed, but it was ‘within normal variations.’ By six months, he had little to no motor control. He seemed, as we described it, ‘jiggly.’ Something was wrong.”

With his post amplified by social media sites like Reddit, over the next year the Might family found nine other families with a child with NGLY1 deficiency.

A Lack of Tears

The Might family’s quest was highlighted by science writer Seth Mnookin in the *New Yorker* (“One of a Kind”) and by CNN (“Kids who Don’t Cry”).

“For families in this situation, the first thing a diagnosis does is to stop their frustrated progress from doctor to doctor,” says Stephen Warren, chair of human genetics at Emory. “And it’s a starting point for figuring out the rest, even if that may take time. The parents can organize and compare experiences.”

About a year after Jessie and Jordan were diagnosed, the Stinchcombs met the Might family, the Wilseys, and other affected families at a 2014 conference devoted to NGLY1 in San Diego at Sanford Burnham Prebys Medical Discovery Institute.

Pam Stinchcomb says she now regularly compares notes with the other parents on caring for their children. “Just having that support is wonderful,” she says. “It’s like having a little NGLY1 family.”

The group has continued to grow. As of the summer of

2015, geneticists have been able to confirm 27 cases of NGLY1 deficiency by sequencing. Lynne Wolfe, coordinator of a study at the National Institutes of Health, and her team have thoroughly examined 12 of those individuals, including both Jessie and Jordan Stinchcomb.

Patients with NGLY1 deficiency appear to have several

core symptoms: involuntary movements, hypotonia (low muscle tone), and an inability to produce tears. EEG abnormalities are common in many of the children identified so far, with overt seizures present in about half.

Most of the children have some level of developmental delay and problems with auditory processing or expressive language, Wolfe says. Still, the degree of developmental delay is variable. Some affected children have a limited vocabulary. Jessie can communicate through whines and glances, but does not speak recognizable words.

Liver disease was thought to be a common feature, but in several children, liver abnormalities have faded as they have become older, Wolfe says.

For the Stinchcombs, seizures have been a dominant and troubling feature of the disorder for Jordan, at least in the past few years.



Medical geneticist Michael Gambello recommended that the family proceed with whole exome sequencing for Jessie, since he suspected a genetic disorder. Her older sister, Jordan, was discovered to have the disorder as well.

Visiting Jessie and Jordan

When entering the Stinchcombs' home, visitors may notice a chirping, bird-like sound.

"Oh, that's just Jessie, watching her favorite DVD," Tony Stinchcomb says.

Jessie enjoys listening to "Clifford the Big Red Dog." She seems to depend on it. When her father brings her into the family's kitchen to eat some applesauce, she does fine as long as the DVD is playing on a rubber-cushioned iPad. She squeals with delight while sitting on Tony's lap and playing with him. But when he turns Clifford off for just a moment, she becomes visibly distressed.

When seated, Jessie's arms are in constant motion. Her room, which she shares with Jordan, is full of large pillows and decorated with *Frozen* movie posters. She can push herself up in her crib and move around by rolling on the pillows but can't crawl in a sustained way.

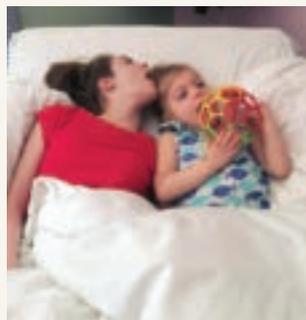
When Jessie does push herself up, her weight rests on the sides of her feet in what looks like an awkward ankle twist. She has corrective braces but finds them painful, her parents say. As part of doctors' efforts to help her stand, she has received botulinum toxin injections in her legs.

The edges of Jessie's and Jordan's eyes often look red. They receive eye drops several times per day to compensate for the lack of tear production.

Jessie and Jordan are both on a specialized formula diet. They have chronic gastrointestinal problems: constipation and reflux. Tony says that he sometimes needs to change his clothes four times per day because of spit-up.

Even before her sister was born, Jordan had taken an anti-seizure medication, levetiracetam, with doctors occasionally increasing the dose. Her parents became concerned that she seemed to be falling asleep repeatedly and had her taken to a hospital to perform a 72-hour EEG, in which "abnormal brain activity" was detected. In February 2014, Jordan had a frightening series of seizures in which she stopped breathing.

