FINDINGS

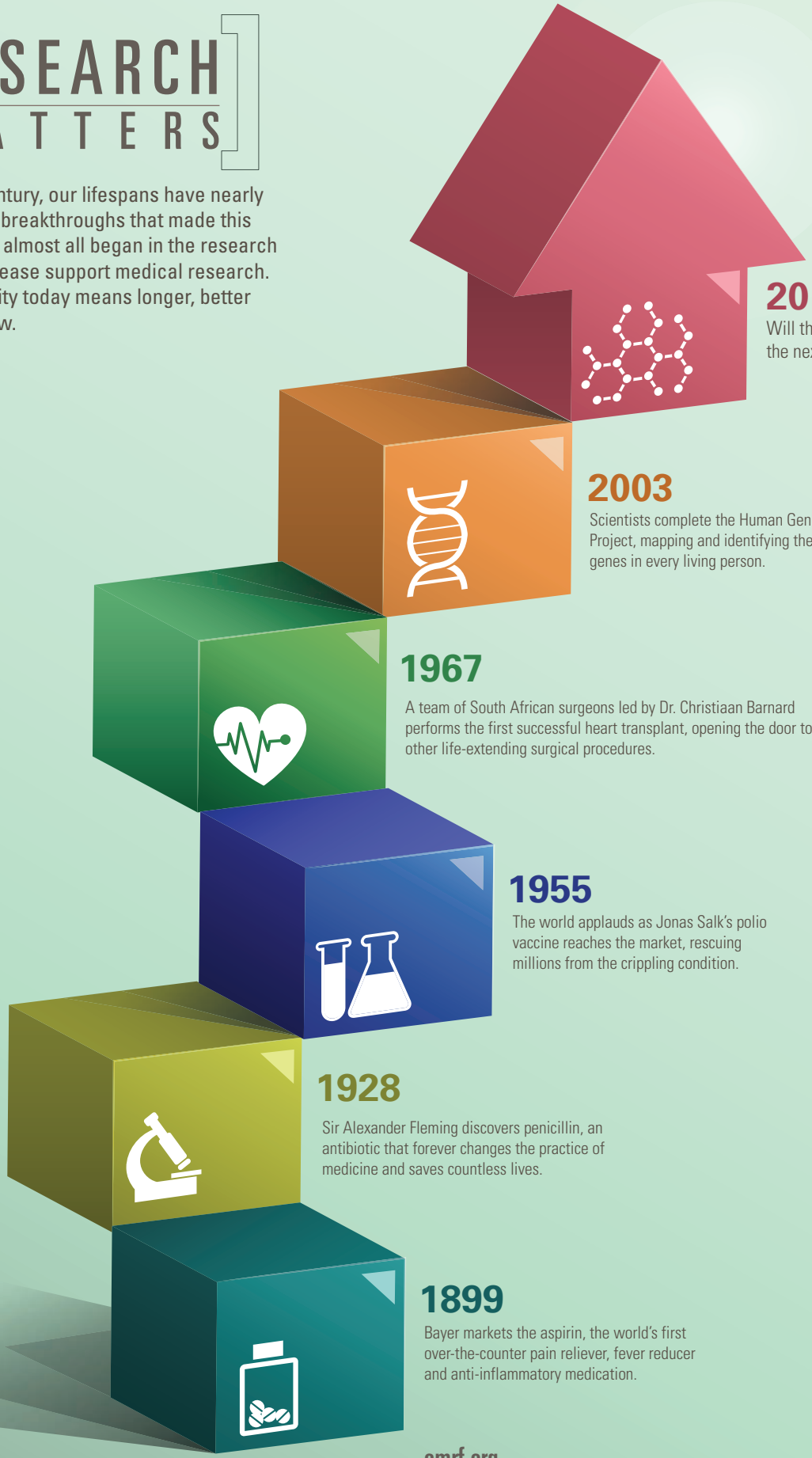
Summer/Fall 2014

Mystery Man

The only thing more puzzling than how Ryan Eisner nearly died is how he survived.

RESEARCH MATTERS

In the last century, our lifespans have nearly doubled. The breakthroughs that made this leap possible almost all began in the research laboratory. Please support medical research. Your generosity today means longer, better lives tomorrow.



2014

Will this be the year for the next big breakthrough?

2003

Scientists complete the Human Genome Project, mapping and identifying the 20,500 genes in every living person.

1967

A team of South African surgeons led by Dr. Christiaan Barnard performs the first successful heart transplant, opening the door to other life-extending surgical procedures.

1955

The world applauds as Jonas Salk's polio vaccine reaches the market, rescuing millions from the crippling condition.

1928

Sir Alexander Fleming discovers penicillin, an antibiotic that forever changes the practice of medicine and saves countless lives.

1899

Bayer markets the aspirin, the world's first over-the-counter pain reliever, fever reducer and anti-inflammatory medication.

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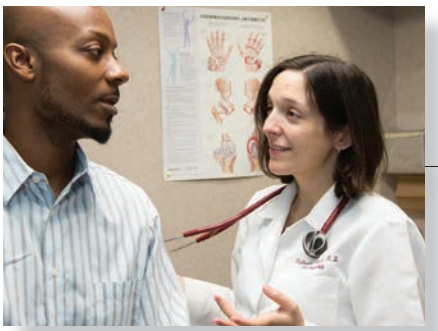

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OMRF

Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as Alzheimer's disease, cancer, lupus and cardiovascular disease.

A United Way Partner Agency

PREDICTING LUPUS FLARES

DRS. JUDITH JAMES, MELISSA MUNROE AND COLLEAGUES HAVE DISCOVERED A WAY TO PEER INTO THE FUTURE THAT COULD EASE PATIENTS' SYMPTOMS

> "Patients' immune systems are warning us that a flare is coming."
>
> DR. JUDITH JAMES

IN LUPUS PATIENTS, the immune system is usually out of balance. But when inflammation outweighs regulation, the mechanisms designed to protect the body become overwhelmed, causing flares that can lead to tissue and organ damage.

Patients usually don't know when a disease flare is about to occur, which delays treatment and allows inflammation to continue unabated. But when OMRF investigators were researching the effects of the influenza vaccine in lupus patients, their work yielded some unexpected results: a method of assessing certain factors in the blood that could forecast a flare on the horizon.

The researchers monitored blood samples from patients before and in the weeks after receiving the vaccine and found a panel of mediators that predict disease flares. These molecules, James and Munroe found, increase or decrease the chance of a lupus flare by driving or suppressing inflammation. Physicians can use this information to "score" patients to predict who might need pre-flare treatment up to three months in advance.

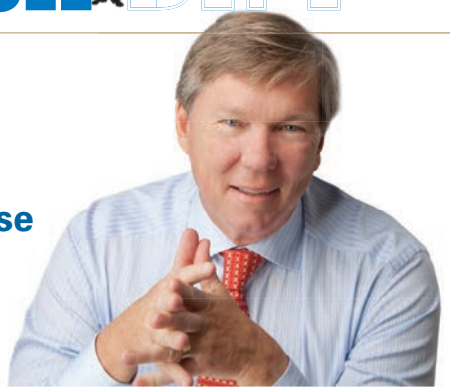
"Even if patients aren't feeling too bad, their immune systems are warning us that a flare is coming," says James, who holds the Lou C. Kerr Endowed Chair in Biomedical Research. Doctors can then initiate treatment to try to prevent or lessen disease activity. Conversely, says James, "If we know they're not going to flare, we can avoid giving them a lot of unnecessary and potentially toxic drugs."

The discovery will help physicians tailor therapies for patients, and it could also have a potential benefit for clinical trials. "One challenge in testing new medications for lupus is discerning if a lack of disease activity is due to a drug's effects or other factors," James says. Doctors could draw on this information to identify patients for clinical trials who are at the highest risk for lupus disease flare and, therefore, have the highest potential benefit from the drug.

"For a clinician, it's an exciting prospect to be able to define patients from a molecular standpoint and really get at precisely what's happening in their disease process," says James.

OMRF has filed for a provisional patent for the discovery. The foundation is searching for a biotechnology partner to help transform the work into a disease-management tool that rheumatologists everywhere could use to manage patient care and treatment.

CYBERCHONDRIA



How do you combat the overabundance of false information on the Internet? Patients always seem to have a diagnosis and want to insist that the doctor is wrong.

