

rocket science

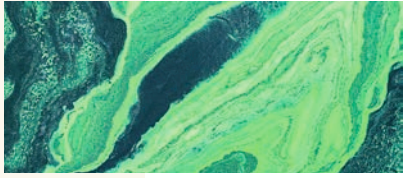
THE UNIVERSITY OF TOLEDO
COLLEGE OF MEDICINE AND LIFE SCIENCES

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PROOF

Biomarkers: Leading the way
to improved outcomes See inside





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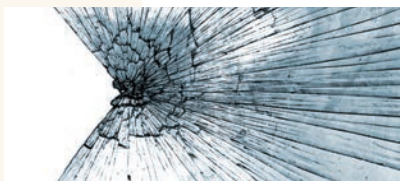


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In this issue of Rocket Science, you will see several new research themes that faculty from the College of Medicine and Life Sciences are investigating. An important area is microcystin, the toxin generated by algae in Lake Erie that shut down our region's water supply in 2014. There are several other interesting projects that look at biomarkers for concussions and fatigue measured in saliva, of all places! Two of the articles are regarding the fundamentals of brain health, including changes that occur with post-traumatic stress disorder (PTSD), that we are now evaluating by MRI scans and markers for migraine headaches. All told, it is an interesting issue of Rocket Science that highlights work ranging from the Lake Erie algae problem to fundamentals of brain health.

With the support and guidance of Maryanne Ballas and others, we have started the Medical Research Society, a new program to support scientific discovery. This is a philanthropic organization dedicated to funding early stage projects that have a strong potential to translate into future funding and significant discovery. The Society is an exclusive group consisting of members who have made a \$25,000 or more five-year commitment to help fund biomedical research in the College of Medicine and Life Sciences. The group meets a few times each year to review research projects at social events.

This past June, the first award of the Medical Research Society was made to Dr. Kathryn Eisenmann for her work in ovarian cancer. The members of the committee were strongly supportive of her ideas and several had family members or friends who had been affected by this terrible disease. The Medical Research Society monitors her activity and is expecting great things from Dr. Eisenmann. This summer, we anticipate a new round of applicants and awards.

Some may wonder why our medical school, as well as most medical schools, go to such lengths to support and conduct research. Shouldn't we just train doctors to take care of patients? The process of biomedical discovery has been and continues to be a critical and integral component of medical education in the U.S. It:

- creates new treatments and cures
- helps us understand health and disease
- links medical care to scientific evidence
- provides training opportunities for aspiring doctors, scientists and others

For these reasons, we are entirely grateful to the members of the Medical Research Society for their support and to the scientists who improve our lives.

Sincerely,

A handwritten signature in black ink that reads "C. J. Cooper". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Christopher J. Cooper, M.D.
Executive Vice President for Clinical Affairs
Dean of the College of Medicine and Life Sciences



UT SCIENTISTS DEVELOP
STATE-OF-THE-ART TEST TO MEASURE
**MICROCYSTIN
LEVELS**

When more than 400,000 Toledo area residents were left without safe drinking water in the arid days of August 2014, microcystin suddenly became a household word. Television viewers repeatedly saw the infamous glass of green water from Lake Erie and, understandably, had many questions. What was it? What was considered a safe level of microcystin in the water? What would happen if residents drank contaminated water?

With a two-year grant from the Ohio State Board of Regents Sea Grant Program, several UT researchers are working to find new ways to measure microcystin levels in the human body and to help remove the toxin from Lake Erie waters.

The principal investigators in the study are Dr. Kenneth Hensley, Associate Professor of Pathology, Dr. Jason Huntley, Assistant Professor of Medical Microbiology and Immunology, Dr. Thomas Sodeman, Professor and Chief of Gastroenterology and Hepatology, and Dr. Youngwoo Seo, Associate Professor of the Department of Civil Engineering.

“The primary issue is that there is currently no fast and convenient way to measure microcystin and the glutathione metabolite it creates in the body,” explained Dr. Hensley, who is developing state-of-the-art mass spectrometry assays to do just that. “Once the body ingests the microcystin, it begins to metabolize the toxin and excrete it, which makes it difficult to measure the exposure of the toxin in the body through blood and urine samples.”

By creating an assay that can measure exposure in the human body, hospitals and health care providers would be able to determine the level of the metabolite and whether it poses a risk to the general public, and specifically to persons with liver damage, where the microcystin conjugates with glutathione.

Dr. Sodeman has been researching the impact of microcystin on persons with liver disease through studies on mice with liver disease (fatty livers). The study will help determine if certain individuals are more sensitive to microcystin. With about a third of Americans having fat in their livers, and about 10 percent of those having liver damage as a result, understanding the impact of microcystin on the liver is particularly important for Northwest Ohioans. While the study cannot determine the toxic level of microcystin in the body, its results can help persons with fatty livers or those with liver disease be aware of their increased sensitivity to the toxin. The information may offer practical applications, such as recommending that persons with increased sensitivity avoid the water during active algal blooms.

According to the EPA, “harmful algal blooms are a major environmental problem in all 50 states.” It is estimated that microcystin is found in 30 percent of lakes in the U.S.

The ideal scenario to avoid toxic levels of microcystin in the water is to remove them from Lake Erie. Dr. Huntley, who has extensive experience in studying biofilms (thin layers of bacteria) and their role in bacterial virulence, is using a similar approach to provide a safe, chemical-free way to remove microcystin toxins in municipal water treatment plants. The biofilters, which are water filters coated with a non-toxic, living bacteria, will help degrade microcystin by essentially creating a battle in which bacteria fights bacteria. In this scenario, the biofilters win and cities have a safer method for treating lake waters for toxins.

Dr. Huntley’s team is currently isolating and growing naturally occurring microcystin-degrading bacteria from Lake Erie. They will screen the samples for the most efficient strains, then use those strains to form biofilms on common water filtration filters. Dr. Seo, an expert in water treatment plants, is testing municipal water filters and filtration systems.

Once they achieve optimal biofilm formation conditions, the ultimate goal is to develop a large-scale water filtration system in the lab, and test the biofilter with water spiked with microcystin. Dr. Seo and municipal water filtration experts will then design large-scale biofilters that could be used in municipal water treatment plants, such as the city of Toledo’s.

MICROCYSTINS

- Microcystins are naturally-occurring toxic chemical substances produced by *Microcystis*, a waterborne photosynthetic bacteria. Although not true algae, they are sometimes referred to as "blue-green algae," and are found in "algal" blooms. The microcystin toxin is released when the *Microcystis* cells die and break open.
- Algal blooms can develop quickly in lakes with high nutrient levels, particularly phosphorus and nitrogen, and can expand rapidly in calm, warm weather.
- It is believed that global warming, terrestrial runoffs from fertilizers used on farms and lawns, and leaky septic tanks have all fueled an increase in algal blooms.
- As the shallowest of the Great Lakes, Lake Erie is most at risk for algal blooms, particularly the western basin, which is less than 26 feet deep.
- According to the Environmental Protection Agency (EPA), these blooms "can persist with adequate levels of phosphorous and nitrogen, temperatures in the 5 to 30 degree C (41 to 86 degrees F) range and pH in the 6 to 9 range, with most blooms occurring in late summer and early fall."
- Because microcystin toxins are stable at high temperatures, boiling tap water does not kill the toxin, and can make the problem worse by killing *Microcystis* bacteria, releasing more toxin.
- The EPA's most recent guidelines regarding microcystin levels in drinking water are:
 - For children younger than school age, the limit is 0.3 parts per billion.
 - For all others, the threshold is 1.6 parts per billion.
- Toxic levels of microcystin can cause nausea, dizziness, diarrhea, numbness, and liver inflammation.
- Animals that drink or swim in water with algal blooms can be exposed to deadly levels of microcystin.

