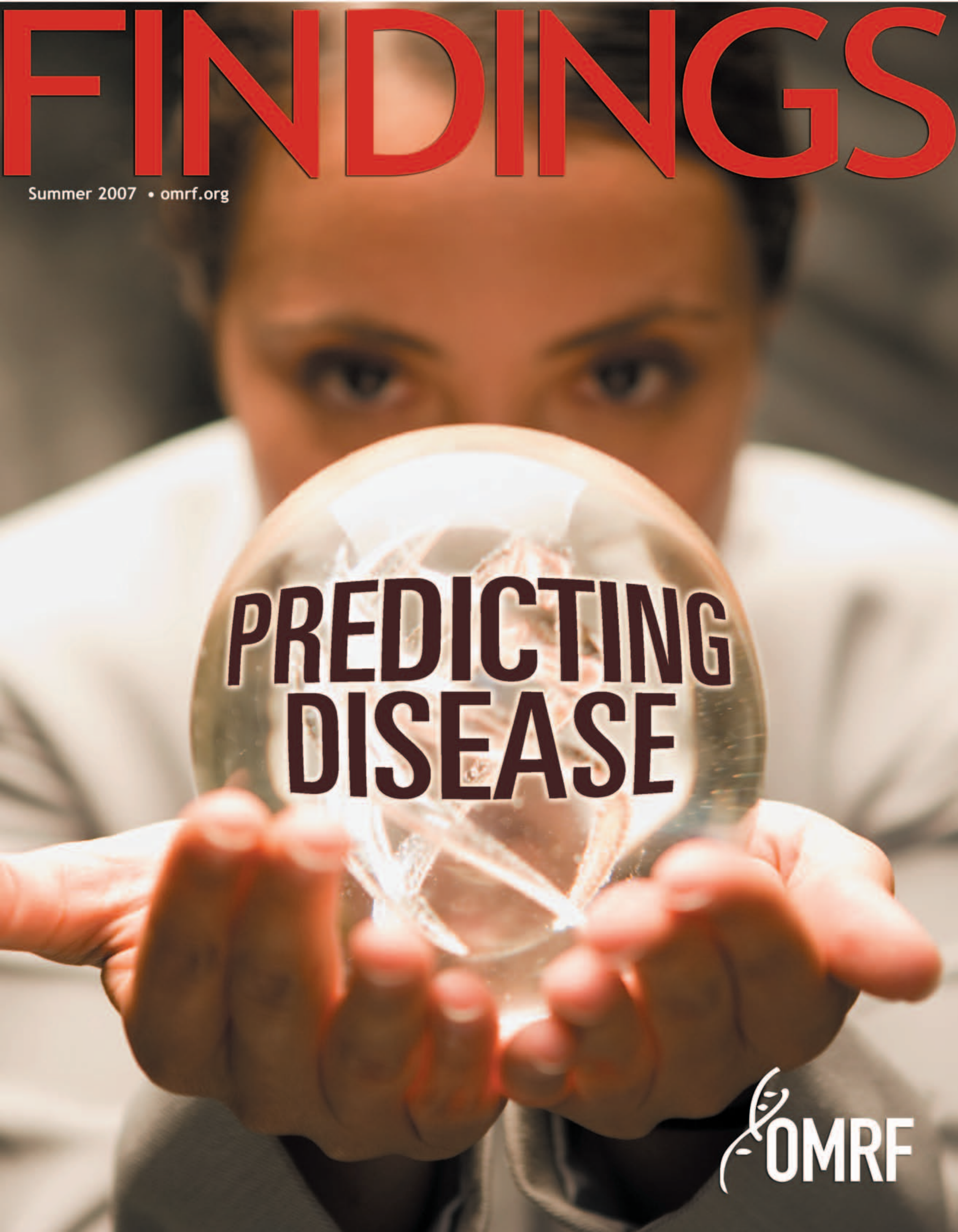
FINDINGS

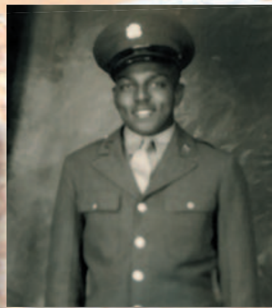
Summer 2007 • omrf.org



PREDICTING DISEASE

OMRF

Remember who they were with a meaningful tribute



Touch the lives of future generations

For six decades, the scientists at the Oklahoma Medical Research Foundation have probed the mysteries of human disease. They have helped develop medications that fight deadly illnesses. They have saved lives.

What better way to remember the special people in your life than to make a donation to OMRF in their memory? Through your generosity, they can live on. And their legacy can make a difference in the battle against human disease. To make a gift in memory of a loved one, please use the enclosed envelope or call the OMRF development office at (405) 271-8646.