- APRIL RUTLEDGE

Every day, the news carries another story about some new health finding. One day you hear, "drink more coffee" or "eat this berry." The next, you hear "avoid coffee," and "eat bananas, not berries." So-called health experts pepper the airwaves and internet around the clock, touting their cures for every condition under the sun.

It's confusing and, in some cases, downright dangerous. Anyone can post anything on the Internet with little or no training in any specific area. One person's opinion can travel like wildfire. But even if it sounds trustworthy, often you'll find little scientific basis in the "health" advice you find online.

I'm particularly skeptical of epidemiological studies based on diet and behavior. By definition, these are observational studies and simply make associations and assumptions with little or no real scientific basis. That's where things can get risky, especially if you have other health issues. You might come up with one connection that pertains to you, but it takes a real medical professional to know which are reliable and which are not.

Don't get me wrong: The Internet contains lots of useful information that can help you better understand your body. But stay skeptical. And resist the urge to diagnose yourself. Leave that to your doctor or other health professional, someone who knows your specific needs and condition.

Three Folk Remedies Debunked

1. Eat this berry!

When the acai (ah-sigh-EE) berry appeared on the scene, many touted it as a cure-all and a weight-loss wonder. Acai may provide fiber and antioxidants, but other health claims have yet to be proven. Eat up, but don't expect miracles from these tiny morsels.

2. Wear this bracelet!

Since time immemorial, people have donned copper bracelets to ward off arthritis. More recently, folks have also begun wearing magnetic wrist straps to ease bone and joint pain. But 2009 and 2013 studies found that the wristwear delivered no specific therapeutic benefits to patients suffering either from osteoarthritis or rheumatoid arthritis. Beliefs about the bracelets' powers most likely stem from that engine that drives many a folk remedy: the placebo effect.

3. Drink this juice!

Generations have chugged orange juice in hopes of warding off colds. But it turns out that O.J. only helps if you're already deficient in vitamin C, which is rare. If you want to stay healthy during cold season, your best bets are staying rested and washing your hands frequently.

Sources: Mayo Clinic, National Health Service (United Kingdom), National Institutes of Health

ARE THERE MUTANTS AMONG US?

(HINT: YOU'RE ONE OF THEM)

THIS SUMMER, WOLVERINE, Mystique, Storm and the rest of the Marvel superhero gang invaded movie theaters in "X-Men: Days of Future Past." Their task: Stop a group of robots programmed to hunt mutants.

Sounds far-fetched, huh?

Well, maybe the robot part.

"Mutants are actually extremely common," says OMRF scientist Dr. Chris Sansam. "Someone without any mutations would be the real anomaly."

Mutations are changes to a person's genetic code, and they can come about from exposure to an external environmental factor, such as cigarette smoke or radiation. An error in cell division also can cause a spontaneous alteration in a person's DNA. Once that change occurs, it gets replicated in a person's children, grandchildren and each generation that follows. "A new copy of your DNA is made every time a cell divides, so any changes are passed on to every cell made from that line," says Sansam.

Unlike in Hollywood, mutations don't give us superpowers like X-ray vision or the power to regenerate our limbs. Still, these genetic changes can prove beneficial. For instance, scientists observed that the natives of a certain community in Italy seemed not to develop atherosclerosis, the build-up of fats and cholesterol on artery walls. After analyzing blood samples, researchers determined that this group of people all shared a common genetic mutation (almost certainly from a common ancestor) that made them resistant to the artery-hardening disease.

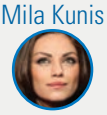
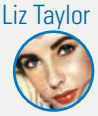
While genes that render immunity to heart disease are rare, other mutations occur more frequently. These variations, known as polymorphisms, account for many of the "normal" differences among us—things like eye color, hair color and blood type. Most polymorphisms, and most mutations in general, have neither a beneficial nor negative effect on a person's health.

Scientists at OMRF and elsewhere, though, are most interested in a third group of mutations: those that can increase a person's chances of developing certain diseases. For example, researchers have identified mutations that sharply increase a woman's risk for breast cancer or, in another case, ensure a person will develop the neurodegenerative disorder Huntington's disease.

Genetic sequencing technology only recently has progressed to the point where researchers can determine the precise genetic sequence in each of us. "This is only the beginning for this discipline," says Sansam. "It may not seem as thrilling as firing laser beams from your eyes to fight flying robots, but I'm excited to see how we researchers can use this knowledge to fight human disease."

Altered States

Genetic mutations aren't necessarily a bad thing.

Mutation	Which Means…	Mutant
Heterochromia	Different colored eyes	Mila Kunis 
Distichiasis	Double eyelashes	Liz Taylor 
MC1R dysfunction	Red hair and freckles	Ron Howard 
Chin dimple	Cleft chin	Kirk Douglas 

CHICKASAWS MAKE A MAJOR DONATION TO CANCER RESEARCH

A NATION OF GIVERS

THE CHICKASAW NATION has taken a lead role in supporting health initiatives throughout the State of Oklahoma. As part of that effort, the tribal nation, headquartered in Ada, this spring made a significant gift to support the expansion of cancer research programs at OMRF. The donation will create the Chickasaw Nation Laboratory for Cancer Research, a newly renovated lab facility where OMRF scientists will focus on identifying therapeutics for cancer.

"We are investing in this research laboratory because we strongly believe the innovative work being done by the Oklahoman Medical Research Foundation will make a meaningful difference in the fight against this devastating disease," says Chickasaw Nation Gov. Bill Anoatubby. "We are confident we will see a great return on our investment in the form of cancer treatment strategies that will make a positive impact for decades to come."

The laboratory will be home to a team of internationally recognized cancer researchers who were recently recruited to OMRF from the University of Utah's Huntsman Cancer Institute.

Over the past three decades, OMRF researchers have made important contributions to the understanding of cancers such as leukemias and lymphomas. Discoveries at OMRF have also given birth to an experimental brain cancer treatment that's currently undergoing clinical trials in patients at the University of Oklahoma's Peggy and Charles Stephenson Cancer Center.

Still, according to Dr. David Jones, who joined OMRF last year to lead the new cancer initiative, there is much more to be done. In particular, he says, OMRF cancer researchers will focus their efforts on developing new "targeted" treatments for breast and colon cancers.

"We want to use the technologies at our disposal to more precisely understand the causes of disease in patients and then find the tools that will be most effective in their treatment," says Jones, who holds the Jeannine Tuttle Rainbolt Endowed Chair in Cancer Research at OMRF. "And thanks to the tremendous faith and support of the Chickasaw Nation and Gov. Anoatubby, we will be able to do that."

The gift comes on the heels of a new partnership between OMRF and the Chickasaw Nation to provide rheumatology care to the tribal clinic while helping researchers better understand the role race plays in rheumatoid arthritis and related diseases.

"We are extremely excited about all the ways in which the Chickasaw Nation and OMRF are collaborating," says OMRF President Dr. Stephen Prescott. "By working together, we can make an impact in the fight against cancer and other devastating diseases."

Chickasaw Nation Gov. Bill Anoatubby (far right) presented a gift to OMRF's cancer research programs, which are led by Dr. David Jones (second from right). Gene Rainbolt and Christy Everest, who are leading fundraising efforts to expand cancer research at OMRF, joined them at the ceremony.

OMRF SCIENCE NIGHT

LEARNING WITH A BOOM!

HOW DO YOU TEACH DOZENS of gradeschoolers basic science principles? Well, one way is to disguise the lessons as a big, fun disaster area. This spring, Drs. Courtney and Tim Griffin led a team of OMRF scientists to wage a guerilla science assault on Oklahoma City's Wilson Elementary School. From bag bombs and cloud bubbles to "elephant toothpaste" (a foamy substance caused by the rapid decomposition of hydrogen peroxide), students conducted a battery of simple experiments using common household materials. In the process, lots of eager young minds got an ooey-gooey, up-close look at science.

Dr. Patrick Crosswhite helped students make Oobleck, a cornstarch-and-water concoction that draws its name from a Dr. Seuss book. "Oobleck works like quicksand," says Crosswhite. The compound can be hard and grabby, but if you move your hands through it slowly, they'll slide right through. "So it's a great way to show kids how simple changes in pressure can alter the properties of something."