Toledo is Not Alone

30%

**of U.S. lakes
contain microcystin**

- According to the EPA, "harmful algal blooms are a major environmental problem in all 50 states." The agency estimates that microcystin is found in 30 percent of lakes in the U.S.

- According to the National Oceanic and Atmospheric Administration, "the economic damage of algal blooms across the country exceeds \$100 million [annually], including expenses related to public health, coastal monitoring and management, and losses for fishing and the tourism industries."

\$100M

**estimate of annual
national economic
damage due to
algal blooms**



60+ dolphins



120+ manatees



50+ sea lions



fish kills

- Toxic algal blooms likely killed as many as 60 dolphins and 120 manatees in Florida in 2013 and have also caused massive fish kills. In 2015, a large algal bloom in waters off California closed recreational and commercial fishing and resulted in the deaths of as many as 50 sea lions in northern California.

SALIVARY BIOMARKERS MAY TAKE THE GUESSWORK OUT OF CONCUSSION DIAGNOSIS

A concussion was once a rite of passage for young athletes. A hit to the head, a few wobbly stumbles, and then a return to the game were worn like badges of honor. Today, concussions are more likely to be considered a flag on the play. An increased awareness of the long-term impact of concussions, the untimely deaths of athletes, and questions regarding the safety of contact sports, particularly football, have left many parents hesitant, and coaches and trainers more cautious when concussions come into play.

For decades, diagnosing a concussion has been an Achilles' heel of sports medicine.

"The diagnosis of a concussion is still subjective," said Dr. Kris Brickman, Chairman of the Department of Emergency Medicine at UTMC. "A player might have some blurred vision or ringing in the ears, but there is no scientific way of determining if he or she has had a concussion, and, if he has, how severe that concussion is. There is no definitive marker that tells us that this person should come out of the game, this person can go back to play, or this person needs medical care.

"Most concussions do not cause immediate cognitive impairment, so the current subjective methods are less than ideal," he added. "Even an MRI will not show the difference between a mild or severe concussion."

As more reports surface of athletes suffering from chronic traumatic encephalopathy, a degenerative disease directly related to repeated brain injuries, parents, in particular, are questioning if children should engage in contact sports.

Stories like those of Kosta Karageorge, the Ohio State University defensive lineman who died from a self-inflicted gunshot wound after telling his mother "these concussions have my head all messed up," add to the awareness of the sometimes dire results of concussions.

Dr. Brickman is leading a local research study that could take diagnosing a concussion into a decidedly more scientific realm. The team also includes Dr. Kenneth Hensley, Associate Professor in the Department of Pathology, Dr. Daniel Gaudin, Assistant Professor in the Department of Surgery, and Dr. David Giovannucci, Professor in the Department of Neurosciences.

The team is measuring a salivary biomarker in high school football players at St. John's Jesuit High School, where Dr. Brickman is the school's team physician.

"We took initial saliva samples from the players when practice began," Dr. Brickman said. The samples have been frozen and will be compared against additional saliva samples throughout the season, particularly after a suspected concussion has occurred.

The salivary biomarker they are studying is a phosphoprotein, CRMP-2, part of the collapsin response mediator protein family. The researchers will compare the levels of CRMP-2 in the saliva before the season began with the saliva samples taken after suspected concussions.

"Some proteins show an elevation after an injury," said Dr. Hensley, a pioneer in assessing the role of CRMP-2 in neurodegenerative diseases such as Alzheimer disease and Parkinson disease. Dr. Hensley is performing the assays on the saliva samples. "When we look at the CRMP-2 after a concussion or blow to the head, we see a cleaved form of CRMP-2 (a process in which a small part of the protein breaks off)."

"The applications are enormous not just for sports, but for the military, and many other places where concussions occur," said Dr. Brickman.

"Football is the new boxing. There is a price to pay for continued trauma to the head.

"Eventually, we hope to develop a device that could detect these biomarkers through a saliva test done in the field," he added. "It's non-invasive and you would get immediate results, which would allow trainers and coaches to determine if a player needs medical attention or is cleared for play."

The CRMP-2 marker could also help determine if an individual has had multiple concussions.

"If an athlete plays with an undiagnosed concussion, and then suffers another concussion, the medical repercussions increase tremendously," said Dr. Brickman.

"MOST CONCUSSIONS DO NOT
CAUSE IMMEDIATE COGNITIVE
IMPAIRMENT, SO THE CURRENT
SUBJECTIVE METHODS ARE LESS
THAN IDEAL."



“A BIOMARKER WILL HELP US DETERMINE WHAT DRUGS AND WHAT DOSAGES WILL BEST TREAT THE INJURIES.”

“The human brain is designed to have kids fall on their faces,” said Dr. Hensley. “But it is not designed to have them fall on their faces again, and again, and again.”

“Helmets can only do so much,” he said. “Protective gear can help shunt the force of an external blow, but it cannot stop the deceleration of the brain and keep it from hitting the skull.”

Every hit to the head, Dr. Hensley continued, is unique, with varying levels and degrees of harm to brain tissue. The goal is to diagnose and treat concussions as appropriately as possible to mitigate this damage.

Using biomarkers like CRMP-2 could also have tremendous applications not only in diagnosis, but in treating concussions and traumatic brain injuries, according to Dr. Hensley.

“A biomarker will help us determine what drugs and what dosages will best treat the injuries.”

A JOLT TO THE HEAD

- Each year, an estimated 136,000 to 300,000 high school concussions are reported. (American Journal of Sports Medicine)
- According to the Centers for Disease Control and Prevention, the estimated number of sports and recreation-related traumatic brain injury visits to emergency departments increased 62 percent from 2001-09.
- A 2012 study by the National Academy of Sciences found that football players sustain the most concussions of all high school-aged athletes, with 11.2 concussions reported per 10,000 athletic exposures.
- Soccer is the highest risk sport of concussions for girls, with 6.7 reported injuries per 10,000 athletic exposures, according to a 2012 NAS study.
- High school athletes who sustain a concussion are three times more likely to sustain a second concussion, according to the American Journal of Sports Medicine.
- More than 45 percent of athletes do not report feeling any symptoms after suffering a concussive blow.

CONCUSSIONS

According to Dr. Hensley, a concussion, also referred to as a mild traumatic brain injury, can be caused by a bump, blow, or jolt to either the head or the body. The force causes the brain to rapidly accelerate and then decelerate within the skull. The brain hits the inside of the skull on acceleration and again on deceleration.

A rotational concussion can also occur, in which the head swings rapidly from side to side, causing shearing of the brain tissues.