OMRF

825 N.E. 13th Street • Oklahoma City, OK 73104 • omrf.org

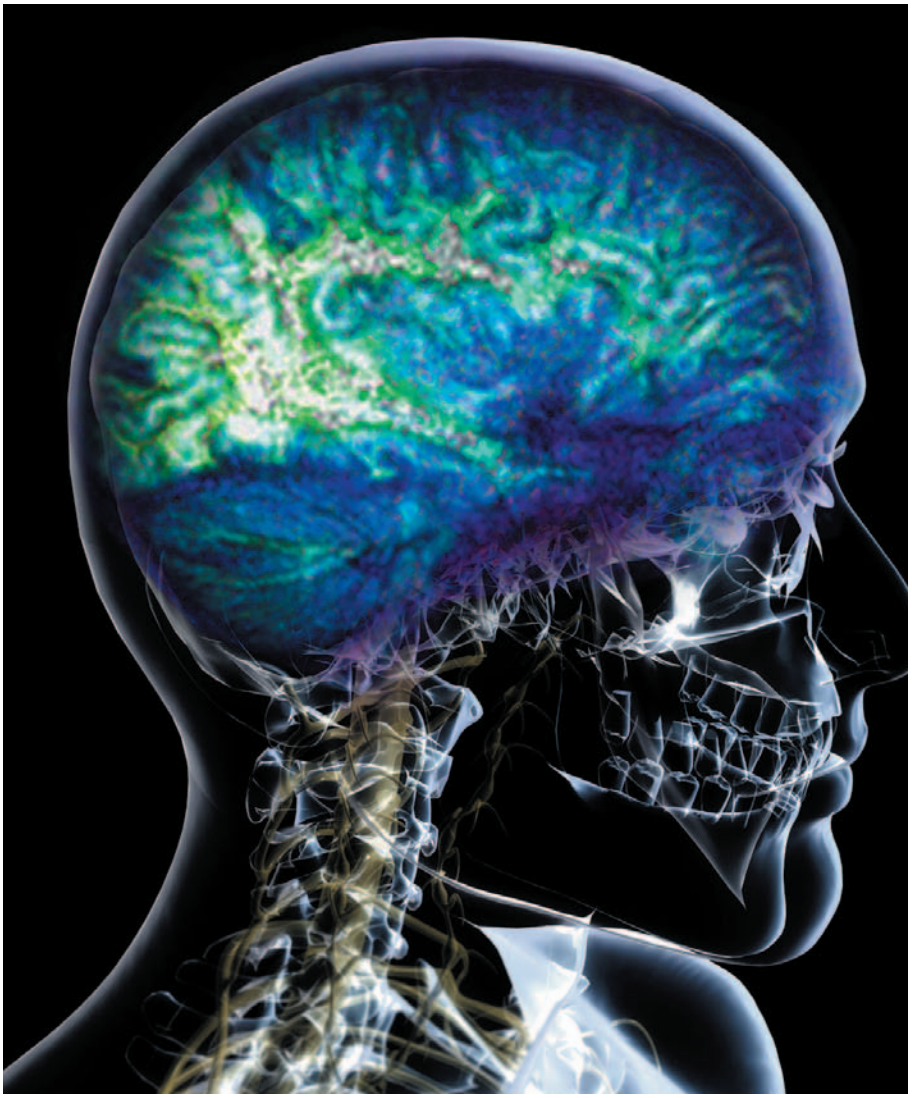
Discoveries That Make A Difference

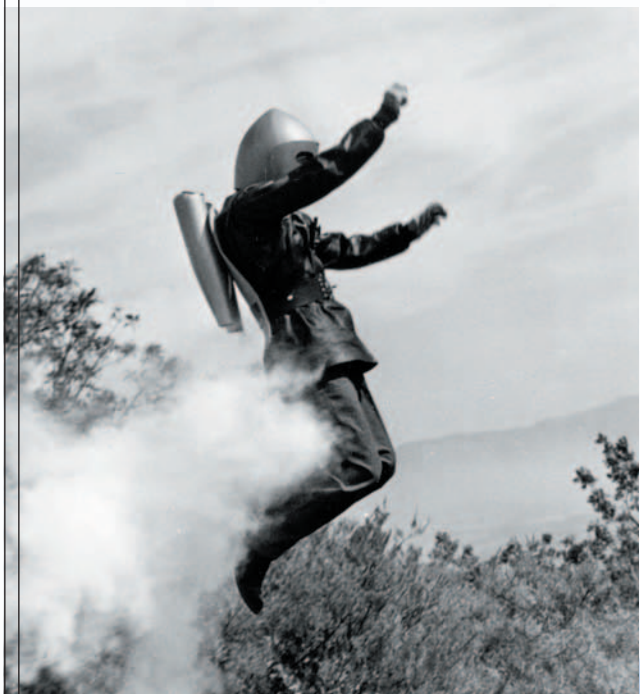
FINDINGS

Summer 2007
omrf.org

405-271-8537
800-522-0211
findings@omrf.org

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.





What's Next

A few years back, a BBC series told the story of an old Texas oilman who'd offered a fortune to anyone who could prevent him from dying.

He didn't figure he'd have to wait long, no more than a decade, before scientists had figured out how to reverse the aging process and bestow immortality on him. Once they had, this fellow had a pretty clear idea of what he'd be doing for eternity: "I'll do a lot a traveling, find me a very nice girlfriend, and enjoy life. After that, I'll get back to work, find some oil and read the newspaper."

I'm not sure what's become of this would-be immortal. But I do know that, clever offer notwithstanding (after all, when, exactly, would a scientist get paid?), he's proved no more successful than Ponce de Leon at finding the fountain of youth.

Still, countless researchers around the globe are striving to reach this goal. Most wouldn't speak of their quest in such grandiose terms. At OMRF, Dr. Jordan Tang might tell you that his lab is searching out ways to prevent the onset of Alzheimer's disease. And Dr. Paul Kincade, who heads our Immunobiology and Cancer Research Program, would explain that he's trying to understand what causes leukemias and lymphomas so that we can stop those deadly cancers in their tracks. The unifying theme here is simple: keeping us healthy and functional for as long as possible.

Don't get me wrong here. I'm not claiming OMRF or anyone else has discovered the elixir of the gods. But when you look—as we are in this issue—to the frontiers of medical research, it's important to take the long view. To think big.

The last centuries have brought us health advances once unimaginable, from antibiotics and clean drinking water to unmasking the structure of DNA and mapping the human genome. And those advances have had a staggering impact: The average lifespan in the U.S. jumped from 47 years in 1900 to 77 in 2000.