After crushing breakfast cereal into a fine powder, students used magnets to determine the iron content of their morning meals. "When little black bits of metal jumped from the piles of crushed cereal onto their magnets, they couldn't believe it," says Dr. John Ice (left), who, with assistance from graduate student Gary O'Mealey, led the experiment. "But that's what iron looks like, even in cereal!"

FOR MORE EXPERIMENTS: OMRF.ORG/SCIENCE NIGHT

FOR ONE INDIAN PHYSICIAN, A YEAR AT OMRF IS JUST WHAT THE DOCTOR ORDERED

AS HEAD OF THE CLINICAL IMMUNOLOGY and Rheumatology Department at Christian Medical College in Vellore, India, Dr. Debashish Danda is accustomed to a hectic schedule. Danda leads a 10-member staff of physicians, residents and consultants that treats about 40,000 patients annually. But after years in the clinic, Danda wanted to know more about the genetic roots of the autoimmune diseases he sees every day, conditions like lupus, Sjögren's syndrome and rheumatoid arthritis.


Danda

When a group of OMRF scientists visited Christian Medical College and formed a partnership between the two institutions, it created the perfect opportunity for Danda. So for the past year, he's taken leave of his clinical duties to do research at OMRF into the cause of autoimmunity in his diverse Indian patient base.

"Essentially, I'm a physician with an enormous patient population," he says. "Expanding my research by collaborating with scientists at OMRF will make a big difference to Vellore and the people of India."

While on sabbatical at OMRF, Danda has kept as busy in the lab as he typically does treating patients. His work has included studies of people suffering from Sjögren's syndrome (an autoimmune disease that attacks the body's moisture-producing glands), an analysis of the damage caused by highly reactive oxygen molecules known as free radicals, and understanding the role of Indian spices in the diet as health modifications.

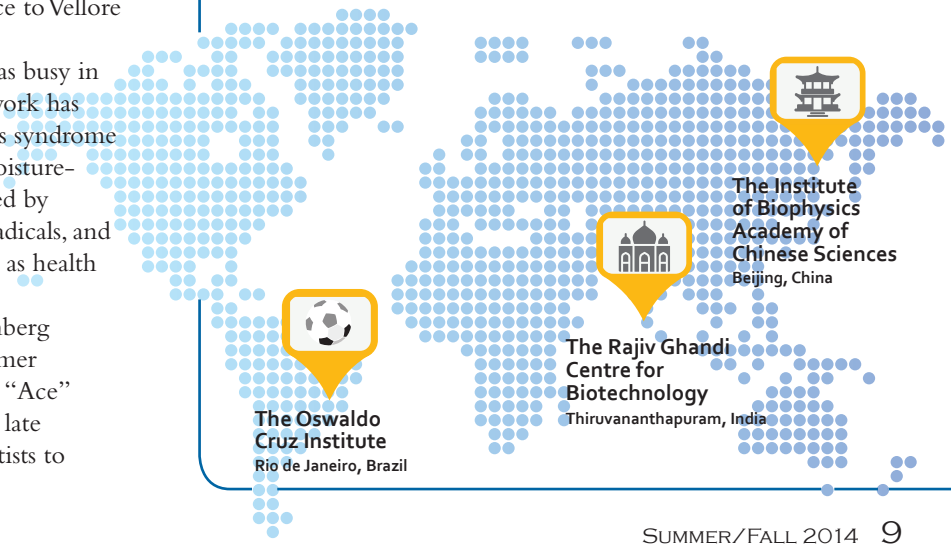
Danda comes to OMRF as the Esther Z. Greenberg Scholar in Biomedical Research. Endowed by former Bear Stearns chairman and Oklahoma native Alan "Ace" Greenberg, the program is named for Greenberg's late mother. It brings distinguished international scientists to Oklahoma to enhance existing research at OMRF and foster overseas partnerships.

"International collaboration has long been a focus here," says OMRF President Dr. Stephen Prescott. "To do the best research possible, we need to work with experts in every field, all around the world."

OMRF's Dr. Hal Scofield first met Danda in India and was excited to bring him to Oklahoma to build a research partnership. "He's doing amazing work in Vellore, but he was interested in learning new techniques and focusing on lab-based, genetic research," Scofield says. "When you treat so many patients, you get ideas you want to test, and that falls right in line with the clinical, translational research we're doing here."

Science Without Borders

In addition to its collaboration with Christian Medical College in Vellore, OMRF has also formed partnerships with a trio of other international research centers.

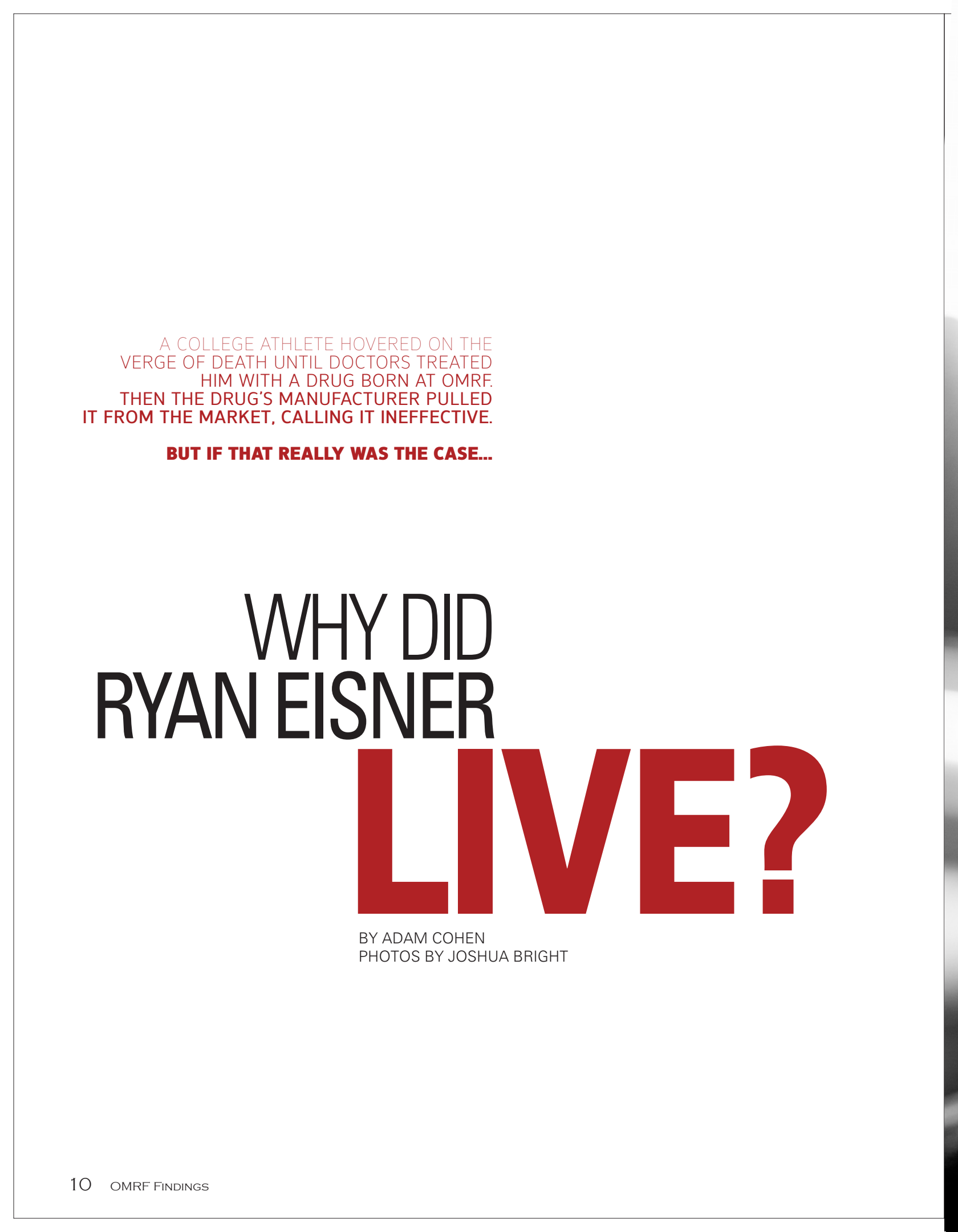


A COLLEGE ATHLETE HOVERED ON THE VERGE OF DEATH UNTIL DOCTORS TREATED HIM WITH A DRUG BORN AT OMRF. THEN THE DRUG'S MANUFACTURER PULLED IT FROM THE MARKET, CALLING IT INEFFECTIVE.