The U.S. Department of Health and Human Services, Centers for Disease Control and Prevention has published the following list of signs, symptoms and behaviors consistent with a concussion:

Symptoms Reported by Athlete

- Headache
- Nausea
- Balance problems or dizziness
- Double or fuzzy vision
- Sensitivity to light or noise
- Feeling sluggish
- Feeling foggy or groggy
- Concentration or memory problems
- Confusion

Signs Observed by Others

- Appears dazed or stunned
- Is confused about assignment
- Forgets plays
- Is unsure of game, score, or opponent
- Moves clumsily
- Answers questions slowly
- Loses consciousness
- Shows behavior or personality changes
- Cannot recall events prior to hit
- Cannot recall events after hit



RETURN-TO-PLAY PROTOCOL

“If a student is removed from practice or competition due to a suspected concussion or head injury, the coach or referee who removes the student shall not permit the student, **ON THE SAME DAY THE STUDENT IS REMOVED**, to return to that practice or competition or to participate in any other practice or competition for which the coach or contest official is responsible. Thereafter, which means no earlier than the next day, the coach or contest officials shall not permit the student to return to practice or competition until both of the following conditions are satisfied:

- 1) The student’s condition is assessed by either of the following:
 - a. A physician, who is a person authorized under Chapter 4731 of the Ohio Revised Code to practice medicine and surgery or osteopathic medicine or surgery (M.D. or D.O.)
 - b. Any other licensed health care provider that the school district board of education or other governing authority of a chartered or non-chartered nonpublic school, authorizes to assess the student who has been removed from practice or competition
- 2) The student receives written authorization that it is safe for the student to return to practice or competition from a physician or other licensed health care provider authorized to grant the clearance.”

CAMPUS CAPSULES

DR. JUAME NAMED CHIEF OF ENDOCRINOLOGY

Dr. Juan Jaume, Professor of Medicine, has been named Chief of Endocrinology, Diabetes and Metabolism and Clinical Director of the Center for Diabetes and Endocrine Research (CeDER). Dr. Jaume relocated to Toledo in 2014 from the University of Wisconsin-Madison. He completed his training at Albert Einstein College of Medicine in New York and the University of California-San Francisco, where he also completed a molecular medicine fellowship.

Dr. Jaume oversees UT's, Division of Endocrinology, Diabetes and Metabolism and co-directs CeDER. This year, he also became Co-Director of the MD/PhD program for the College of Medicine and Life Sciences. His research focuses on endocrine-immune dysfunction as it affects different glands, such as endocrine/pancreas in Type 1 diabetes and the thyroid in hypo/hyperthyroidism, as well as tumor immunity in thyroid cancer. Dr. Jaume has more than 75 peer-reviewed publications and authors chapters in best-selling cancer and endocrine textbooks. His research has been funded by federal and private institutions.



GEORGE ISSAC, IN MEMORIAM



Longtime supporter of the Medical College of Ohio and former Chairman of the MCO Board of Trustees George Isaac passed away Jan. 11, 2015. A native of Bryan and the youngest of nine children, Mr. Isaac was appointed to a nine-year term on the Medical College Board of Trustees in 1987 by then-Gov. Richard Celeste. Mr. Isaac became Chairman in 1991. He was also a past trustee of the Medical College of Ohio Foundation and established the George Isaac Endowed Professorship in Cancer Research at the Medical College of Ohio, which awarded him an honorary Doctor of Humane Letters degree.

Mr. Isaac also established the George Isaac Presidential Scholarship, a full-tuition scholarship awarded to a first-year medical student who demonstrates exceptional academic performance and leadership potential in the field of medicine.

In 2006, Mr. Isaac donated \$1 million toward an outpatient surgery center. The facility was later named the George Isaac Minimally Invasive Surgery Center. The center is equipped with leading-edge technology and the area's leading specialists in gastrointestinal conditions, colorectal concerns, cosmetic/reconstructive surgery, skin cancer/cyst removal, kidney stones and orthopaedic repair.

ANNUAL GOLF OUTING SUPPORTS SCHOLARSHIP

The 6th Annual UT College of Medicine and Life Sciences Golf Classic was held in June 2015 at the Toledo Country Club. The event supports the Better Together Scholarship Fund, established in 2011 by ProMedica Health System and The University of Toledo. Income from this fund provides scholarships for entering and continuing University of Toledo Medical Center students from one of the 27 counties in the ProMedica/UT service areas. The Better Together Scholarship Fund has awarded \$444,700 to scholarship recipients. The scholarship provides a minimum of \$25,000 per year to each of eight students; two additional scholarships are offered annually.



DR. KHOURI NAMED ENDOWED PROFESSOR

Dr. Samir Khouri, Director of Non-Invasive Cardiology at UT Health, has been named the Adela and Alfred Mundt Endowed Professor in Transplantation Cardiology. Dr. Khouri's area of expertise is the diagnosis of diastolic heart failure and pulmonary hypertension, as well as the interaction between the kidney and the heart. He earned his medical degree at Damascus University College of Medicine, completed his residency in internal medicine at Indiana University, and completed a fellowship in cardiology at Ohio State University.

In May 2015, Dr. Khouri participated in a UT Health-funded mission to the poverty-stricken city of La Ceiba, a city of 250,000 in Honduras. He was the first cardiologist to treat patients in the city.



RESEARCH SOCIETY AWARDS FIRST GRANT

The University of Toledo Medical Research Society awarded its first grant to a professor working to develop a life-saving ovarian cancer treatment. Dr. Kathryn Eisenmann, Assistant Professor in the College of Medicine and Life Sciences, received the \$50,000 grant to support her research to develop a drug that will allow cancer-fighting treatments to more effectively penetrate tumor cells.

"Many anti-cancer drugs work poorly because they do not penetrate tumors. Tumor cells are packed so tightly that drugs cannot easily pass through these cells," Dr. Eisenmann said. "My research is going to look at a new drug that blocks tumor cells from binding so tightly together. If successful, combining this new drug with current drugs used to treat ovarian cancer will allow more of the cancer-fighting drugs to enter and kill the tumor."

The Medical Research Society, which consists of 30 individuals representing community and medical leadership, selected Dr. Eisenmann's proposal because she had the potential to secure additional funding and make a significant difference in the fight against ovarian cancer.

The society's founding member, Marianne Ballas, the owner of Ballas Buick, GMC and a member of the UT College of Medicine Advisory Council, founded the Medical Research Society in 2014 to help junior faculty who are just starting their scientific careers. Since then, the society has gained 30 members who each have made \$25,000 commitments and together garnered a \$1 million matching donation from The University of Toledo Physicians (UTP).

CAMPUS CAPSULES

IISC CELEBRATES ANNIVERSARY

The University of Toledo's Lloyd A. Jacobs Interprofessional Immersive Simulation Center marked its one-year anniversary in April 2015. The three-story, 65,000 square-foot facility features 3D and virtual immersive environments for medical education. The first floor features a virtual immersive reality center, an advanced clinical simulation center is on the second floor, and a progressive anatomy and surgical skills center is on the third floor.

The center allows for preparation for team training; electronic learning; competency assessment; and outcomes measurement as routine components of training for all health professionals.

In addition, the IISC serves as a hub for innovation and the fostering of partnerships with industry to create and develop new products, processes and procedures that enhance patient care.

The center is named for Lloyd A. Jacobs, who served as UT's president from 2006-2014 and oversaw the merger between the Medical College of Ohio and UT. He was the sixth president of MCO before the merger. Dr. Jacobs' presidential portrait was unveiled at the event.



DR. GRUBB RECEIVES NATIONAL AWARD

Dr. Blair Grubb, Professor of Medicine and Director of Electrophysiology, was named 2015 Physician of the Year by Dysautonomia International. A world-renowned autonomic specialist, Dr. Grubb received the award in Washington D.C. Dr. Grubb is a globally recognized cardiologist and an expert in syncope (unexplained and unpredictable fainting) and postural orthostatic tachycardia syndrome (POTS), a malfunction of the autonomic nervous system. In addition to this recent award, Dr. Grubb was recognized as one of America's Top Doctors in 2002 and from 2004-2007.

Dysautonomia, which mainly afflicts women, affects the nerves that carry information from the brain and spinal cord to the heart, bladder, intestines, sweat glands, pupils, and blood vessels. Dr. Grubb has treated patients from across the globe, including Australia, Saudi Arabia, Israel, and Great Britain.