"Her lips were turning scary blue," recalls Tony, who yelled for his son, Jake,



Family togetherness: The Stinchcombs on a beach vacation; Jessie on her adaptive tricycle; Jake and Jordan enjoy a fall day; Jordan and Jessie snuggle; Jessie with mom, Pam, and dad, Tony.

to call 911 while he tried to revive her. Jordan was unable to travel to California that spring to meet other NGLY1-affected families.

Then in March of 2015, she experienced more than a dozen seizures. For the several days that month she spent in the hospital, Jordan was non-responsive and had no muscle tone, her mother recalls. "She did wake up from time to time, look at us, and even smile," Pam says.

Doctors managed to find a drug, phenytoin, that could stop the cluster episodes, and Jordan is back at home, taking that drug and other anti-seizure medications regularly.

Before the seizures

Jordan is now less mobile than Jessie, although that wasn't always the case. She used to be able to stand by herself and move around with a walker. Before her recent seizure episodes, Jordan could recognize her printed name and could roll a ball back and forth or engage in tug-of-war play with her sister, her parents say. She enjoyed going to her brother Jake's weekend baseball or basketball games, where she would devour hot dogs, and she liked to splash around in the family's pool.

When Jordan was a small child, her parents took her several times to New Orleans for hyperbaric oxygen treatments. They say the oxygen treatment helped her become more alert, sleep through the night, and track objects with her eyes more accurately, although the general effectiveness of this type of treatment has been debated.

Jordan attended a specialized day care center in nearby Gainesville and then public schools. Her parents pulled her out of public school after she experienced several falls and had frequent respiratory infections. For a while, her parents worked grueling split shifts to take care of her. Then Tony decided to stop working at a nearby rock crushing plant, where his relatives still work, and care for Jordan full-time.

In May 2014, after the Stinchcombs returned from meeting other NGLY1-affected families in California, a community fundraiser enabled them to buy a hand-

icapped-accessible van that can transport both girls' wheelchairs.

Around the same time, a friend's foundation built the Stinchcombs a spacious shower, which allows them to bathe Jordan more easily.

Chain of sugars

The NGLY1-affected families have sparked a surge of research into how the absence of the N-glycanase 1 enzyme affects cells and the entire body, with an eye toward possible treatments.

The enzyme encoded by the NGLY1 gene is thought to be involved in protein quality control. Some form of this enzyme can be found in yeast, worms, flies, and even plants. NGLY1's basic function is to remove a chain of sugars from unfolded proteins. If proteins become unfolded while they are being synthesized, the cell destroys them in the proteasome, a kind of molecular "garbage disposal."

Up until the discovery of the NGLY1-affected families, scientists who studied the enzyme thought that the chain of sugars acted like a trash tag, telling the cell what to do with some of the unfolded proteins. If the NGLY1 enzyme is absent from cells, then the garbage disposal might go astray. But which other proteins' production or processing is disturbed and what causes the array of symptoms, nobody knows.

Because nervous system development is derailed, it's a good bet that NGLY1-dependent changes can be seen in neurons and/or glial cells, Emory's Michael Gambello says.

He has been working on engineering mice that are deficient in NGLY1. Gambello's preliminary findings show some differences between human patients and the mice, in that the mice don't seem to have a movement disorder.

Still, it is common for geneticists to find discrepancies between human genetic disorders and their mouse models. Gambello is also checking whether the NGLY1-deficient mice are more prone to seizures.

Hudson Freeze and his colleagues at Sanford Burnham Prebys Medical Discovery Institute have been examining cells obtained from NGLY1-affected patients. Their findings are going against previous assumptions about how the enzyme deficiency would affect cells, he says.

His team has looked for signs that unfolded proteins accumulate in patient cells and has not seen them. The same goes for accumulation of cellular structures (lysosomes) where proteins are recycled, he says.

These findings illustrate that scientists are still figuring out how NGLY1 is involved in protein processing and trash removal.

Several other rare diseases are caused by inherited problems with enzymes whose job it is to add chains of sugars to proteins. NGLY1 does the opposite and removes the sugar chains.

Despite the divergence, these deficiencies both interfere with brain development, and affected individuals often have developmental delays, movement disorders, and seizures.

Fathers Matt Might and Matt Wilsey have written that the NGLY1 disorder's rapid emergence is an example of how discovery can be sped up when families, physicians, and geneticists work together to determine causes and potential treatments.