BUT IF THAT REALLY WAS THE CASE...

WHY DID RYAN EISNER LIVE?

BY ADAM COHEN
PHOTOS BY JOSHUA BRIGHT



TWO DAYS BEFORE HE NEARLY DIED, Ryan Eisner felt great. In fact, if you'd asked him, he would've told you he was in the best shape of his life.

Ryan had grown up playing basketball in Bayside, a neighborhood in the New York City borough of Queens. As a freshman, he made the varsity at Bayside High. Even though he stood only 5 foot 10 inches tall, he had an explosive first step and a nose for the basket. By the end of his junior year, he'd established himself as a prolific scorer, and colleges began to contact him.

That summer, Ryan showcased his talents in a tournament featuring a who's who of young prospects, including future National Basketball Association players like Joakim Noah and J.R. Smith. In one of those competitions, as a gym full of coaches watched, Ryan scored at will. To him, the basket looked as big as an ocean, and every shot he threw up seemed to splash in. After one quarter, he'd already rung up 20 points.

On the first play of the second period, Ryan got the ball and made a quick juke toward the basket. The fake sent the defender flying into the air, and when he came down, he landed on Ryan's leg.

When people sever ligaments in their knees, many describe feeling a pop. Or hearing one. But Ryan didn't feel or hear anything. Still, his anterior cruciate ligament had snapped. And just like that, his high school basketball career ended.

Surgeons repaired the ACL that winter, and Ryan worked hard to rehabilitate his knee. While the big universities no longer showed interest in a short kid with the surgically repaired knee, some smaller schools still saw promise in him. When Drew University, a 1,500-student liberal arts college in New Jersey, offered him the chance to come and play, Ryan took it.

Playing college basketball had been Ryan's lifelong dream. And even though that dream now had a few asterisks—smaller stage, gimpy knee that couldn't do what it used to—he made the most of his chance. As a freshman guard, he came off the bench. He showed enough hustle and talent to earn some starts as a sophomore, scoring as many as 14 points in a game. When the season ended, the coach took him aside and said, "Listen, you're going to have an opportunity next year. This will be your team to drive."

Ryan worked out hard all summer and showed up for his junior year in 2007 as fit as he'd ever been. "I was really excited. I was ready to go," he says. "I knew I was going to blow it out of the water."

At the first practice on a Tuesday morning in August, he registered the lowest body-fat percentage on the team. The coaches had the players run a mile around the track, and, again, Ryan bested all of his teammates. But during a series of sprints that followed, Ryan did something he'd never done during a workout: He vomited.

"YOU NEED TO KEEP MY SON HERE," MITCHELL EISNER SAID "YOU NEED TO FIGURE OUT WHAT'S **WRONG WITH HIM."**

That afternoon, the players gathered for a second practice at the gym. Ryan plodded through the ball-handling drills and a scrimmage. The session ended with a series of "suicides," where players sprint up and down the court. Ryan finished the drills, but barely.

When he got back to his dorm, he felt as if someone had sucked the life from his body. He lay down to gather his energy. When he tried to get back up after a few minutes, his head felt heavier than a boulder. Sure, two practices the first day back should leave you tired. But not like this.

Ryan went to the student health service. A nurse took his temperature: 104 degrees. Immediately, the on-call doctor sent him to a nearby hospital. There, a physician in the ER diagnosed him with a respiratory virus. The doctor administered some intravenous fluids and prescribed some steroids to help Ryan's breathing, then released him.

But the next morning brought no relief. Ryan's head still felt like it was on fire. When he walked to the bathroom, he grew dizzy, and his legs buckled. He called his parents. "You've got to come get me," he croaked. "I'm really, really sick." Mitchell and Karen Eisner drove the hour to New Jersey to pick up their son, then whisked him to a doctor they knew. She listened to his heart and his lungs but didn't hear anything out of the ordinary. "It's a virus," the doctor reassured the Eisners. "It will run its course over time." In the meantime, she told Ryan, "Go home. Get some rest."

By the next morning, Ryan's body shook uncontrollably with the chills. His fingers had turned blue. His mother brought him to a different doctor, who took Ryan's vitals. "He had the heart rate of a guy running a marathon," remembers Mitchell Eisner. With Ryan's fever also continuing to burn out of control, the physician sent him straight to the emergency room.

As his mother drove him to the hospital, Ryan huddled in the passenger seat, shivering and laboring with each breath. Occasionally, he'd repeat a single sentence: "Mom, I think I'm going to die." But at the Long Island Jewish Medical Center-North Shore, all of Ryan's tests again came back negative. And, once more, the doctors instructed him to go home and rest.

Mitchell Eisner felt like he was caught in a bad dream. Please, he pleaded with the physicians, don't turn us away. In just two days, his son had gone from fine to dramatically ill. He felt certain that Ryan was suffering from more than a garden-variety virus. "You need to keep him here," Mitchell told the doctors. "You need to figure out what's wrong with him."

There Will Be Blood

DR. CHARLES ESMON HAS DEVOTED pretty much his entire life to studying blood and how it clots. As a graduate student at Washington University in St. Louis, he haunted slaughterhouses, collecting buckets of the red liquid from cows for analysis. When it came time to establish his own independent research laboratory in the mid-1970s, one of the reasons he chose Oklahoma City was its stockyards. "We could get about 100 gallons of blood every two weeks," he recalls. "And that helped us learn a lot."

In his lab at the Oklahoma Medical Research Foundation, Esmon figured out how to isolate and purify a particular protein from the bovine blood. That protein, known as protein C, occurs naturally in the blood of cows—and people—to prevent clotting.

At about that same time, a pair of researchers identified a rare condition in children born without protein C. Without the protein, blood coagulated in their veins, a life-threatening condition that manifested itself in the form of enormous purplish blotches on the skin. As he gazed at photos of the infants in a medical journal, Esmon realized that their symptoms looked an awful lot like those of people suffering from another condition: meningococcemia, a potentially fatal bacterial infection.

What, Esmon wondered, would happen if he isolated protein C from human blood? Could he take that protein, chemically activate it, and then use it to save people infected with meningococcemia?

Building on his work with bovine samples, Esmon devised a way to isolate protein C from human blood. In collaboration with fellow OMRF researcher Dr. Fletcher Taylor, Esmon tested his theory in pre-clinical models. Repeatedly, activated protein C showed promise for treating the infection. But the experiments suggested that the compound might rescue not only people with meningococcemia but also those suffering from other life-threatening blood infections, a broad category of illness known as sepsis.

Sepsis can begin in many different ways: a virus, a skin infection, food poisoning, or a traumatic injury like a bullet wound or car crash. But not everyone who experiences these conditions becomes septic. What distinguishes the illness from its more innocuous counterparts is that in sepsis, the body's

PICTURE PERFECT
Ryan Eisner was poised to lead the basketball team as a junior at Drew University until he developed sepsis.

immune system fails to repel the unwelcome pathogen (a virus, bacteria or fungus) that has entered the body. When the invader hangs around long enough, it can find its way into the blood stream. And then, says Esmon, "All heck breaks loose."

The body responds by calling in its heaviest artillery: an overwhelming, system-wide counterattack. Blood vessels become inflamed, and their cell walls leak fluid. The clotting system goes awry, simultaneously causing bleeding and throwing clots that block the tiny blood vessels that feed organs.

Sepsis has proven particularly problematic to treat because of its chameleonic nature, which can render it indistinguishable from other, less dangerous conditions. So physicians often miss its early signs. The frightening speed at which sepsis progresses compounds the problem, moving in a matter of hours from an apparently mild infection to life-threatening shock—a drastic drop in blood pressure, often followed by organ failure. As a result, doctors are often too late to launch the standard courses of treatment, which include antibiotics to wipe out the infection, medications to keep blood pressure from nosediving, and a ventilator to pump oxygen-rich air into patients' lungs. And the later these treatments start, the worse a patient's chance of survival.

All told, roughly one-third of the people who develop sepsis die. It's the leading killer in intensive care units in the US, claiming an estimated 250,000 lives each year. ICU doctors have a saying about the condition: "Fine in the morning, dead in the evening."