Dr. Grubb has been a faculty member at UTMC since 1988 and published more than 250 journal articles. He is working on isolating antibodies causing POTS, which would allow for the development of a standardized blood test.



BRYAN COMMONS REDEDICATED

A spot for relaxation and reflection at The University of Toledo Medical Center received a rejuvenation this summer.

UTMC refurbished the landscaping and replaced the monument at the Dorothy and Ashel Bryan Academic Commons, which is located between the Eleanor N. Dana Cancer Center and the Radisson Hotel.

Howard Newman, UT Associate Vice President for Development, said the improvements revitalized the garden area, which is enjoyed by patients, visitors and UTMC staff.

“We have always been so appreciative of the Bryans and their generosity, so we wanted to make sure that their namesake was well maintained and represented the intent of their donation.”

David Bryan’s family started the Bryan Commons more than 20 years ago. His late father, Ashel, served on the Board of Trustees at the former Medical College of Ohio.

“It was my father’s idea because he knew that families of patients might stay in the hotel and want to go to the garden after a long and stressful day,” Bryan said. “He thought there should be a peaceful place to spend quiet time given their situation.”

Bryan said his father worked with the hospital and designers to make sure the area, which includes a small water fountain, was beautiful and soothing.

“I am very happy with the improvements. I think this is an example of my parents’ philanthropy and it shows that they were thoughtful about their philanthropy,” Bryan said.



DR. BINA JOE NAMED CHAIR

Dr. Bina Joe has been named Chairman of Physiology and Pharmacology of The University of Toledo College of Medicine and Life Sciences. Dr. Joe is the founding Director of UTMC’s Center for Hypertension and Personalized Medicine.



DR. SELMAN HONORED AT RETIREMENT

The University of Toledo’s Department of Urology Library was renamed the Dr. Steven H. Selman Urology Library in July 2015, on the occasion of his retirement. Dr. Selman was Chair and Professor, Urology Director, and Director of the Urological Research Residency Program. A native of Toledo, Dr. Selman joined MCO in 1981. He is a pioneer in laser and photodynamic therapy of urologic diseases.

PUTTING FATIGUE TO REST:

UT RESEARCHERS IDENTIFY
SALIVARY BIOMARKERS
FOR FATIGUE AND DEVELOP
MOLECULAR SENSOR
MODEL TO MEASURE
FATIGUE LEVELS



It is not surprising that in a society where most Americans have grown accustomed to a 24/7 world, and where Red Bull touts a \$1.6 billion global brand, fatigue has become a major issue in nearly every profession.

How to measure fatigue remains at the crux of nearly all those professions.

“There is currently no gold standard for determining the level of fatigue in individuals,” said Dr. David Giovannucci, Professor of Neurosciences in The University of Toledo College of Medicine and Life Sciences. “People tend to self report fatigue, but we need a more definitive test.” A rapid, quantitative test could assist everyone from the Air Force, to the medical profession, to the transportation industry.

Dr. Giovannucci and a team of researchers are studying salivary biomarkers that could provide that quantitative test. The three-year, \$1,200,000 study, which began in 2013, is funded by a grant from the United States Air Force Office of Scientific Research with matching funds from the UT College of Medicine and Life Sciences.

Other members of the team include Dr. Dragan Isailovic, UT Associate Professor of Chemistry, Dr. Brent Cameron, UT Professor of Bioengineering, and Dr. Kenneth Hensley, UT Associate Professor of Pathology.

“Fatigue puts all types of persons at risk,” said Dr. Giovannucci. “It diminishes performance, affects decision making, and can cause extensive collateral damage and injuries in some professions.”

In fact, most experts believe fatigue was partly to blame for the largest oil spill in U.S. waters when the Exxon Valdez spilled nearly 11 million gallons of crude oil into Alaska’s Prince William Sound. Fatigue factors into thousands of automobile crashes each year as well. According to the National Highway Traffic Safety Administration, of the police-reported crashes that occur annually, more than 100,000 are the direct result of driver fatigue. These crashes result in an estimated 1,550 deaths, 71,000 injuries, and \$12.5 billion in monetary losses.

“FATIGUE PUTS ALL TYPES OF PERSONS AT RISK ... ”

Using saliva biomarkers as the basis for measuring fatigue offers a number advantages.

“Saliva is easy to collect; it’s rich in chemical markers, and it’s a noninvasive process,” said Dr. Giovannucci. Humans produce an average of 1.5 liters of saliva each day, and the watery substance contains more than 1,000 proteins.

The research team is using a liquid chromatography mass spectrometry, which can identify hundreds of proteins in the saliva. They are looking for changes in proteins and protein modifications in response to fatigue.

Dr. Giovannucci’s team has already identified more than 60 different proteins that could potentially be novel biomarkers. Of those, two have shown promise in identifying and measuring fatigue.

“The levels of these two proteins biomarkers are increased two- to six-fold in saliva as a response to stressors associated with stress or fatigue,” said Dr. Giovannucci.

The study involves collecting saliva samples from medical residents before and after they complete a number of simulated medical activities over a period of one to two hours. The team will examine about 100 residents throughout the three-year study.

“We’ve partnered with the UT Advanced Clinical Simulation Center to create real-world scenarios that residents deal with in an emergency room setting,” said Dr. Giovannucci. Dr. Paul Rega designed the scenarios, which can be as easy as evaluating a child complaining of a stomach ache, to as intense as dealing with multiple victims suffering from blast trauma.



“ULTIMATELY, WE WOULD LIKE TO IDENTIFY A PANEL OF PROTEINS THAT CHANGE IN RESPONSE TO FATIGUE.”

A physician assesses the residents’ performance or a technician presents psychometric tests to the residents to provide a snapshot of their cognitive state. The research team compares saliva samples from the residents taken before and after the simulation activities. The saliva samples are compared to a baseline “waking” saliva and attempts are made to account for time-of-day variances.

“We’re looking for chemical signatures such as specific proteins that could eventually be used to create sensors for measuring fatigue,” said Dr. Giovannucci.

“Ultimately, we would like to identify a panel of proteins that change in response to fatigue. The more proteins we identify, the better the sensor we can develop.”

Dr. Cameron is designing a molecular sensor model that could be used to obtain and measure fatigue in the field.

“The ideal sensor is one that could be used anywhere,” said Dr. Giovannucci. “For example, pilots could wear remote sensors that measure fatigue levels and relay those levels back to a command center.”

Early results of the study have already garnered additional support from the Air Force. Following a site visit to UTMC in 2014, the Air Force awarded the team another \$900,000 grant for a high-resolution mass spectrometer.

FATIGUE VERSUS TIRED

The terms fatigue and tired are often used interchangeably, but the differences are actually quite pronounced. Being tired or sleepy is the body’s natural response to working, being active and in an awake state. It is usually alleviated by a good night’s rest. Fatigue, on the other hand, is a more pronounced and chronic state of a persistent lack of energy. It can lead to impaired judgment, slowed response time, decreased alertness, low energy, and an inability to start or complete a task. A good night’s sleep will not automatically relieve fatigue.