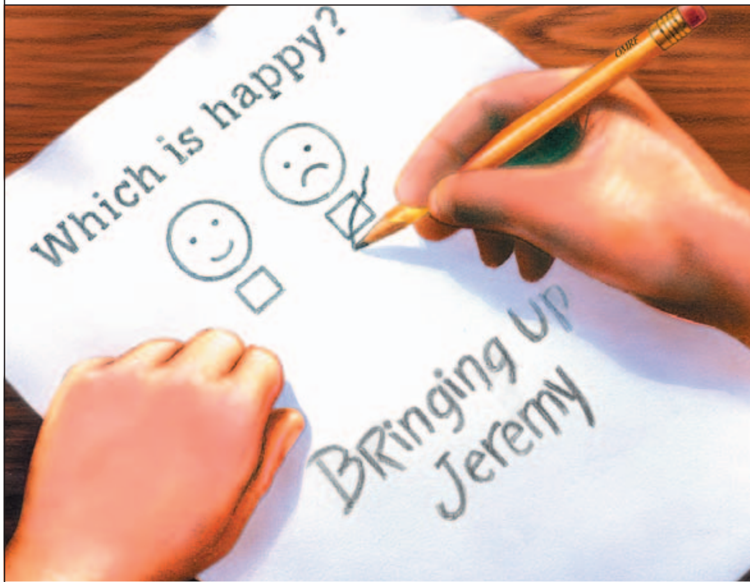
As we look to the horizon, it's hard to imagine that we can keep making discoveries that will, in the short term, add so many years to our lives so quickly. Simply put, the most obvious, high-impact ground (things like sanitation, antibiotics and vaccines) has been covered. The progress we make now comes in smaller steps, involving projects and technologies so complex, time-consuming and expensive they would boggle the minds of Dr. Jonas Salk and Sir Alexander Fleming.

Yet I can't help but get excited when I see what's already happening at OMRF and the promise it holds for tomorrow. I'm talking about discovering antibodies that predict disease before it strikes. Using magnets 100,000 times more powerful than the earth's magnetic field to revolutionize the diagnosis and treatment of illness. It's heady stuff, and I hope that reading about the brave, new world of medical research will energize you as much as it does me.

Now, crystal-ball-gazing is always dicey. Personalized jetpacks. Colonies on Mars and the moon. Moving sidewalks. Yesterday's visions of the future tend to look as off-target and quaint as a visit to Disney's Tomorrowland. But in my boldest, most hopeful moments, I can foresee a world that no longer needs medical research institutes. A time when we all can expect to live out the number of our days without illnesses that rob us of energy and enjoyment of life.

There's one problem, though, with my vision of the future: Even if we get there, I doubt that Texas oilman would pay up.

Stephen M. Prescott



Living With Autism

WE WILL USE YOUR *Findings* magazines in CARE Center's upcoming volunteer/staff discussions on autism. The article "Bringing Up Jeremy" is wonderfully informative, interesting and inspiring. My nephew, now in his mid-40s, has Asperger's syndrome. I remember how difficult it was for all of us when he was a youngster, growing up without knowing what made him seem "different." It took years of effort by his parents to diagnose him, but it helped us all understand. He now leads a life of service—not only to others with autism but also to people with a variety of disabilities and needs. The story about Jeremy Rand, his parents, their efforts to advance the understanding and appreciation of autism, and the research that Dr. Rand is doing show in a very tangible way the great work that is accomplished through OMRF. Thank you for all that you do.

KATY DAVIS
OKLAHOMA CITY

IT WAS WITH INTEREST that we read your article on the autistic young man, a son of one of your researchers. We, too, are parents of a diagnosed autistic child. It is overwhelming, at first, but in reality, we are given a special gift to be able to work with such a unique young man. My husband and I have had to make many adjustments in our lifestyles, but it is definitely worth every change. Initially, we felt as though we were punished, but in reality, we have been totally blessed. Not all days are good, in fact, some parents would throw up their hands, but any progress is a huge delight! As the article pointed out, this disability does not have to be a disadvantage; it is a lifetime living experience. Thanks for doing such an article. The idea of public awareness is so important to ensure further research.

BEVERLY AND DAN SKIDDER
OKLAHOMA CITY

I WOULD LIKE to thank OMRF for allowing Will and me to tell our story in "First Person" (Winter/Spring 2007). Several people have recognized us as a result, and when they ask, it gives me an opportunity to discuss our experience with autism. Surprisingly, a copy was being passed around his school within days. Speaking of school, Will has blossomed so much this year–largely due to the staff at his school, most notably principal Robert Romines, teacher Nancy Davisson and aide Lin Jenkins. I am sure their understanding and responsiveness is the result of heightened awareness created by organizations such as yours.

MIKE KELLUM
MOORE

SURVIVING AND THRIVING

YOU DID SUCH a beautiful job writing my story ("The Survivor"), and the pictures are just great. I hope it will help OMRF and that people can see how much research is needed on many things. I am a survivor because of all of your hard work and all that OMRF stands for. I wouldn't be here if it wasn't for the dedication of everyone at OMRF and those who donated. Thank you for giving me another beautiful memory to keep in my heart.

HUGUETTE WHITE
PHOENIX, AZ

SPOTLIGHT LETTER

THANK YOU FOR YOUR ARTICLE on the Rand family and their engagement on autism. Our 7-year-old son Noah has Asperger's syndrome, so we read a constant stream of magazine articles on the subject. Your piece was especially good–it was one of the few where one could imagine someone who's unfamiliar with Asperger's reading it and actually having a clear sense of what the condition is about and how it affects children and their families. The upsurge in research and understanding, thanks to people like the Rands, is of huge benefit for families like ours with younger kids on the autism spectrum.

DAVID BLATT AND PATTY HIPSHER
TULSA

write to us!

Send your letters to *Findings*, 825 Northeast 13th Street, Oklahoma City, OK 73104 or e-mail us at findings@omrf.org. Please include your name and address. If we publish your letter, you'll receive an OMRF T-shirt.

Zeroing in on the Roots of Alzheimer's

Scientists have known for more than a decade that individuals with a certain gene are at higher risk for developing Alzheimer's disease. Now a new study led by OMRF's **Dr. Jordan Tang** helps explain why this is so.