With the families comparing notes, ideas are exchanged, ranging from the use of cocoa extract to carnitine, a dietary supplement that the Stinchcombs have found helps with Jessie's gastrointestinal problems.

With the choice of anti-seizure drugs, an issue that was urgent for the Stinchcombs, it's less clear that crowd-sourcing has made a difference.

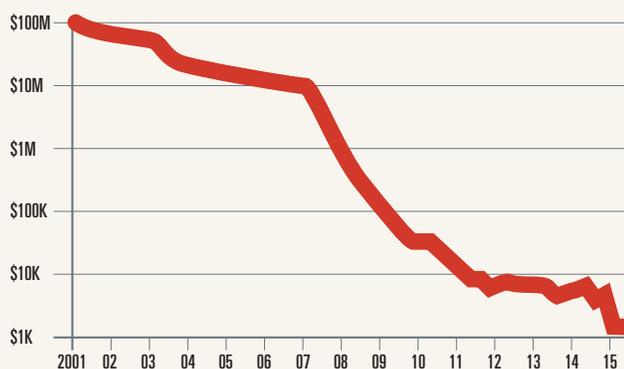
"It's hard to say what 'usually works' when the number of affected patients is so small," Gambello says. "Even with other types of epilepsy, the process of choosing effective anti-seizure medication is often one of trial and error, and this is a new disorder."

Freeze's team has already tested one option for treatment of NGLY1 deficiency, without success.

Many inherited diseases, this one included, involve introduction of a premature stop signal into the part of a gene that encodes a protein. Read-through agents, a group of compounds that includes some antibiotics and a drug in cystic fibrosis clinical trials, are supposed to coax the cell into "reading through" the genetic glitch. However, Freeze found that these compounds didn't restore enzyme activity in NGLY1-deficient human cells.

Whole exome sequencing was first used to discover the cause of a rare inherited disorder in 2009 and has rapidly grown in popularity as a viable diagnostic approach. In whole exome sequencing, scientists scan just the 1 percent of the genome that codes for proteins, which is where disease-causing mutations are more likely to be. This provides a significant diagnostic yield at a moderate cost, compared with sequencing the entire genome.

Cost per genome



National Human Genome Research Institute
genome.gov/sequencingcosts

Other potential drug treatments have been proposed, such as EPI-743, a potent antioxidant developed for inherited mitochondrial diseases.

Freeze has been testing this drug on NGLY1-deficient patient cells as well. Japanese researchers led by Tadashi Suzuki recently found that inhibiting another enzyme (ENGase) could compensate for the absence of N-glycanase 1 in mouse cells.

Additional insights into the variability of NGLY1 deficiency may emerge from the NIH study, with Jordan being one of the oldest known affected individuals at age 19.

“Jordan is writing the book on this disease,” Pam Stinchcomb says.

The idea that NGLY1 deficiency may be a progressive disorder that worsens with time deeply troubles the Stinchcombs, who were high school sweethearts before marrying and starting a family.

Pam regrets the losses their oldest daughter has endured already, and says, “We don’t accept that it just progresses.”

Still, when asked whether it was worth going through the process of diagnosis, Pam says, “Absolutely. I wouldn’t change anything about that. We know something about what we’re dealing with, and we’re not alone. Even if there is no treatment now, I continue to pray that we will get there while Jessie will be able to benefit.” ■

EMORY GENETICS LABORATORY

Finding the genes associated with rare disorders



EGL Executive Director and clinical molecular geneticist Madhuri Hegde.

While it is only a small part of the genome, the exome accounts for 85 percent of disease-causing gene alterations.

With nearly five decades of clinical experience, Emory Genetics Laboratory (EGL) is the oldest clinical genetics lab in the U.S. and was one of the first labs in the world to launch whole exome sequencing in 2011.

Since then, exome sequencing has proven to be an invaluable diagnostic technique for clinicians seeking molecular confirmation of a suspected genetic disorder.

“We are quickly moving away from the idea of single genes causing single disorders. One gene can cause many disorders,

and many genes can cause one disorder,” says EGL executive director and clinical molecular geneticist Madhuri Hegde. “We have had to change our ideas about data analysis and interpretation of the data.”