"You'd Better Start Praying"

WHEN MITCHELL EISNER REFUSED to take his son home from Long Island Jewish Medical Center-North Shore, physicians at the hospital finally agreed to re-examine Ryan. And when they did, they determined he was suffering from pneumonia.

The doctors admitted him to the hospital and started him on antibiotics. At long last, Ryan had a diagnosis and a course of treatment. "We thought he was going to stay overnight and be fine," says Karen Eisner. Relieved and exhausted, she headed home for the night to get some rest, while Mitchell stayed. A few hours later, at Ryan's request, Mitchell drove to the house to pick up some clothing, books and basketball magazines. When he returned to the hospital 45 minutes later, he found five white-coated doctors huddled around his son's bed.

"Hey, what's going on?" Mitchell asked.

"He crashed," said one of the physicians.

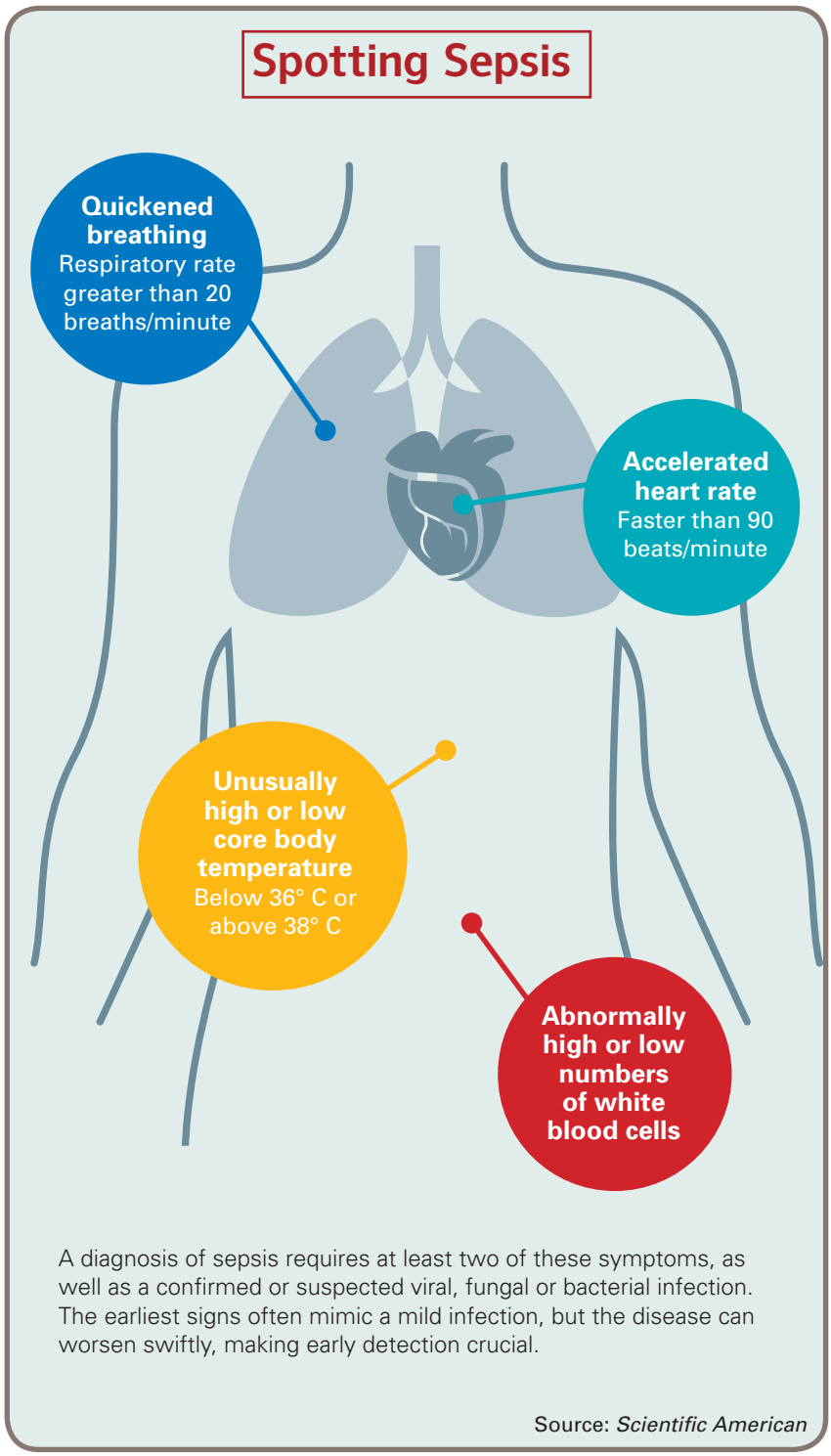
"What do you mean, 'crashed'?"

The physician in charge turned to Mitchell. "He's very sick. We had to intubate." A ventilator huffed in the background, pushing oxygen through a tube that now ran out of Ryan's mouth. "You'd better start praying," the doctor said. "He's going to die."

Mitchell could scarcely process what he'd just heard. Less than an hour ago, he'd been chatting with his 20-year-old son, a college athlete in tip-top shape. And now a doctor was telling him Ryan was as good as dead?

Finally, Mitchell managed to stammer, "When?"

"Anytime," the doctor answered. "It's septic shock."



A diagnosis of sepsis requires at least two of these symptoms, as well as a confirmed or suspected viral, fungal or bacterial infection. The earliest signs often mimic a mild infection, but the disease can worsen swiftly, making early detection crucial.

Source: *Scientific American*

Shock to the System

FOR DECADES, RESEARCHERS HAD been searching for more effective treatments for sepsis. In the 1980s and 1990s, more than 20 experimental drugs failed to show any benefit in treating the condition. But in 2001, the Food and Drug Administration approved Xigris (rhymes with tigress), a synthetic version of the activated protein C Drs. Charles Esmon and Fletcher Taylor had pioneered in their experiments at OMRF. In a clinical trial that had involved 1,700 patients, the drug, which was manufactured by the pharmaceutical Eli Lilly and Company, had cut mortality in those with severe sepsis by 24 percent.

The medical community, though, didn't universally embrace the drug. Half of the panel members who initially reviewed Xigris for the FDA said the agency should not approve the drug without more data. Although the FDA went ahead and gave Xigris the green light, it limited the drug's use to only the sickest patients. Subsequent trials ordered by the FDA failed to show benefit when doctors administered the drug to less ill adults or to children with severe sepsis.

Xigris was also hampered by a serious side effect, internal bleeding. And its $6,800 price tag (a figure that drew heavy criticism of Eli Lilly) further limited its use.

Still, many critical care specialists felt that Xigris served an important unmet therapeutic need. Dr. Gary Kinasewitz, chief of Pulmonary and Criticial Care in the University of Oklahoma Health Science Center's Department of Internal Medicine, participated in the clinical trial that led to the drug's approval. Once Xigris reached the market, he and his colleagues at OU Medical Center continued to prescribe the drug regularly. "We probably used Xigris 100 times a year," he says.

Kinasewitz believes that Xigris helped rescue some of his patients in septic shock. But with doctors simultaneously administering so many different forms of sepsis therapy—multiple antibiotics, fluids, ventilators, blood pressure drugs—it can be virtually impossible to say what, exactly, turned the tide for an individual patient. Still, Kinasewitz remembers one particular case where he feels confident Xigris made the difference between life and death.

He gave the drug to a woman suffering from severe septic shock, and her condition improved dramatically. After 96 hours, the recommended duration of treatment, Kinasewitz stopped the treatment. "Within several hours, her blood pressure had dropped, and she was significantly worse." Kinasewitz decided to re-start her on Xigris, and the patient immediately improved. "Twice more, we tried to stop her treatment." Each time, her condition deteriorated rapidly. And each time it rebounded as soon as Kinasewitz re-initiated

DESPITE PROMISING RESULTS, MANY DOCTORS FAILED TO EMBRACE XIGRIS, THE ONLY DRUG **THE FDA HAS EVER APPROVED TO TREAT SEPSIS**

treatment with Xigris. Eventually, the patient recovered. But Kinasewiz is convinced "she wouldn't have without the drug."