The research, which appeared this spring in *The Journal of Neuroscience*, has uncovered a molecular mechanism that links the susceptibility gene to the process of Alzheimer's disease onset. The findings may lead to new pathways for development of Alzheimer's therapeutics.

Approximately 15 percent of the population carries a gene that causes their bodies to produce a lipoprotein—a combination of fat and protein that transports lipids (fats) in the blood—known as apolipoprotein (Apo) E4. Studies have found that those who inherit the E4 gene from one parent are three times more likely than average to develop Alzheimer's, while those who get the gene from both parents have a tenfold risk of developing the disease.

In the new study, Tang and his OMRF colleagues discovered that ApoE4 (along with other apolipoproteins) attaches itself to a particular receptor on the surface of brain cells. That receptor, in turn, adheres to a protein known as amyloid precursor protein. The brain cells then transport the entire protein mass inside.

Once inside, cutting enzymes—called proteases—attack the amyloid precursor protein. These cuts create protein fragments that, when present in the brain for long periods of time, are believed to cause the cell death, memory loss and neurological dysfunction characteristic of Alzheimer's.

While roughly 1 in 7 people carry the E4 gene, the remainder of the population carries only two variations (known as E2 and E3) of that gene. These individuals have a markedly lower incidence of Alzheimer's than those who carry the E4 gene. The new study found that ApoE4 produced more protein fragments than did E2 or E3.

"ApoE4 apparently interacts better with the receptor than its cousins," says Tang, who holds the J.G. Puterbaugh Chair in Medical Research at OMRF. "This may explain why people who carry the E4 gene have a higher risk of developing Alzheimer's."

The findings, says Tang, "may allow us to investigate the possibility of therapeutic intervention at different points in the process." For example, such efforts might focus on developing a compound to interfere with the receptor's ability to adhere to ApoE4. "There currently is no effective treatment for Alzheimer's disease, so we must explore every possible option to find a way to stop it."

"Dr. Tang's study shows a beautiful biochemical connection between a genetic risk factor and the development of a disease," says OMRF President Stephen Prescott. "This work opens the door to the development of alternate methods for treating—and perhaps even preventing—Alzheimer's."

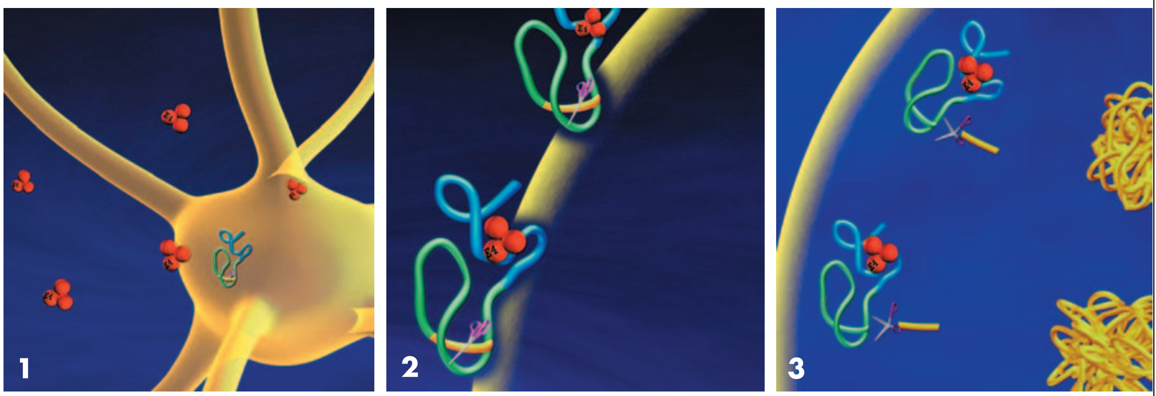
THAT WAS THEN . . .

YOU MAY REMEMBER THAT IN 2000, DR. JORDAN TANG AND HIS COLLEAGUES AT OMRF ANNOUNCED THAT THEY HAD IDENTIFIED THE CUTTING ENZYME BELIEVED TO BE THE CULPRIT BEHIND ALZHEIMER'S. AFTER CLONING THAT ENZYME, HE LED A TEAM OF RESEARCHERS THAT CREATED AN INHIBITOR TO HALT THE ENZYME'S CUTTING ACTION. THAT WORK EARNED TANG THE NATIONAL ALZHEIMER'S ASSOCIATION'S HIGHEST PRIZE: THE PIONEER AWARD.