The EGL is part of Emory’s Department of Human Genetics, which is home to the National Down Syndrome project and serves as one of three national fragile X research centers. EGL contributes to the “Free the Data” movement by giving the clinical and research community open access to its online variant (mutation) database, EmVClass. EGL also serves as the follow-up laboratory for the Georgia Newborn Screening Program.

Hegde has a special interest in the development of next-level sequencing strategies for rare disorders—her clinical work focuses on identifying new genes for muscular dystrophy and developing a follow-up program for newborn confirmatory testing for Duchenne muscular dystrophy.

Lora Bean, lab director at EGL, and Lindsey Mighion, genetic counselor at EGL, remember the Stinchcomb sisters well, and use the case as an example of the diagnostic advantage of whole exome sequencing for patients with suspected genetic disorders.

At first, the lab had a “proband only” sample from a 2-year-old girl with severe developmental delay. In genetics, the proband is the first affected family member who seeks medical attention for a genetic

disorder—in this case, Jessie. Through exome sequencing, they found that each of her parents was a carrier, and her older sister, Jordan, also had the changes in the NGLY1 gene.

“At the time, only one paper had reported this gene,” says Mighion.

They reached out to colleagues in other labs and ultimately found eight affected individuals with NGLY1 deficiency.

“This is a case that we highlight for a couple of reasons—it’s why data sharing is so important. Only because of the large collaboration were we able to show that this gene was truly associated with disease and report this,” Mighion says. “Also, it shows the importance of constantly curating, so we can add genes that used to be of unknown significance to our genes-associated-with-disease categories.”

Genomic sequencing will likely become a routine component of one’s medical “family history,” providing the important variants inherited from each parent and the new mutations that contribute to disease susceptibility.

“This allows us to find better, individualized answers related to rare genetic diseases for more patients with complicated medical issues than we ever could before,” says Dawn Laney, EGL genetic counselor and director of the Emory Genetic Clinical Trial Center.—*Mary Loftus*

For more: geneticslab.emory.edu.

Q&A

with neurologist
Charles Epstein



Despite being the second-most prescribed drug, to more than 30 million Americans, antidepressants don't work for nearly a third of those who try them. Annually, more than 40,000 Americans commit suicide, about half of whom suffered from major depression—and those numbers are rising at an alarming rate. Suicide is now at the highest level in three decades, with increases in nearly every age category. Emory neurologist Charles Epstein helped refine a novel therapy—transcranial magnetic stimulation (TMS)—to become an FDA-approved treatment for depression.

What motivated you to work on a treatment for depression? We had developed an improved transcranial magnetic stimulation (TMS) coil for another purpose, and learned that teams at the Medical University of South Carolina and the National Institutes of Health were just working out a theory of how TMS might treat depression. Our new coil turned out to be ideal for that application.



On a recent visit to Emory, TMS patient Martha Rhodes got to thank Dr. Charles Epstein and speak about her book, *3,000 Pulses Later*. Emory's Technology Transfer Office has created a related video series at bit.ly/tmsdepression.

What are the advantages of TMS to other treatments? It is non-surgical and non-invasive, with very few side effects, and it's been shown to work in patients who have not responded to other treatments.

How exactly does TMS work? A magnetic pulse is delivered by a coil on the surface of the head, generating small bursts of MRI-strength magnetic energy that stimulate nerve cells in one specific area of the brain linked to mood, the left pre-frontal cortex. The stimulation seems to work by "turning on" parts of the brain that are underactive in depression.

How long does it take and how many treatments to you need? Most people need daily treatments for a week to a month to get the full benefit. After that, some people need an occasional "boost" a few times a month.

What have been the results? Neuronetics, the Emory partner and start-up company created for the development of NeuroStar TMS therapy, has safely administered more than 10,000 treatments with clinically significant results: among patients studied, 54 percent responded to the therapy and 33 percent found their depression in remission.

What role did you play in the innovation? More than a quarter-century ago I built my first TMS system, discovered that it needed a lot of power and generated huge amounts of heat, and realized that a more efficient magnetic coil could make a difference. I was able to team up with Kent Davey, a friend and magnetics specialist at Georgia Tech. We had joint research support from Emory and Tech.