FATIGUE TAKES A TOLL

- The National Highway Traffic Safety Administration estimates that 100,000 police-reported crashes are the direct result of driver fatigue each year. These crashes result in an estimated 1,550 deaths, 71,000 injuries, and \$12.5 billion in monetary losses.
- Pilot fatigue factored into 16 of the 228 Class A mishaps that occurred between fiscal 2007 and fiscal 2011, according to the Air Force Safety Center. Class A mishaps are accidents that caused loss of life, aircraft, or \$2 million or more in damage. During that same period, fatigue was a factor in two of the 47 nonaviation-related accidents that the center tracked.
- In the last 16 years, fatigue has been associated with 250 fatalities in air carrier accidents, according to the National Transportation Safety Board
- A study by the Federal Railroad Administration showed that human factor errors are responsible for almost 40 percent of all train accidents over the past five years and that fatigue played a role in approximately 25 percent of the accidents.
- According to the Journal of Occupational and Environmental Medicine, fatigued workers cost employers \$136.4 billion annually in health-related lost productive time, which is almost quadruple that of their non-fatigued counterparts.
- According to the Federal Motor Carrier Safety Administration (FMCSA), more than 750 people die and 20,000 more are injured each year due directly to fatigued commercial vehicle drivers.

The image shows the front of a blue car that has been involved in a collision. The hood and front bumper are crumpled and damaged. The car is parked on a light-colored surface. A semi-transparent blue horizontal band is overlaid across the top half of the image, containing white text. The text reads: "UT RESEARCHER FOCUSES ON Functional MRIs to Help Predict PTSD".

UT RESEARCHER FOCUSES ON

Functional MRIs to Help Predict PTSD

With more than 5 million police-reported car accidents occurring annually, Americans have more to be concerned about than the collisions themselves. Up to 25 percent of accident victims will go on to suffer some form of post-traumatic stress disorder (PTSD) within six weeks of the traumatic event.

PTSD in persons who have experienced a motor vehicle collision can result in anxiety, headaches, sleeplessness, and other debilitating emotional and physical symptoms. The individuals may become afraid to drive, relive the trauma in their minds, or begin to avoid activities or places associated with the trauma.

Dr. Xin Wang, Associate Professor in the Psychiatry, Neurosciences and Radiology departments, is researching biomarkers that could indicate structural and functional changes in the brain that occur in victims of motor vehicle accidents. The research can help develop effective approaches for preventing and treating PTSD.

The research project is funded by the National Institute of Mental Health, The University of Toledo, the Translational Research Stimulus Award from ProMedica and the William Bauer fMRI Research Fund.

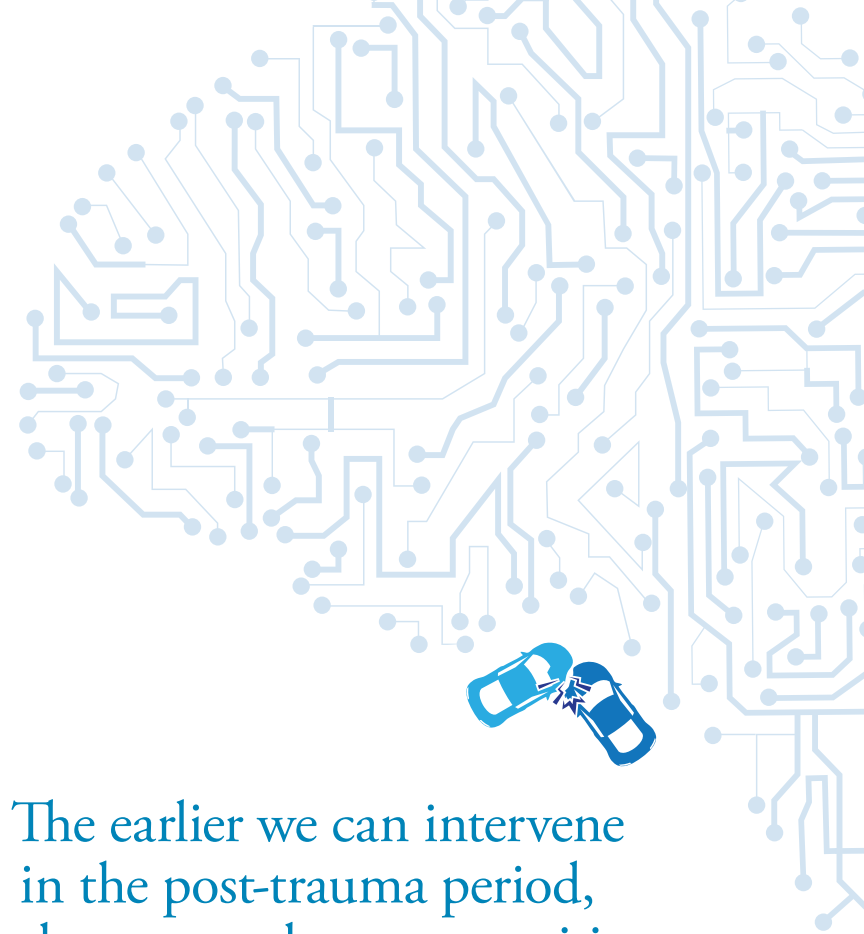
“We are working on proving that not only do some persons involved in motor vehicle collisions suffer trauma which frightens them, they also experience changes in their brains that put them at risk for PTSD.”

“This research fills an important gap in current models of how PTSD develops,” added Dr. Wang. “We are identifying changes in the brain that will help distinguish between a natural recovery following traumatic stress from a maladaptive recovery that leads to PTSD. The earlier we can intervene in the post-trauma period, the greater the opportunities we have to prevent or attenuate PTSD. Earlier diagnoses could minimize the costs and suffering associated with PTSD.”

The research involves studies on persons who have been involved in motor vehicle accidents. The participants are recruited through the hospital’s Emergency Department and evaluated within the initial days of their accidents, then again approximately three months following their accidents. The patients complete surveys, psychological assessments, and also undergo two types of MRIs.

The most critical tool is the use of functional magnetic resonance imaging (fMRI). UPMC is the only hospital in Northwest Ohio that uses this state-of-the-art diagnostic tool.

“A functional MRI is an ideal research tool for several reasons,” said Dr. Wang. “It is extremely safe, non-invasive, and non-radioactive.”



The earlier we can intervene in the post-trauma period, the greater the opportunities we have to prevent or attenuate PTSD.


Dr. Wang’s team used a Reappraisal Emotion Regulations Task (REERT) during the fMRI test. The fMRI measures the brain’s response to certain emotions, such as fear, evoked through images the participants view, such as a car accident.

The research team also conducts high resolution structural MRI scans to examine the brain’s cortical thickness in the participants.

The research indicates that certain regions of the brain experience significant changes in persons with PTSD.

“We found the motor vehicles survivors who developed PTSD have smaller hippocampi and rostral anterior cingulate cortex volumes within 10 days to three months after the accident, compared to the non-PTSD motor vehicle survivors,” said Dr. Wang. “We also found a difference in the progressive changes in the emotion-task activity, volume and thickness of the prefrontal cortex in PTSD and compared to non-PTSD survivors over the same time period.”

Dr. Wang noted that the observed decreases in thickness, volume and activity in certain brain regions over the three-month post-trauma period in PTSD survivors leads to a loss of inhibitory influences on fear emotion generated by the prefrontal cortex, which is a key emotion-regulatory region in humans. These findings suggest that trauma such as that experienced in motor vehicle accidents may cause emotion circuit changes that can contribute to PTSD in some people.



The earlier we can intervene in the post-trauma period, the greater the opportunities we have to prevent or attenuate PTSD.

“Essentially, in some persons, the prefrontal cortex has experienced a deficit in controlling fear,” said Dr. Wang. “When some persons who have been in a car accident receive some cue that reminds them of the trauma, such as seeing the same color car approaching them, they may not be able to control the fear associated with it. This type of response leads to PTSD and can significantly impair their daily lives.