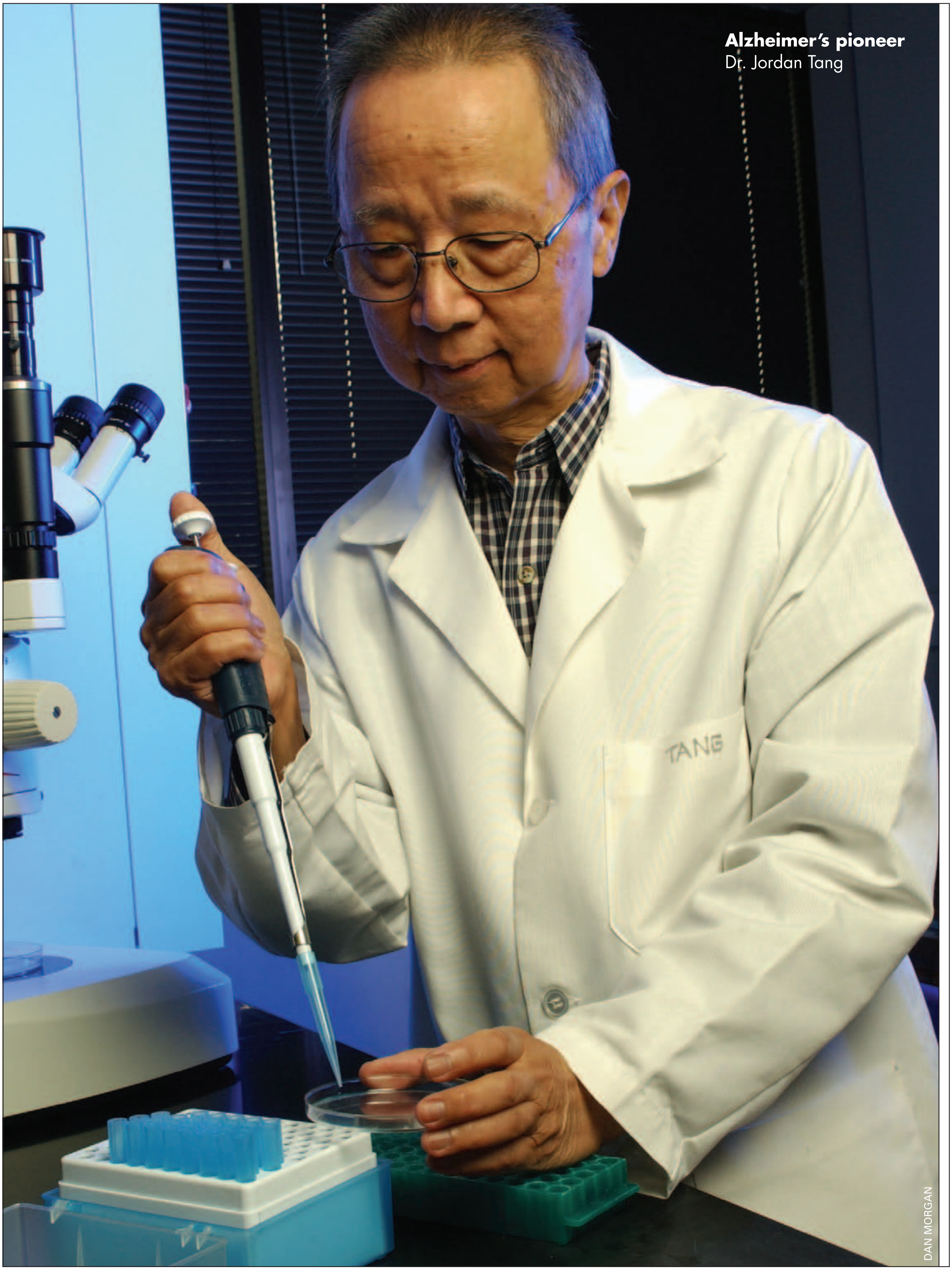
. . . THIS IS NOW

AFTER SEVEN YEARS OF RESEARCH AND DEVELOPMENT, AN EXPERIMENTAL DRUG BASED ON TANG'S INHIBITOR BEGAN HUMAN CLINICAL TRIALS IN JUNE.

THREE STEPS TO FORGETTING



1. In the brain, ApoE4 molecules (red) collide with brain cells, whose surfaces also are home to masses of proteins and cutting enzymes. **2.** ApoE4 binds to a receptor that, in turn, adheres to the mass, and brain cells then transport the entire structure inside. **3.** Once inside, the cutting enzymes attack the mass, creating tangles of protein fragments (yellow) believed to cause Alzheimer's.



Alzheimer's pioneer
Dr. Jordan Tang

DAN MORGAN

Pass the Pistachios, Please

Good news for nut lovers: A new study from OMRF and Penn State University shows that modest intake of pistachios lowers cholesterol levels.

The study, presented at this spring's Experimental Biology meeting in Washington, D.C., also found that a small daily serving of the nuts provides antioxidants normally found in fruits and vegetables.

A research team led by Penn State's Penny Kris-Etherton found that daily intake of 1.5 to 3 ounces—one to two handfuls—of pistachios reduced risk for cardiovascular disease by significantly reducing levels of low density lipoprotein (LDL or "bad") cholesterol. The higher dose (3 ounces per day) significantly reduced ratios of potentially harmful lipoproteins to potentially beneficial lipoproteins.

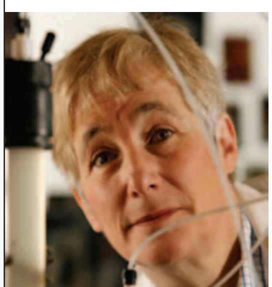
"Among other beneficial effects noted in this study, it showed for the first time that higher dosages of pistachio nuts had lowering effects on the protein component of harmful cholesterol-rich and triglyceride-rich lipoproteins," says OMRF's **Dr. Petar Alaupovic**, who performed the lipid measurements for this study. "These two lipoproteins are considered major risk factors for coronary artery disease."

Study participants ate a normal diet, followed by three sessions (each lasting four weeks) of dieting while adding pistachios. About half of their pistachio intake came in the form of snacks; the remainder was incorporated into other foods. Subsequent blood tests among the 3-ounce intake group revealed a reduction of 8.4 percent in total blood cholesterol and 11.6 percent in LDL.

Pistachios anyone?

Hope for a Rare Disease

FDA Green Lights OMRF-Based Drug



The FDA has approved a medication that has its origins at OMRF as the first biologic treatment for patients with a rare genetic defect. The drug is a treatment for patients with complications related to severe congenital protein C deficiency, a potentially life-threatening clotting disorder found in one to two newborns for every million births.

The drug has roots in discoveries made almost two decades ago by a pair of OMRF scientists: **Drs. Charles and Naomi Esmon**. OMRF filed for patents on those discoveries in 1988, and the patents issued in 1993 and 1994.

Patients with insufficient protein C levels experience abnormally high numbers of blood clots, which can occur in the blood vessels of the skin, eyes, brain, kidneys and elsewhere. The new drug is intended to treat those patients when they are faced with a life-threatening situation from blood clots in the veins or from a skin and systemic clotting disorder known as purpura fulminans (PF). In clinical trials, it was found to be effective in 94 percent of patients suffering from PF and other acute thrombotic episodes.