Dr. Alison Fox-Robichaud, a physician-researcher at McMaster University in Ontario who chairs the examination committee for critical care for Royal College of Physicians and Surgeons of Canada, also participated in the clinical trials and continued to administer Xigris afterward. "I gave it to patients in whom I'm absolutely certain it made a difference in their immediate outcomes: young people at death's door, a gentleman who was dying on multiple medications," says Fox-Robichaud. But she's quick to clarify that Xigris was no magic bullet. "I've had at least two serious bleeding problems, so it's not a drug without risk." Still, she says, "For the people where nothing else that you are doing is working, that is the one thing I could say turned the corner for them."

One Last Hope

AFTER HIS FATHER LEFT THE HOSPITAL to get him some clothes and reading materials, Ryan Eisner began to shake uncontrollably. He recalls someone telling him he needed a breathing tube inserted to save his life. "You have to agree," the person told him.

"Yeah," Ryan responded. "Okay."

Then it all went black.

The infection, which had apparently started with a respiratory virus and blossomed into pneumonia, had now leaked from his lungs into his bloodstream. In response, his immune system had activated its fail-safe mode, launching every white blood cell in a last-ditch effort that destroyed friend and foe alike. Ryan's body was in septic shock, and it was literally killing itself.

Doctors sedated him and put him on a respirator. But his condition failed to stabilize. Every hour brought a new problem, and soon his heart began to give out. Then his lungs. Family and friends had gathered in the waiting room, keeping a vigil, hoping for good news. But there was none. Finally, the doctors told the Eisners there was little they could do for Ryan.

EUREKA!
Dr. Charles Esmon's discoveries about blood clotting led to the creation of the drug Xigris to treat severe sepsis.

Photo: Brett Deering

Nine years later, the memory still haunts Karen. "All the tubes coming out of him. Catheters here and there." She goes quiet. ""You can't imagine how hard it is to see your child like that."

Ryan, though, still had one thing going for him. Despite the fact that all of his other organs were shutting down, his kidneys continued to function, keeping his blood composition stable and preventing his body from shutting down completely.

There's a final Hail Mary we can try, his doctors said. It's a drug that may not work, and it has the risk of causing potentially fatal bleeding.

"They told us, 'It's the only thing we can do to try to keep him alive,'" remembers Karen. Her husband's cousin, a doctor who'd been advising them, encouraged them to try the drug. "He said, 'It really is your only choice.'"

The hospital didn't even have the drug on hand, so it had to be flown in. Then the doctors injected Xigris into Ryan's I.V. line and waited.

Waking From a Nightmare

RYAN REMEMBERS THREE DREAMS from that time of unconsciousness. In the first, he could see his parents in their home, a bright light bathing them. But they were far away, and he couldn't reach them. He was trapped in a dark place, with dirt pouring over his body.

He found himself in some sort of athletic facility in the second dream. That felt sort of familiar, like basketball practice. Except he felt like he was someone else. Everybody around him wore headphones that provided them with some sort of vital fluid. But he had no headphones; he also received no sustenance.

The third dream began with Ryan rising from a tub of water. As he gulped down air, he realized that an Indian doctor sat next to him. "It's time to go home," the man said. And what seemed like an instant later, Ryan awoke in the hospital room.

He saw his mother first. And there was his father. Oh, and he noticed a bird perched on his foot. No, he knew that wasn't really there; it must be the narcotics they'd given him. But that catheter running from his neck to his heart? That was real. And so was the tube in his mouth.

After the doctors removed the tube, someone asked him what day it was.

Ryan's mind felt clouded, slow, but he tried to do some calculations. He'd first gotten sick on Tuesday, come to the hospital Thursday. A few days had probably passed since. "Monday?" he guessed.

It was Friday. He'd been in a medically induced coma for eight days.

Sepsis had devastated Ryan's body. He'd lost 30 pounds. For days, he couldn't lie down for fear that fluid would pool in his lungs and prevent him from breathing. Doctors gave him three blood transfusions a day, and his fever persisted. His white blood count was nowhere close to normal. And his legs were so

weak that he could no longer walk. "I wasn't out of the woods by any stretch of the imagination," he says.

Over time, though, he improved steadily. His fever broke, and he began to add some of the weight he'd lost. He relearned how to walk. "He was so fragile," says Karen. "He was in pain. He was scared." She slept next to her son in his hospital bed each night, worrying over everything. "I felt like I had to save his life the whole time."

Three weeks after he'd first been admitted to the hospital, Ryan was discharged. He returned to school full-time in the spring semester, taking classes and working himself back into shape. The next year, he rejoined the basketball team. By the end of the season, he'd moved from the bench back into the starting lineup, scoring in double digits in 7 of his final 10 games. A few months later, he graduated with his economics degree.

"He's had some tough luck," says Mitchell. "In high school, he was on a Division I course until he tore his ACL. Then he got about as sick as a human can get, and I never thought he'd do anything again. But after the sepsis he said, 'I'm not going to sit there and sulk. If it didn't kill me, it made me stronger.' He's a very resilient kid."

Today, Ryan works as an account executive for a commercial moving company in Queens. He lives in Manhattan and still plays competitive basketball in a men's league. Following his illness, he went to doctors frequently. Each time, he feared they'd tell him they'd found something terrible, some hidden consequence of his bout with sepsis that only now was rearing its ugly head. But the doctors didn't. They told him he was fine. Still, even seven years later, his parents worry whenever he sniffles or coughs. And, admits Ryan, "There's not a day that I don't think about it."

He's started volunteering for the Sepsis Alliance, using his own experience to help raise awareness. Maybe, he thinks, if more people knew about the deadly illness, more lives could be saved.

"He's emphatic about helping people learn about this condition," says Mitchell. "If he can save somebody's life, he'd be the first guy to do it."

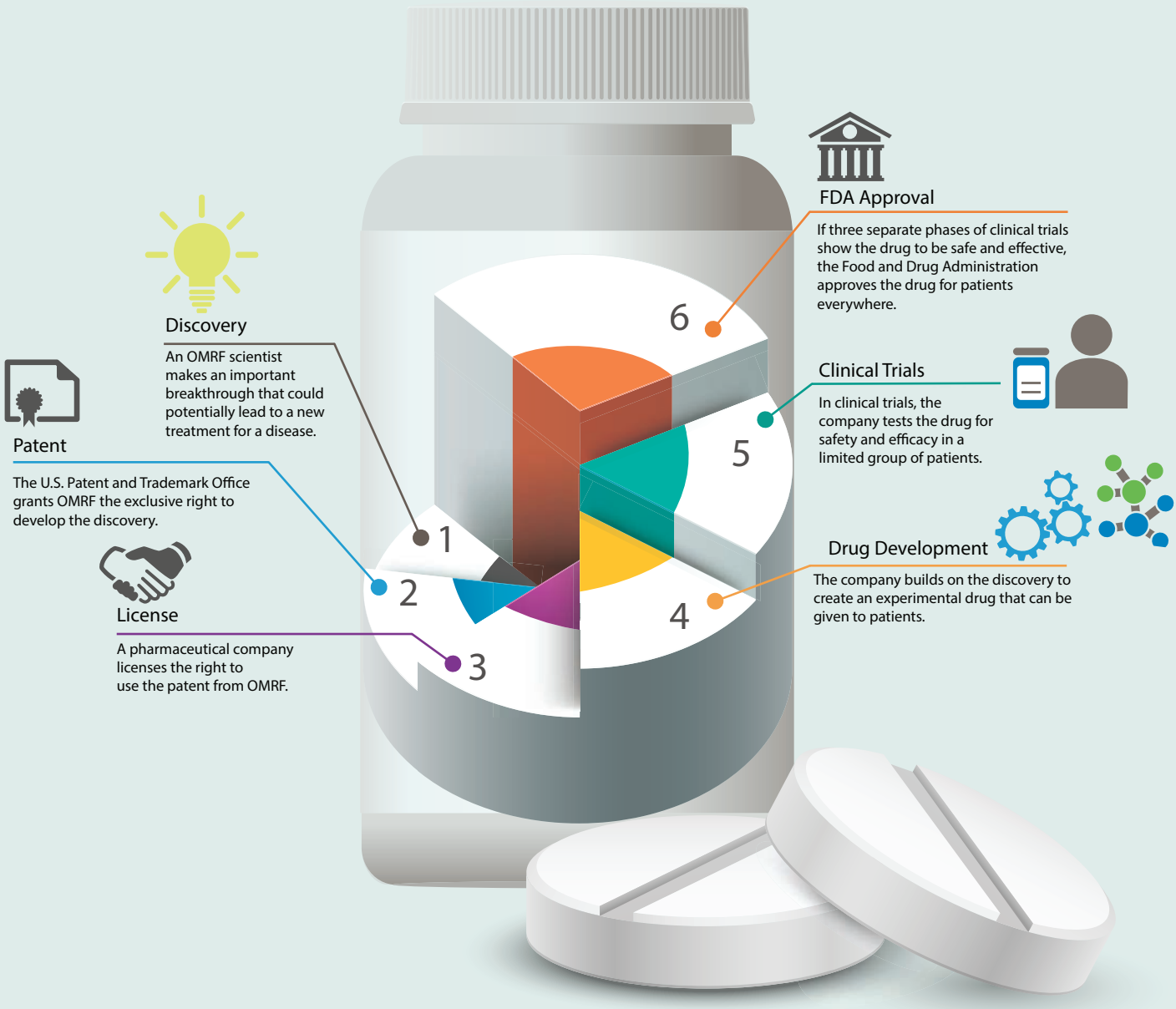
As for his own life, Ryan can't say what, exactly, rescued him from death. After all, he was in a coma at the time. But, he says, "I'm under the impression that Xigris was the miracle drug that helped me."