“These findings, coupled with studies of contributing factors of PTSD, like the level of family support, give us a much more comprehensive understanding of the pathogenesis of PTSD,” said Dr. Wang.

“For the majority of people, PTSD is completely treatable,” he added. “PTSD is vastly underdiagnosed in the United States and many people suffer from it needlessly.”

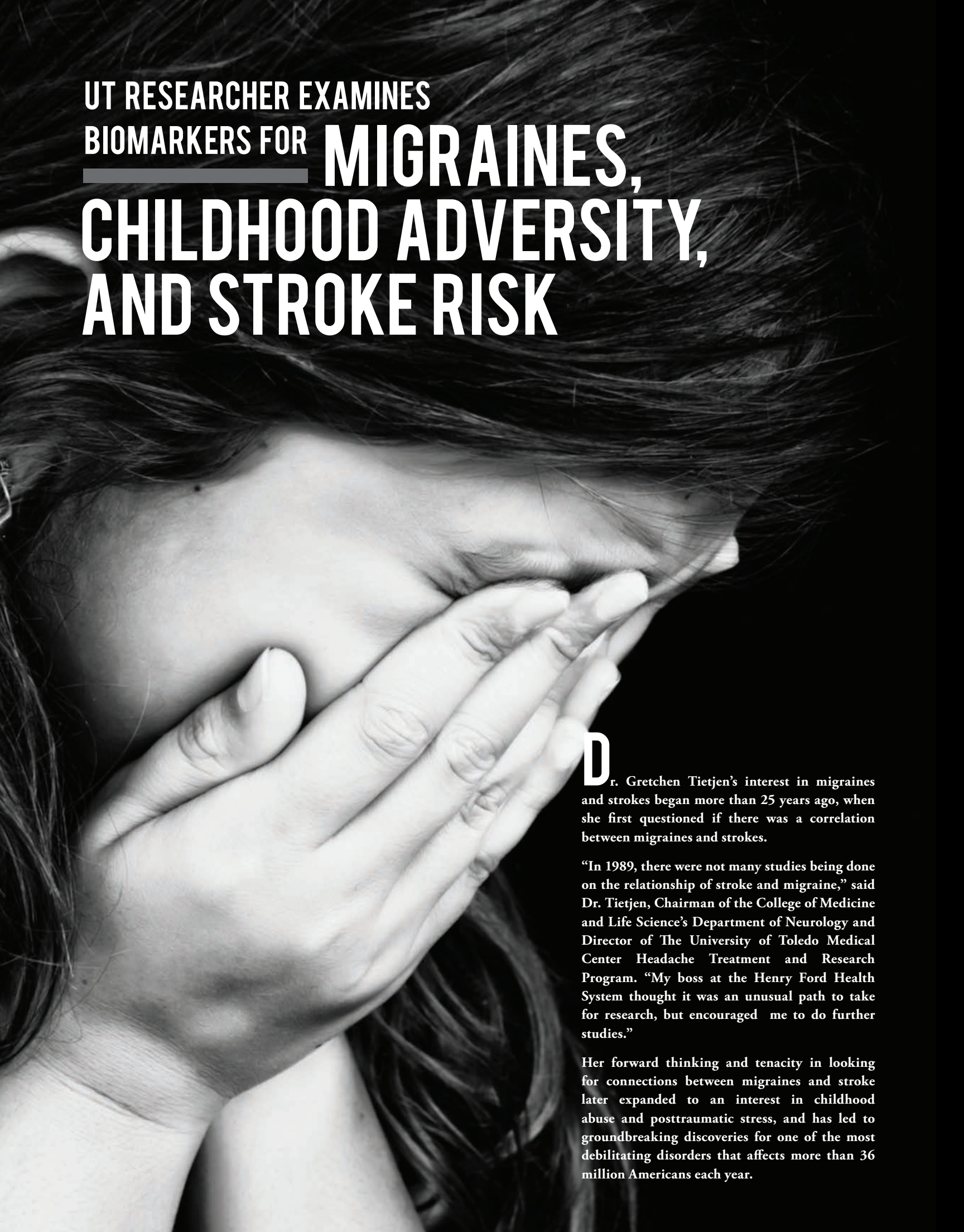
This research, he said, could have a tremendous impact on how PTSD is diagnosed and treated. Biomarkers such as fMRI would help determine which persons are at risk for PTSD and could be used to screen individuals at high risk for trauma, such as firefighters and soldiers. Testing for biomarkers also could help persons who test positive receive treatment much earlier.

POST-TRAUMATIC STRESS DISORDER

According to PTSD United, “70 percent of adults in the U.S. have experienced some type of traumatic event at least once in their lives. This equates to approximately 223.4 million people. Up to 20 percent of these people go on to develop PTSD. Today, that equates to approximately 44.7 million people who were or are struggling with PTSD.”

According to the National Center for PTSD, U.S. Department of Veterans Affairs, motor vehicle accidents account for over three million injuries annually and are one of the most common traumas individuals experience.

Symptoms of post-traumatic stress disorder may include nightmares, flashbacks, avoidance (avoiding situations or activities that make the individual anxious, such as staying away from crowds, or avoiding driving), changes in relationships, paranoia, hyperarousal (feeling keyed up), sleeplessness, trouble concentrating, anxiety, being startled by loud noises, and irritability. PTSD can be relatively minor or totally disruptive to everyday activities.