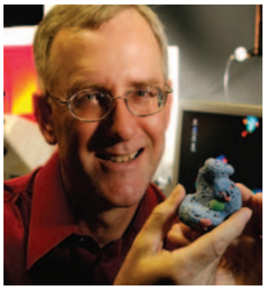
"This drug offers much needed treatment for patients with this severe deficiency, which could lead to blindness, severe brain damage, multi-organ failure and even death," says Charles Esmon. "It is clear that for this group of patients, this therapy offers new hope for a quality life."

The drug is made from the plasma of healthy human blood donors and is a concentrated form of protein C, a substance normally manufactured in the liver that circulates in the plasma in very small amounts.

GOOD THINGS COME IN PAIRS

THIS IS THE SECOND DRUG WITH ROOTS IN CHARLES ESMON'S LAB AT OMRF TO RECEIVE FDA APPROVAL. ESMON'S WORK ALSO LED TO THE DEVELOPMENT OF A TREATMENT FOR SEVERE SEPSIS, A BLOOD INFECTION THAT IS THE LEADING CAUSE OF DEATH IN AMERICA'S INTENSIVE CARE UNITS. THAT DRUG RECEIVED FDA APPROVAL IN 2001.

OF NOTE



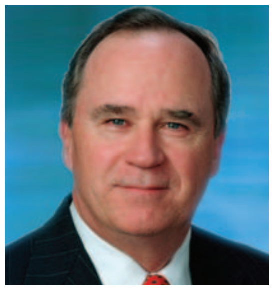
Dr. Michael Dresser

In the May 22 issue of the *Proceedings of the National Academy of Sciences*, Dresser detailed the discovery of a new process that helps prevent formation of abnormal chromosomes. "This opens up a new area of research to understand how cells keep their chromosomes intact to avoid a range of genetic diseases, such as Down syndrome and autism," he says.

Hon. Kathy Taylor

The Tulsa Chapter of Women in Communications presented OMRF director Taylor with its Newsmaker Award on May 1. Taylor, an attorney, served as Oklahoma's Secretary of Commerce and Tourism until she was elected the 38th mayor of Tulsa in 2006.

OKC Business and the Best Companies Group honored OMRF as one of the state's "Best Places to Work" on May 4. Results were based on employee surveys, and this is the second straight year OMRF has been selected as one of Oklahoma's top 25 employers.



W. Lance Benham III

At OMRF's annual honors and awards banquet on May 8, Benham received the Board of Directors Distinguished Service Award. Dr. Linda Thompson also was honored with the Edward L. and Thelma Gaylord Prize for Scientific Achievement, and Dr. Fletcher Taylor was recognized as a Distinguished Career Scientist.

Dr. Joan Merrill

Merrill and Dr. John Harley each gave invited presentations at the 8th annual International Congress on Lupus in Shanghai, China. In conjunction with the Congress, both also helped lead the inaugural "World Walks for Lupus" on May 25. A billboard-sized photo of Merrill leading the walk later appeared in New York's Times Square.

Grants

Dr. Dean Dawson, *Segregation of Error-Prone Chromosomes in Meiosis*, National Institute of General Medical Sciences

Dr. Robert Floyd, *Optimized Oral Treatment of Acute Acoustic Trauma*, Office of Naval Research

Dr. John Harley, *Kirkland Scholar Award*, Mary Kirkland Center for Lupus Research and Rheuminations; *Genetic Linkage in Lupus*, National Institute of Allergy and Infectious Diseases; *Genetic Association in American Blacks with Lupus*, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Kenneth Hensley, *Acetaminophen for Amyotrophic Lateral Sclerosis*, Muscular Dystrophy Association

Dr. Paul Kincade, *Developmental Stage-Related Changes in Lymphopoiesis*, National Institute of Allergy and Infectious Diseases

Dr. Shinichiro Kurosawa, *Primate Model and Pathogenesis of Anthrax Sepsis*, National Institute of Allergy and Infectious Diseases

Dr. Florea Lupu, *Targeting Nuclear Transport of HIFIA As Sepsis Therapy*, Oklahoma Center for the Advancement of Science and Technology

Dr. Kenneth Miller, *Signaling Pathways That Regulate Synaptic Transmission*, National Institute of General Medical Sciences

Dr. Swapan Nath, *Identifying the Novel SLE Susceptibility Gene on 5p15.3*, National Institute of Allergy and Infectious Diseases

Dr. Xiao-Hong Sun, *Mechanism of T Cell Lymphoma in E Protein Deficiency*, National Cancer Institute; *E2A Turnover and Notch-Controlled Lymphocyte Development*, National Institute of Allergy and Infectious Diseases

Dr. Linda Thompson, *The Regulation of Inflammatory Responses by CD73*, National Institute of Allergy and Infectious Diseases

Dr. Rheal Towner, *Molecular-Specific Detection of Tumors: MRI Investigations*, National Cancer Institute; *Anti-Cancer Activity in Nitrones in Animal Models*, Oklahoma Center for the Advancement of Science and Technology

Dr. Carol Webb, *Bright Function in the Immune System*, National Institute of Allergy and Infectious Diseases

Grants Awarded *January-April, 2007*

LIVE LONG AND PROSPER

Who says TV is bad for kids? For OMRF's **Dr. Judith James**, Vulcans and Klingons helped inspire a striking new way of predicting disease.

By Michael Bratcher
Photos by Steve Sisney

G

GROWING UP, JUDITH JAMES rarely passed up an episode of *Star Trek*. From her living room in Pond Creek, she sat transfixed as Captain Kirk, Mr. Spock and the crew of the *U.S.S. Enterprise* boldly went where no man had gone before. For the future physician and medical researcher, the workings of the ship's doctor, "Bones" McCoy, held a special interest.

"I was always intrigued when Dr. McCoy scanned his fellow shipmates with a tricorder," says James. On the show, which was set in the 23rd century, the—fictional—handheld device allowed McCoy to scan individuals (human or alien) to diagnose illness. The medical tricorder even predicted when an apparently healthy being eventually would fall prey to disease.