How was your TMS system better? To give you a sense of the power requirement for

TMS: A standard old-fashioned lightbulb uses 100 watts of electrical power, which gives a fair amount of light. TMS treatment comes in pulses, usually 10 pulses over and over. For other systems, a single pulse requires up to 5 million watts. That's 50,000 standard light bulbs going off at once for about one ten-thousandth of a second. What we invented takes a quarter of the power and produces eight times less heat on a person's head. We no longer needed to keep air and water running around the coil to cool it.

Has TMS been accepted by the psychiatric community as an alternative treatment for depression? The mental health community is enthusiastic. Antidepressant medicine and talk therapies do not help everyone. Something else is needed. Electroshock therapy is a very effective treatment for depression but is plagued by complexity and side effects, with memory impairment being the most frequent.

What is it like to meet a patient like Martha Rhodes, whose life has been changed by your technology? It's fantastic! To have built something in the basement that is out there treating thousands of people, changing their lives and making them better, is amazing.

Did you know?

This red-haired daughter of a rural physician became Emory's first female medical graduate.

After gaining a master's degree in biology at Emory in 1931, she was appointed an instructor in the medical school. Despite being on faculty, however, she was not allowed to be a medical student since that was "reserved for men."

She pursued her doctorate in bacteriology and parasitology, focusing on malaria, at the University of Chicago while still teaching at Emory, taking the train up on weekends. She returned to Atlanta in 1937 with her brand new PhD, a container of mosquitoes, and a few malaria-infected canaries.

She wrote a letter in 1942 to Emory's medical school and President Goodrich C. White saying it was "a sin" for women to be excluded as students and enclosing a formal application.

After causing much deliberation, she was accepted in 1943 as a "rare exception" to the all-male rule and, in 1944, the rule was revoked. She practiced medicine in the Atlanta area for 30 years. Her name? **Dr. Winton Elizabeth Gambrell.**



windows

OF OPPORTUNITY

If you've been touched by a story or stories in this issue of *Emory Medicine*, these windows can open up ways for you to turn your inspiration into action. Here you'll see how you can invest in the people, places, and programs you're reading about. Gifts to Emory produce powerful, lasting returns: they help create knowledge, advance research, strengthen communities, improve health, and much more.

Find your window.



PAGE

5 BEST EATING FOR HEART HEALTH



As demonstrated by the leadership of Emory Heart and Vascular Center cardiologist Laurence Sperling in the *U.S. News and World Report's* Best Diets rankings, the Emory Division of Cardiology is known for its expertise in the prevention and treatment of cardiovascular disease. Research by the internationally recognized faculty has contributed to understand-

ing new approaches to precision medicine, population-based health promotion, and disease prevention. To support exciting breakthroughs in heart health, contact Gabrielle Stearns, director of development for cardiology, at 404.727.2512 or gabrielle.stearns@emory.edu.

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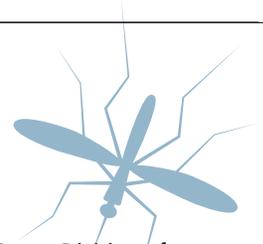
22 PINNING DOWN DIFFICULT DIAGNOSES

Emory Special Diagnostic Services attracts patients with unusual and uncommon diseases that are difficult to diagnose or easy to misdiagnose. The clinical group also determines when typical diseases present in a way that is atypical.

To find out more about supporting this detective work, contact Vicki J. Riedel, executive director of development, at 404.778.5939 or vriedel@emory.edu.

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9 BATTLING ZIKA AND BEYOND



When the Zika virus spread, attention turned to the Emory Division of Infectious Diseases and its research, education, and clinical care. Gifts to the Emory Infectious Diseases Fund for Excellence support the division's national leadership role in the development of safe and effective methods to treat serious contagious diseases. The Division of Infectious Diseases subspecialty training program has graduated more than 125 physicians and, over the last decade, 83 percent of the fellows completing the Emory infectious diseases fellowship training program have pursued careers in academic medicine or public health.

To support this critical work, contact Steven Wagner, senior director of development, at 404.727.9110 or steven.wagner@emory.edu.

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32 SUPPORTING BREAKTHROUGH TECHNOLOGY

Transcranial Magnetic Stimulation (TMS), which stimulates nerve cells in the brain with small bursts of MRI-strength magnetic energy, is helping patients with treatment-resistant depression find their way back to health. Neurologist Charles Epstein, founder/director of the Laboratory for Magnetic Stimulation at Emory, co-invented the core technology for NeuroStar TMS Therapy, the only TMS therapy approved by the FDA for treatment of depression.