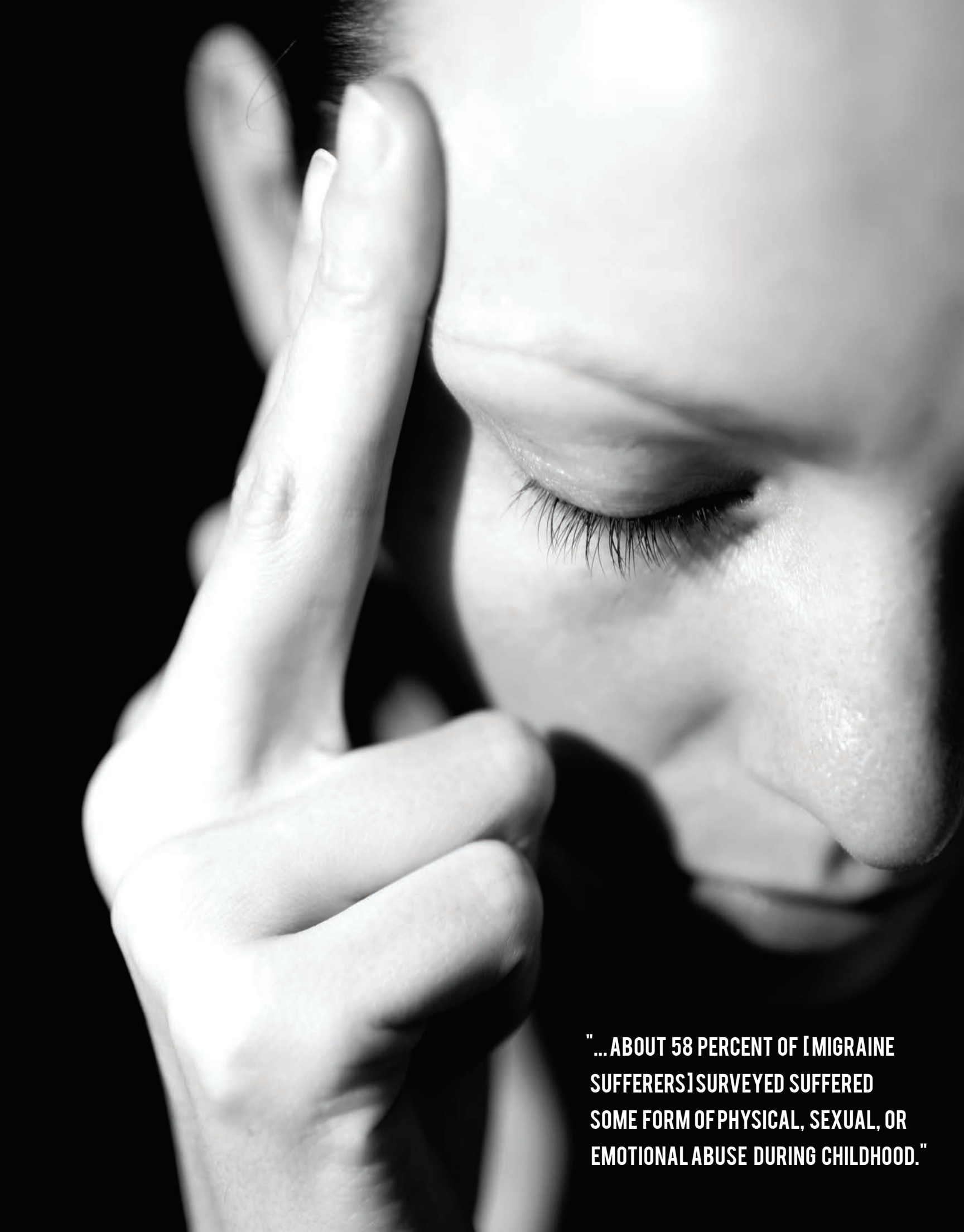


UT RESEARCHER EXAMINES
BIOMARKERS FOR **MIGRAINES,**
CHILDHOOD ADVERSITY,
AND STROKE RISK

Dr. Gretchen Tietjen's interest in migraines and strokes began more than 25 years ago, when she first questioned if there was a correlation between migraines and strokes.

"In 1989, there were not many studies being done on the relationship of stroke and migraine," said Dr. Tietjen, Chairman of the College of Medicine and Life Science's Department of Neurology and Director of The University of Toledo Medical Center Headache Treatment and Research Program. "My boss at the Henry Ford Health System thought it was an unusual path to take for research, but encouraged me to do further studies."

Her forward thinking and tenacity in looking for connections between migraines and stroke later expanded to an interest in childhood abuse and posttraumatic stress, and has led to groundbreaking discoveries for one of the most debilitating disorders that affects more than 36 million Americans each year.



"...ABOUT 58 PERCENT OF [MIGRAINE SUFFERERS] SURVEYED SUFFERED SOME FORM OF PHYSICAL, SEXUAL, OR EMOTIONAL ABUSE DURING CHILDHOOD."

Migraines are much more than a bad headache. Their symptoms—which can include nausea, vomiting, dizziness, sensitivity to light, sound, touch, and smell, intense throbbing on one side of the head, and visual disturbances—negatively impact careers, social activities, relationships, and education. According to the Migraine Research Foundation, “Over 10 percent of the population suffers from migraines, and American employers lose more than \$13 billion each year as a result of 113 million lost workdays due to migraine.”

Dr. Tietjen’s research has included studies of how childhood maltreatment alters brain development and, as a result, how these individuals may respond differently to stress and experience migraines as well as other chronic pain conditions, such as chronic fatigue syndrome, arthritis, and irritable bowel syndrome. In an earlier study, Tietjen’s research team collected data on childhood maltreatment from 1,348 people with migraines who were seen at 11 outpatient headache centers. The results indicated that about 58 percent of those surveyed suffered some form of physical, sexual, or emotional abuse during childhood. More than 60 percent also had another type of painful disorder.

As an adjunct to that study, Dr. Tietjen conducted additional research on a group of premenopausal women who had been part of a study between 2006 and 2008 regarding biomarkers and migraines. That initial study indicated a strong correlation between migraines and biomarkers for endothelial activation (a reactive state of the cells that line blood vessels), including oxidative stress, coagulation (clotting) and inflammation in interictal (or period between attacks of migraine).

“We had a tremendous response rate — 80 percent of the women from the first study responded to our second study,” said Dr. Tietjen. “The group included 120 women who had [assessments for] biomarkers for migraines and 50 women who were the control group.

“Our objective was to determine if adverse childhood experiences in this same group of premenopausal women were linked to migraine and to biomarkers of oxidative stress, coagulation, and inflammation.”

The women were asked to complete an adverse childhood experience (ACE) questionnaire, which included questions about emotional and physical neglect, and emotional, physical, and sexual abuse before the age of 18. The women were also asked if they were exposed to a dysfunctional household; one in which there was violence against a mother or stepmother, parental substance abuse, mental illness, criminal behavior or parental separation or divorce. An ACE score is determined by adding the total number of these types of exposures.

“We found that 71 percent of migraine patients reported at least one adverse childhood experience, compared to 46 percent of persons without migraine, and the average ACE score was three times higher,” said Dr. Tietjen. “We also found that the headaches presented earlier and more frequently in these individuals than those who had not been subjected to



abuse. But most exciting was the finding that biomarkers of endothelial activation, in particular those of inflammation, were higher in persons with early childhood adversity.”

The findings are significant for several reasons.

“Our study was the first to examine the association of biomarkers for endothelial dysfunction, migraine, and childhood adversity in the same cohort,” said Dr. Tietjen.

“Our early studies indicated that these women had biomarkers that are tied to increased stroke risk,” she said. “It follows that adverse childhood experiences may also play a role in the association of migraine and stroke.” The work suggests that childhood stress may lead to long-term abnormalities of blood vessels that, in turn, increase a patient’s risk for migraines and for stroke.

Dr. Tietjen explained that with endothelial dysfunction, vasodilators like nitric oxide are not as readily available to the blood vessel’s muscle layer. Endothelial dysfunction also results in vascular inflammation and elevated levels of proteins which cause coagulation. Since both migraines and stroke involve abnormal function of blood vessels in the brain, the endothelial dysfunction likely contributes to both conditions. In another study, Dr. Tietjen also found that livedo reticularis, a mottling of the skin that also results from abnormalities of blood vessels, was more prevalent in women with migraines. All of these markers could be used for determining a person’s risk for stroke.

“Our research could help us develop a more personalized treatment for people with migraines,” said Dr. Tietjen. “If their biomarkers indicate endothelial dysfunction and it’s determined they are at a high risk for strokes, we may determine they should be taking daily medications, such as aspirin and statins.

“There might also be cognitive behavioral therapies that could alter how some individuals respond to stressors, particularly stressors tied to headaches,” Dr. Tietjen continued. “Modifying how the person responds to stress could help lessen inflammation and endothelial dysfunction. That, in turn, could help prevent the occurrence of vascular diseases like stroke.”

COLLEGE OF MEDICINE AND LIFE SCIENCES CLASS NOTES

Dr. Thomas Wakefield (A/S '75, MED '78), head of vascular surgery at the University of Michigan Medical Center, has been appointed as a director of the University of Michigan Frankel Cardiovascular Center. The Frankel Cardiovascular Center combines advanced patient care, ground-breaking research, educational opportunities and a culture of collaboration and respect.

Dr. Joel Hellman (RES '87), a cardiologist, has joined SwedishAmerican Health System and Midwest Heart Specialists in Rockford, Ill. He will see patients at the SwedishAmerican Renaissance Pavilion in Rockford.