"I loved the idea that you could tell people they were going to get sick before it happened," says James. "But I thought that concept was completely in outer space, far beyond anything that would happen in my own lifetime."

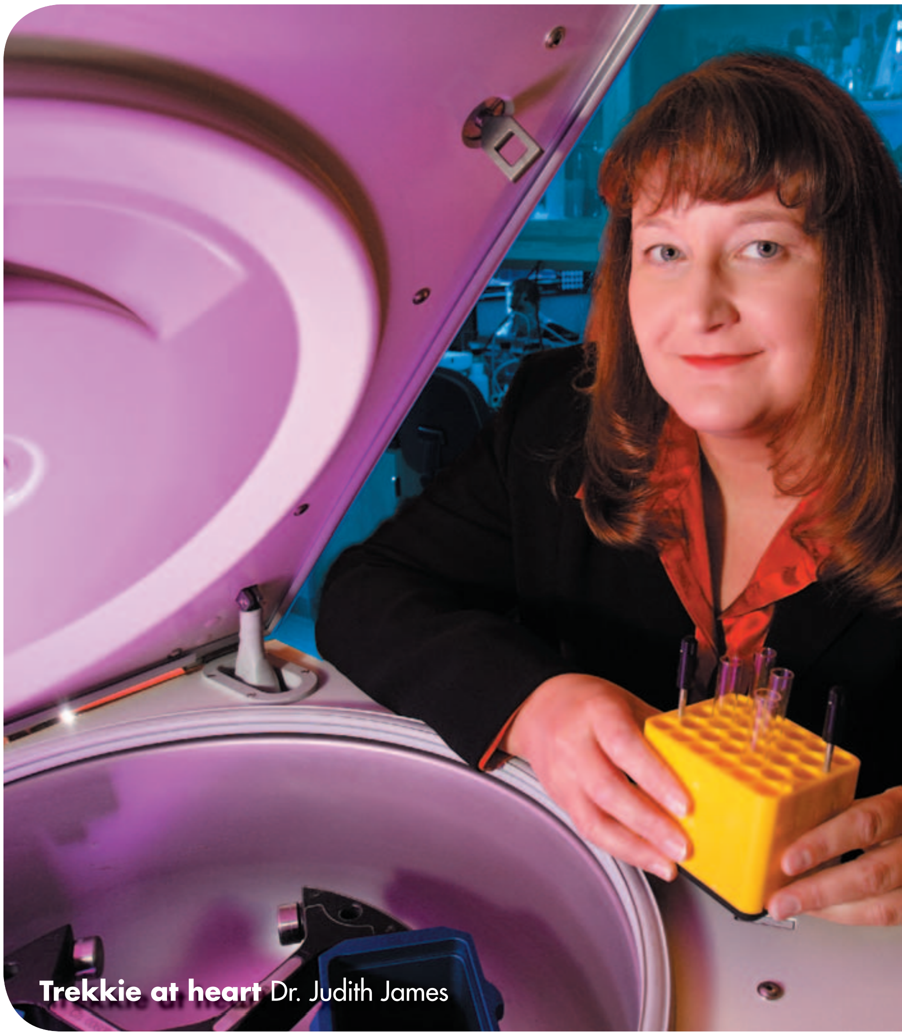
Turns out that future may not be so far away. And the one-time Trekkie is at the forefront of transforming yesterday's science fiction into today's reality.

James, who now holds the Lou C. Kerr Chair in Biomedical Research at OMRF, has pioneered the study of how molecules called autoantibodies can predict whether a healthy person will one day develop an autoimmune disease, a broad category of disorders that encompasses conditions such as lupus, multiple sclerosis, rheumatoid arthritis and type I diabetes. A simple blood test can detect the presence (or absence) of autoantibodies.

In a groundbreaking study published in *The New England Journal of Medicine*, James and fellow OMRF researchers Drs. John Harley and Hal Scofield showed that in patients who ultimately developed lupus, certain autoantibodies appeared in their blood years before they developed symptoms. That work, which was the product of almost two decades of research, represented a crucial milestone in the emerging field of predicting disease.

Using autoantibodies as a sort of diagnostic crystal ball, doctors may soon be able to tell seemingly healthy people that they will develop lupus or other autoimmune diseases. Yet this work holds the potential to do more than see the future. "With this kind of information," says James, "we also could begin fighting disease before symptoms ever appear."

It's a mind-boggling concept, the idea of treating a disease before it's done any harm. Perhaps those treatments could delay disease onset. Perhaps they also could lessen the brunt of the illness when it eventually reared its head. Or maybe, just maybe, therapy could prevent that disease altogether.



Trekkie at heart Dr. Judith James

FRIENDLY FIRE

With her colleagues in OMRF's Arthritis and Immunology Research Program, James focuses her work on disorders known as autoimmune diseases, conditions in which the body confuses its own tissue with outside invaders like viruses and bacteria. As a result, the immune system mistakenly unleashes its weapons against itself. These "friendly fire" attacks are at the heart of more than 40 disorders, which range from relatively common conditions like rheumatoid arthritis, multiple sclerosis, lupus and type I diabetes to rare and little-known disorders such as Wegener's granulomatosis and scleroderma. All told, these diseases affect between 5 and 8 percent of the U.S. population—up to 23.5 million Americans—and together constitute the third leading cause of illness in this country, ranking behind only heart disease and cancer.

Normally, the immune system relies on Y-shaped proteins known as antibodies to identify and neutralize foreign pathogens that may be a threat to the body. But in autoimmune diseases, certain rogue antibodies (known as "auto"-antibodies) attack the body's own cells.

Researchers have long known that these autoantibodies could be found in people suffering from lupus and other autoimmune disorders. Indeed, Dr. Morris Reichlin, her colleague at OMRF, had done pioneering work in understanding how and

why certain people's bodies produce autoantibodies. But, James wondered, when do autoantibodies first show up? Is it possible they actually appear in the body before the first symptoms of disease?