To find out more about supporting this project, contact Gayathri Srinivasan, director of public and private partnerships, at 404.727.9843 or gayathris@emory.edu.

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14 TRAINING THE RESPONDERS

A health care team of dozens, from a Grady trauma surgeon to an Emory plastic surgeon, saved Sylvia Ennis's life and got her back on her feet after a near-fatal impalement. The School of Medicine is training the next generation of physicians and specialists to provide team-based care that saves and improves lives.

To give to medical education, contact Andrew Christopherson, director of development, at 404.727.8253 or andrew.christopherson@emory.edu.



GIFTS OF NOTE



Eva and Charles Lipman's recent gift will support breakthrough treatments for cystic fibrosis through the recruitment of Eric J. Sorscher, MD, an internationally recognized scientific leader dedicated to CF research. The aim is to develop effective new drug therapies and a cure. The gift—which will contribute substantially to Sorscher's laboratory—was an important factor in his decision to move to Atlanta. Recruited by the Department of Pediatrics at Emory School of Medicine, Children's Healthcare of Atlanta, and the Georgia Research Alliance, Sorscher previously directed the CF Research Center at the University of Alabama at Birmingham. He is a Georgia Research Alliance Eminent Scholar and Hertz Professor in Cystic Fibrosis Research, and he co-chairs the International CFTR Folding Consortium, a respected group of researchers supported by the Cystic Fibrosis Foundation and dedicated to understanding how mutations in the CFTR protein lead to the development of CF. "The Lipman family contribution will have a substantial impact on that effort over the next three years, and we are very grateful for their support," Sorscher says.

James H. Lewis of Douglasville, Ga., made a generous bequest in memory of his parents, Sheila R. Lewis and Ira B. Lewis. When realized, the gift will benefit Winship Cancer Institute's research in lung and colon cancer, and the School of Medicine's research into Alzheimer's disease. Lewis has made a separate planned gift to Emory Eye Center for research in glaucoma and Graves' disease, inspired by reading *Emory Eye* magazine during an eye-related appointment at Emory.

A new endowed scholarship honors the life and career of M. Brittain Moore Jr. 51C 56M, an infectious disease specialist and dermatologist from Lakeland, Fla. His daughter Laura Brittain Moore 80B funded the scholarship to recognize his commitment to helping others and his contributions to fighting infectious diseases. In the 1950s, Moore fulfilled his military service through the U.S. Public Health Service,



treating syphilis in Appalachia. He became director of the Venereal Disease Research Laboratory at what would become the Centers for Disease Control and Prevention. Later, when he was in private practice at the Watson Clinic, his familiarity with skin diseases such as Kaposi's sarcoma led him to treat some of the first AIDS patients. "At that time, there was a lot of fear about transmission of the disease, but he volunteered to do all the internal medical work needed for them," his daughter says. "For him, the patients were always more important. Part of what we want to leave is the ability for Emory medical students to continue to help people." Moore died in December 2015 at age 85.

To address visual impairment as an international public health problem, the Alcon Foundation has made a pledge to establish the Global Ophthalmology Fellowship at Rollins School of Public Health and Emory Eye Center. Each fellow also will train at the University of Addis Ababa and Aravind Eye Care System in India, a World Health Organization



(WHO) collaborating center for prevention of blindness. WHO estimates that 285 million people are visually impaired worldwide, and that 80 percent of these eye problems can be prevented or cured. Only four global ophthalmology fellowship programs exist in the U.S. The Emory recipient will participate in service activities with the Georgia Lions Lighthouse, Grady Eye Center, Prevent Blindness Georgia, and South Georgia Farmworker Health Project.

Emory Healthcare employees have contributed more than \$12,000 in money and hygiene supplies to Mercy Care Atlanta for distribution to people who are homeless. The tradition of collecting resources for the Mercy Care Atlanta street medicine program began at Emory Saint Joseph's Hospital in 1985, honoring the legacy of the four Sisters of Mercy who established Atlanta's first hospital. Emory Healthcare joined the effort in 2014. Mercy Care needs more than 500 hygiene kits a month to assist people in need, and this year's donations equal more than 3,200 kits.