Dr. Raji Jacob (RES '10) has joined Perry Memorial Hospital in Princeton, Ill. as a new physician. She is board certified in nephrology and internal medicine. Dr. Jacob is employed with the Illinois Kidney Disease and Hypertension Center in Peoria.

Dr. Karen LaSalle (MED '10) has joined New Beginnings Pediatrics in Norwalk, Ohio. She also will join the medical staff at the Fisher-Titus Medical Center in Norwalk and the Bellevue, Ohio hospital.

Dr. Scott A. Frederick (UTCTC '88, Ed '91, MED '95, MED '01, RES '04) is now an Assistant Professor in the College of Medicine and Life Sciences at The University of Toledo. Dr. Frederick is teaching in the Internal Medicine Department.

Dr. Andrew Smock (MED '09) is a new physician at Genesis HealthCare System, located in Zanesville, Ohio. Dr. Smock specializes in urology.

Dr. Richard Paat (MED '86) was recognized at the 25th anniversary Diamante Awards. The awards recognize individuals and organizations for outstanding achievement and service to the Latino and greater Toledo community. The event is a collaboration between Bowling Green State University, Herzing University, Lourdes University, Owens Community College and The University of Toledo. Dr. Paat has provided free health care to the Latino communities of northwest Ohio, Guatemala and Honduras for more than 15 years.

Ben Batey (MPH '10) was selected as the Wood County Health District health commissioner. Batey has most recently served as chief executive for the Wood County Community Health and Wellness Center. He has also held other health district positions including epidemiologist and director of nursing.

Andrew Vollmar (MED '14) and Christine Carr were married on May 24, 2014 at Saint Peter Catholic Church in Canton, Ohio. Their reception was held at Congress Lake Country Club in Hartville, Ohio. They reside in Columbus, where Andrew is a resident in family medicine at Riverside Methodist Hospital.

Dr. Farhaan Mir (MED '08) has joined Grand Traverse Radiologists in Traverse City, Mich. and will specialize in diagnostic radiology and vascular and interventional radiology

Dr. Stacey Hoffman (MED '10) has joined Kingston HealthCare as the medical director and attending physician. Dr. Hoffman's initial focus is to manage Kingston's stroke recovery program and other specialized services that will enhance Kingston's clinical expertise. She will immediately serve patients at Kingston Rehabilitation in Perrysburg, Ohio.

Dr. Steve Huffman (A/S '87, A/S '88, MED '92) was elected to the Ohio House of Representatives for the 80th District. Dr. Huffman currently serves as the coroner in Miami County. He also played football at UT. Dr. Huffman was a three-year starter for the Rockets, a two-time all Mid-American Conference selection as linebacker and served as team captain in 1987. He also was a two-time all-MAC academic performer and the 1987 Jim Nicholson honoree.

Dr. Asma Taj (RES '11) joined St. Mary's of Michigan's medical staff as a medical oncologist. Dr. Taj is certified by the American Board of Internal Medicine and practices at St. Mary's of Michigan Towne Center in Saginaw, Mich.

Michael Ayre (MBA '86) has accepted the position of director of human resources at Wacker Chemical Corporation, located in Adrian, Mich.

Sara Martino (HHS '03, MPH '04, MHHS '07) received the 20 Under 40 Leadership Award for contributions to her community. Martino is a physician assistant in the emergency department at the UT Medical Center. One of her community contributions is her involvement with the Junior League for eight years, and she currently serves as sustainer representative to the volunteer resources council and has served as the nominating and placement chair, as well as board secretary.

Dr. Stephen M. Wojdyla (RES '01, MS '02) has joined Lima Dental Associates, located in Lima, Ohio. Dr. Wojdyla is a member of the American Dental Association, the Ohio Dental Association, Toledo Dental Society and the American Academy of Pediatric Dentistry. He is also a published author.

Dr. Meghan Zysik (MED '10) joined Albany Medical Center in New York as an assistant professor of obstetrics and gynecology. Dr. Zysik has an interest in contraception and family planning, abnormal bleeding and minimally invasive techniques.

Dr. Paul LoVerme (RES '85) has been named a "top doctor" in New Jersey Monthly Magazine for the 12th year in a row. Dr. LoVerme is a board certified plastic surgeon in Verona, N.J.

Dr. James Greene (MED '81) has been appointed deputy director for the Center for Health Statistics and Informatics at the California Department of Public Health, located in Sacramento, Calif.

Dr. Chris Goliver (MED '00) was named the medical director of Mercy Perrysburg Medical Center in Perrysburg, Ohio. Dr. Goliver is an emergency room physician. He also will oversee a similar facility slated to open in 2015 in Sylvania, Ohio.

Dr. Henry Housam Naddaf (MPH '90, MED '06) was inducted as the 157th president of the Academy of Medicine of Toledo and Lucas County.

Dr. Muhammad Hameed (RES '12) joined the medical oncology/hematology team at the West Michigan Cancer Center in Kalamazoo, Mich.

Dr. Robert Fiala (MED '11) and Rachel Franklyn announced their engagement and plan to wed in 2016. Dr. Fiala is finishing his residency in anesthesiology at Jackson Memorial Hospital in Miami, Fla. Dr. Franklyn recently began her residency in ob-gyn.

Dr. Thomas Tusiliak (MED '80) was honored as the 2014 Humanitarian Physician of the Year by Medina Hospital, located in Medina, Ohio. Dr. Tusiliak began a family practice in 1983 and founded Brunswick Family Practice. He has served on the Medina Hospital medical staff for more than 31 years. He also served as chair of the department of medicine and as pediatrics chair at the hospital.

Dr. Thomas J. Rutherford (PhD '86, MED '89) was named network physician director of cancer services at Western Connecticut Health Network. Dr. Rutherford is nationally known as an expert in the area of ovarian cancer. Western Connecticut Health Network is located in Danbury, Conn.

Dr. Michael Day (MED '72) wrote a book about his career as a doctor in Lafayette, Ind. His 30-chapter book, "Lessons My Patients Taught Me," contains many anecdotes about his patients. All proceeds are going to charities and medical organizations.

Dr. Teresa Ghazoul (MED '85) joined Avita Health System as a medical specialist in the field of plastic and reconstructive surgery. Her office is located in Ontario, Ohio.

Dr. Jennifer Christner (MED '95) has been named Dean of the School of Medicine at Baylor College of Medicine, located in Houston, Texas.

Dr. Steven Yarinsky (RES '89) was named a Regional Top Doctor for 2014, recognizing him as one of the leading physicians in the Saratoga Springs, N.Y. area. This honor indicates that Dr. Yarinsky is a medical leader in the community and metropolitan areas surrounding Saratoga Springs.

Dr. Paul LoVerme (RES '85) has been elected to serve on the American Association for Accreditation of Ambulatory Surgical Facilities, Inc. board of directors. AAAASF provides accreditation to independent and/or office-based surgery centers that meet and maintain several strict standards of safety and care. Dr. LoVerme is a plastic surgeon in Verona, N.J.

Dr. Allison Parkman (MED '03) has been named medical director of FASTLane Urgent Care by Lane Regional Medical Center, located in Zachary, La. Dr. Parkman is a board-certified family medicine practitioner with more than seven years of urgent care and family medicine experience.

Dr. Nicole (Fortier) O'Brien (MED '02) is a physician in the division of critical care medicine and director of the global health certificate program at Nationwide Children's Hospital in Columbus, Ohio. Dr. O'Brien is the recipient of a prestigious Fulbright Scholarship. She plans to travel to the Democratic Republic of the Congo to study the epidemiology, treatment and outcome of pediatric traumatic brain injury.

Rocket Science

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to improved outcomes** See inside