Karen Eisner, though, harbors no doubts. "I know that drug saved his life. Thank God for Xigris."

BOUNCING BACK
Now recovered from sepsis, Ryan Eisner works as an account executive and still plays basketball competitively.

An OMRF Drug

As a nonprofit medical research institute, OMRF doesn't manufacture drugs. But the work that takes place in OMRF's labs can lead to the creation of a drug like Xigris to treat patients in hospitals and clinics. Here's how:



Sometimes, after a drug reaches the market, companies will conduct post-marketing surveillance trials to monitor a drug's long-term effectiveness. Such a study led Eli Lilly to remove Xigris from the market.

The End for Xigris

WHILE THE STORY OF RYAN EISNER has a happy ending, the story of Xigris does not.

In the face of ongoing concerns about its effectiveness, Eli Lilly conducted a second clinical trial to assess the drug. But unlike the initial trial, this one showed that patients treated with Xigris fared no better than those who did not receive the drug. When Lilly received the results of the study in 2011, it pulled the Xigris from the market.

OMRF's Dr. Charles Esmon had spent years of his life doing the pioneering research that led to the creation of Xigris. When he learned that it would no longer be available to treat critically ill patients, he thought "it was very unfortunate." But Dr. Naomi Esmon, his wife and life-long research collaborator, had a more visceral reaction. "I cried. Out of frustration and sadness. And I thought, 'People will die without this drug.'"

Indeed, through the years, the Esmons had read about cases like Ryan's. And they'd met people who felt certain that Xigris had saved them or a family member. From these accounts, the Esmons developed a theory: While the drug may not have worked in everyone suffering from severe sepsis, for particular groups of patients it could mean the difference between life and death.

Charles Esmon hypothesizes that one group consists of people who, like Ryan, were young and healthy prior to developing sepsis. "In the clinic, many of the patients treated for sepsis will also have hypertension, atherosclerosis, diabetes. All of these co-morbidities create complications." So he's not surprised that Xigris didn't prove effective in every case. "A one-size-fits-all approach was probably not feasible."

The University of Oklahoma's Dr. Gary Kinasewitz agrees. "I still think there are patients who would benefit from Xigris," he says. Like Esmon, he believes that young, previously healthy patients would be one such category, but he also cites sepsis cases stemming from a rare form of infection as another example. But, he says, "When you have a clinical trial, you have very broad criteria." So only a small portion might respond to Xigris. And in a clinical trial involving thousands of patients, those cases would be no more evident than needles in a haystack.

Another complicating factor, says Kinasewitz, is that physicians have improved the level of care for sepsis since Xigris first came on the market in 2001. "Up until the late 1990s, many physicians didn't recognize sepsis or treat it with urgency," he says. "Since that time, there's been an emphasis on early identification and intervention"—with antibiotics to stem the infection, I.V. fluids to maintain blood pressure, respiratory treatment to maintain oxygen levels. The result, he says, is that more patients are surviving. "So it's harder to show the benefit of any therapy like Xigris," especially if doctors don't give it until all other treatments have failed and the patient is nearly dead.

XIGRIS WORKED, SAYS ESMON. "I'M 100 **PERCENT CONVINCED IT SAVED SOME LIVES."**

If nothing else, says McMaster University's Dr. Alison Fox-Robichaud, she would like to have the drug available for situations like Ryan's. "This was our most desperate measure to try and reverse a patient's shock when nothing else was working. So what do we do now when we get that case?"

A Bittersweet Legacy

WITH XIGRIS GONE FROM THE MARKET, critical care physicians no longer have any compounds specifically approved to treat sepsis. Yet against the backdrop of the drug's failure and the hundreds of millions of dollars Lilly incurred in clinical trials, pharmaceutical companies have shied away from further efforts to develop new therapies for the illness.

In his laboratory at OMRF, Charles Esmon has identified another protein—this one called a histone—that appears to play a crucial role in the body's inflammatory and coagulation responses. He's now working on histone-based therapies for traumas like car accidents and gunshot wounds. Down the line, he may also target organ transplant and stroke. Yet even though experimental results indicate that blocking histones might offer a promising new method for treating sepsis, he's decided not to explore this avenue. Quite simply, he says, it comes down to money. "The costs of pre-clinical and clinical trials are prohibitive without a drug company on board."

Still, he looks with satisfaction on the work that started at the stockyards all those years ago. "The insights we gained are very fundamental. All that stuff is now in the major textbooks." He ticks off a list of conditions—cancer, Crohn's disease, diabetes, thrombosis—where researchers are now studying the role of activated protein C.

But what about sepsis? Was that just a case of shooting at the wrong bullseye?

"It was the most rational target at the time," he says. "We showed that activated protein C should work against sepsis. And it did work. I'm 100 percent convinced it saved some lives."

Karen Eisner, for one, would agree.

Thanks a million

by Shari Hawkins • photo by Brett Deering

When a group of teens lost a friend, they decided that the best way to remember her was to lead a fundraising effort that they'd never forget.

Sixty years ago, a group of Classen High School (now Classen School of Advanced Studies) sophomores entered Mary Pruitt's geometry class expecting another dry lecture on shapes, angles and planes. Instead, their teacher posed one question: What would a million of something look like? That simple query set her students on a quest, one that would resonate with them for the next six decades.

"We really couldn't imagine a million of anything," recalls Linda Kennedy Rosser, one of Pruitt's students. None of the teens could say for certain that they'd ever seen a million of anything all in one place. When Pruitt told a story of some Wisconsin teens who'd gathered a million pennies as a fundraising drive, her students decided they'd do the same—in the span of a single year. So on Feb. 8, 1954, the "Million Penny Round-Up" was born.

The teens realized that even though they'd be collecting pennies, their efforts would net a lot more than chump change. So they earmarked the $10,000 they'd collect for two causes. First, they'd pay tribute to Jackie Wright, a former classmate who had died of cancer by landscaping a courtyard in her memory at Oklahoma City's brand new Northwest Classen High School—where many of the Classen sophomores would transfer and eventually graduate. They decided that the remaining funds would go to cancer research at the Oklahoma Medical Research Foundation, where Wright had spent the last days of her life.

• • •

Jackie Wright dreamed of a singing career. A student at Taft Middle School, the outgoing girl with the beautiful voice sang at every opportunity, endearing herself to her classmates.

A bone cancer diagnosis derailed Wright's dreams when she was in eighth grade. The disease progressed quickly, and students organized prayer vigils during the school day. Wright applied for and gained admission to Classen High for her freshman year, but her illness prevented her from ever setting foot inside the school.

When Wright's condition worsened, her doctors sent her to the OMRF research hospital. Opened in 1952, the hospital specialized in administering experimental treatments to patients with cancer.

For Oklahomans, OMRF's hospital was a godsend, a place where the sickest patients received the newest, most innovative cancer treatments available. "We all knew about OMRF and its hospital," says Mary Thompson Denman, a classmate of Wright's who served as secretary for the Million Penny Round-Up. "It was brand new, and we all thought it was incredible to have a cancer research hospital here in Oklahoma City."