The Emory Cardiology Training Fund benefits from donations at the Hurst, Logue, Wenger



Cardiovascular Dinner. Florida cardiologist James T. Cook III 65C 69M 70MR 77MR (left, standing) gave in honor of Willis Hurst and R. Bruce Logue (left, seated). His father, James T. Cook Jr. 35OX 37C

41M, trained under Logue in 1948, and Logue and Hurst accepted the younger Cook as a cardiology fellow in 1976. "Dr. Hurst taught me the pursuit of excellence, and Dr. Logue taught me to be a complete physician," Cook III says. The Emory Cardiology Training Fund supports educational and training activities for fellows.

The Curious Boy

Samir was polite, helpful, and full of questions—Where were we from? How did we become doctors? And we, in turn, wonder what his future will hold.

Inspired by my daughters, Amal, a dentist, and Zeena, a senior at Emory College, I decided to accompany them on a volunteer medical mission trip to Al-Zaatari refugee camp, about 50 miles north of Amman, Jordan, in January.

Since 2012 the camp has been home to Syrians who are fleeing violence in the ongoing Syrian civil war. In an orientation before our trip, we learned that Zaatari, which resembles a small city, is home to 86,000 inhabitants—mostly women and children and, to a lesser degree, older men. On the first two days, I volunteered in the emergency room, where I saw several children with second-degree burns on their arms, legs, and chests from scalding water.

Being a cardiothoracic surgeon, I was out of my specialty for those few days. There was no cardiac surgical operating room, no ICU, and no surgical team. I became the local "expert surgeon," seeing potential surgical patients who needed further evaluation.

During the rest of the visit, while Amal worked in the dental clinic with two other young American dentists, Zeena and I helped with screening exams in the eye clinic. We saw patients as young as 2 through their late 70s. My friend, Bill Burke, president of Prevent Blindness Georgia, had brought with him individually wrapped candies to give to each child after their exam. Pretty quickly, the eye clinic became the "candy store" for the camp kids. Three young boys, ages 9 or 10, showed up on the first day for their exams. Each had good eyesight, each was given a piece of candy. They came back with several new young kids to be examined and take a candy.

Quickly we realized these three children—Samir, Abdullah, and Abdul Kader—were our strongest recruiters. They would inform parents about the free eye exams and bring children in. They became de-facto members of our team, telling other children where to stand and how to focus. The next day, Samir, the most vocal and assertive of the three, showed up and wanted to help Zeena. To our surprise, he never asked for another piece of candy. Samir was cooperative, always showing up on our arrival, leaving at 11 a.m. to attend his school, and returning before our afternoon departure.

He was a skinny kid, weighing barely 50 pounds, round faced, skin burnt by the sun's summer rays, with dirty blond



Emory surgeon Omar Lattouf volunteered with his daughters, Zeena and Amal (below) at the Al-Zaatari refugee camp, where they met Samir (above, left, with Zeena).

hair and piercing eyes. He was inquisitive but polite—always wanting to help but never getting in the way.

Samir would ask questions about where we came from and how we became doctors. I could tell there was a lot of thinking going on in that child's mind. Seizing the opportunity, I encouraged him to take school seriously. He seemed to understand that to become a doctor, he had to intently focus on his education. We all took a liking to Samir. We would inquire about him when he was not around, and realized that we looked forward to seeing him every day.

And so came the day that we were winding up our work in the mission, having examined the eyes of more than 350 patients and referring about 40 with major vision issues. My daughter, Amal, and her colleagues had treated

300-plus dental patients. We were ready to head back home. As we waited for the bus to leave, I noticed a child sitting on the side of the road, his head pointed down, almost motionless. I looked closer and realized the boy was Samir. Zeena got off the bus and walked over to him, extending her hand with some candy. I could see Samir's hand reaching out, with his head still pointing to his feet. A few minutes later, Zeena came back to the bus and took her seat, tears flowing.

As we pulled out, Samir faded from view, but not from our thoughts and hearts. He has become a living symbol of the Al-Zaatari camp and will stay with us for many years to come.

Goodbye, Samir, my friend. I hope we will meet again.



Omar Lattouf, a cardiothoracic surgeon at Emory University Hospital Midtown and professor of surgery at Emory School of Medicine, wrote about his trip to Al-Zaatari refugee camp for ArabAmerica.com. A condensed version appears here.

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