At the research hospital, Wright's friends would congregate for hours at her bedside, trying to boost her spirits. Pruitt tutored her through a homebound student program sponsored by Oklahoma City Public Schools.

Wright spent three months at OMRF. In spite of her physicians' best efforts, they could not slow her cancer, and Wright died on Nov. 7, 1953. She was 15.

Now and Then

See more photos from the Million Penny Round-Up at omrf.org/million

Though only teens, when it came time to memorialize their departed classmate, the Round-Up kids set out with a dedication and purpose that was decidedly adult. They formed a club, elected officers and started fundraising in earnest just months after Wright had died. And anything they could think of to raise money, they gave it a try.

With no guidance from professional marketers or public relations consultants, the little army of high schoolers pooled their ideas and launched a cavalcade of fundraising ploys. Rosser wrote a letter to parents, business people and Classen alumni. Round-Up officers glued a shiny new copper penny to each letter, which entreated readers to "Please help this penny grow into a million!" When Oklahoma's then-governor, Johnston Murray, visited the school, he praised the effort and even added his own contribution to the growing collection.

Students took odd jobs, hired themselves out as babysitters and held scrap paper drives. They auctioned or sold cakes, pies, cookies and cupcakes in the school cafeteria and around town. They gave talks at civic club and church meetings. Many of Classen's 2,000 students signed pledges to earn $2 each to add to the total. "They had to earn it, not just get it from their parents," says Rosser, who served as co-chair of the Round-Up. One student's father built a wishing well, where pupils could deposit their donations between classes.

Central State Bank officials converted the money raised into pennies and corralled the cache in a large plexiglass box in the bank's lobby. The pennies piled higher and higher, but four weeks shy of their deadline, students found themselves short and at risk of missing their goal. Employing every fundraising skill in their arsenal, the Round-Up officers led the charge to the finish line. Students canvassed neighborhoods collecting coins. Some even claimed to have gone hungry many times to add their lunch money to the cause.

The students' dedication paid huge dividends, as a whopping $5,000 poured in during the final days. Exactly one year after their geometry teacher had couched her question, the Round-Up kids had raised a grand total of $11,762. With those funds, they were able not only to create their landscape memorial to Wright, but they also made a significant donation to cancer research at OMRF.

Although she's long since left behind the "Round-Up Kid" label, Rosser says the true worth of those pennies has only increased through the years. "When you learn at a young age the value of community service," she says, "it stays with you."

Dynamic Duo

As high school sophomores, Million Penny Round-Up officers Linda Kennedy Rosser and Mary Thompson Denman helped bring in funds for OMRF cancer research and in memory of a former classmate. They surpassed their goal, netting $11,762—about $83,000 in today's dollars.

7 Things You Didn't Know about

Manu Nair

As OMRF's new vice president of technology ventures, Manu Nair will focus on transforming OMRF's laboratory breakthroughs into products that doctors can use to diagnose and treat human disease. But while the position is new to Manu, OMRF is not. He first worked at the foundation from 2004 to 2009, learning the ins and outs of technology licensing. He left Oklahoma for a position with the Mayo Clinic in Minnesota but returned this spring to put his people skills and deal-making experience to work for OMRF. Manu and his wife, Athira, have a four-year-old son, Jai.

1.

I was the first one of my family to come to the United States. They call me "the pilgrim."

In India, I was a divorce lawyer. Every day for an entire year I spent hearing the worst about people.

My wife and I had an arranged marriage. The concept was normal for us. You marry the family, not just the person. It worked for me, thanks to my wife, but I don't expect my kids to do that.

My older brother is a country-and-western music fan. As kids we'd pool our money to buy Kenny Rogers or John Denver albums. Today, I listen to a lot of Keith Urban.

I never get tired of washing dishes. Some days, my mind is racing to the point where I can't sleep. Tending to the dishes lets me put things in order and completely clear my mind.

When my dad died, I was unable to attend his funeral. He was my best friend. I almost gave up my green card status to go home for the service, but my family reminded me to carry on with my life—our dad would have wanted it that way.

Before my son was born, I was quite a risk-taker. Now I'm more careful. Fatherhood has made me wiser.

7.

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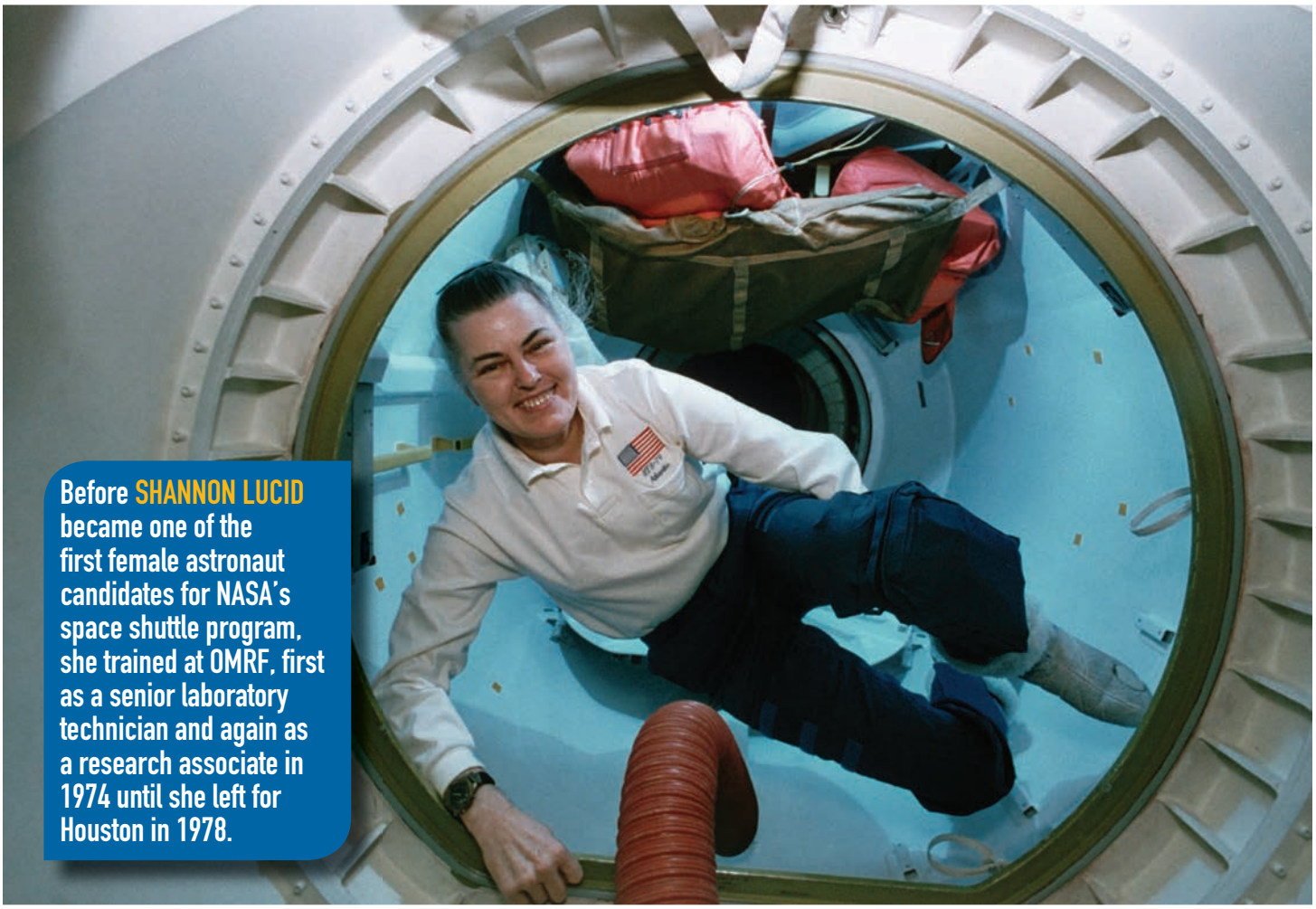

Before **SHANNON LUCID** became one of the first female astronaut candidates for NASA's space shuttle program, she trained at OMRF, first as a senior laboratory technician and again as a research associate in 1974 until she left for Houston in 1978.