The idea was striking. But there was one, big hurdle: You can't go back in time to test the blood of lupus patients before their first symptoms arose.

"If you look at the literature and all the studies being done on lupus, more than 95 percent of publications are based on data obtained after people have been diagnosed," says James. "These early events were in many ways uncharted territory. People don't come into the office and say, 'I think I might get lupus in 10 years, so will you enroll me in a study and check my blood every three months until then?'"

So, reasoned James, "We needed to find a way to work backwards."

She knew that the U.S. military collected biological samples from enlisted personnel and kept those samples, along with the individuals' medical records, for many years. If she and her research team could comb through tens of thousands of medical records and find soldiers and sailors who eventually developed the disease, they could then request blood samples—taken prior to the onset of symptoms—and test them for autoantibodies.

It took James and the OMRF team nearly 20 years to gain access to the U.S. Department of Defense serum repository and conduct their own testing. But when they did, the results spoke for themselves: Of 130 servicemen and women who ultimately developed lupus, 88 percent of those patients had telltale autoantibodies before they showed clinical symptoms. For many of these patients, the autoantibodies appeared in the blood years before disease onset.

The work holds exciting clinical potential: Tests to detect these molecules could become a standard part of routine checkups for high-risk individuals, and a positive test could signal the need to take preventive action. Yet, cautions James, "We're not at the point now where we have all the answers in that magic ball. There are a lot of normal, healthy individuals who will never be sick a day in their lives who still have some of these autoantibodies in their blood." And because the causes of lupus are not yet known, preventive measures are far from guaranteed to be effective. "Fortunately, with lupus, we do have some evolving literature that shows if we could change some markers, we could change the course of the disease."

Dr. Noel Rose, director of the Center for Autoimmune Disease Research at Johns Hopkins Bloomberg School of Public Health in Baltimore, began researching the possibility of predicting disease nearly 25 years ago. And since, he's kept a close eye on the research being conducted at OMRF. His studies have shown that autoantibodies may predict autoimmune thyroid disease in the brothers and sisters of children who have the disease.

"That really got me to thinking about using antibodies as predictors of disease before it is clinically apparent," Rose says. "And that is what the Oklahoma group did with lupus."

OMRF's work, says Rose, "is on the leading edge of predictive antibodies. And if we can begin to identify people at a very early stage before the disease is clinically evident, the chance of using targeted intervention would be much greater." Intervening before symptoms arise could cut drug doses, shorten courses of treatment and, as James puts it, "help physicians reset the body's thermostat instead of keeping it turned off for the rest of patients' lives."

James, Rose and their collaborators (who come from as far away as Austria) recently presented their findings at the 2007 meeting of the American Association for the Advancement of Science, the world's largest interdisciplinary scientific forum. That work also was featured in a recent issue of *Scientific American*, in a cover story entitled "New Predictors of Disease."

THE NEXT GENERATION

Will there come a time when you can visit a doctor and learn whether you're susceptible for disease? In autoimmune diseases like lupus, that day may not be too far off.

"The question is can we do the same type of thing by looking at high-risk individuals for other disorders?" James says. And if so, do we really want to know?

From a public health perspective, Rose warns that such predictive screenings shouldn't occur until a treatment is available. "If we just have predictors and no way to intervene, that's not really helping the patient," says James.

And then there are the insurance issues. If an autoantibody test determines you may someday develop lupus, what information must you share with your insurer? "People have to weigh the consequences," Rose says. "The insurance company can say, 'We'll double your rate or not carry you at all.' Or you can withhold information. It's a real problem."

Many national policy meetings and working groups are assembling to grapple with insurance issues. Their primary focus is to keep early detection from becoming a hurdle to insurability, because this predictive data holds too much clinical value to ignore. "We're identifying biomarkers that can be detected in the bloodstream before a patient experiences an active flare of a disease," says James. "If doctors treat these flares proactively, they potentially can be averted, and that can prevent damage that can't be reversed."

James' research has been cited on CNN, MSNBC, the Fox News Network, as well as in *The New York Times*. This work has played a key role in advancing the new frontier of preventive medicine, a world not so far from what she saw on *Star Trek* as a child. So what's next?

"I guess I'll just look forward to the day when I can fly to OMRF in a car like George Jetson's," she says, smiling. Or maybe Scotty will just beam her to work. OMRF

Star Trek ® is a registered trademark of Paramount Pictures. This article is not approved or authorized by Paramount Pictures.

BY ADAM COHEN

THIS IS MY BRAIN ON 3-TESLA MRI

"That's not good," Dr. James Brewer says to me.

I blink, shifting my eyes from the watery blue of the Pacific Ocean to Brewer's worried face. We're sitting on the deck of a restaurant perched a few hundred feet above the water, our half-finished bowls of pasta warmed by the California sun. A line of gulls rides the sea breeze above us. What could be not good about this?

"You have metal in your body," says Brewer. "And if you have any metal in your body, MRI"—magnetic resonance imaging—"can be a problem."

Don't worry, I tell him. It was only jaw surgery. Surely a few pins won't interfere with his 15,000-pound magnet. And the operation was 13 years ago. Brewer pokes his sesame noodles and shakes his head. "Older is worse."

But I have not flown 1,500 miles just to eat lunch. I've traveled to La Jolla to get a brain scan in the Human Memory Laboratory at the University of California, San Diego. I want to see the future of medical research, to view my own brain through a 3-tesla MRI, a human scanner twice as powerful as any in Oklahoma and strong enough to see both the structure of my brain and what parts I'm using when I perform certain tasks.

And while I'm in the magnet, I want to learn if my hippocampus shows any signs of Alzheimer's disease.

For the past year, Brewer has been collaborating with Dr. Rheal Towner and his team in OMRF's small animal imaging facility. The facility is unique in Oklahoma and one of only two dozen of its kind in the nation. Using a research-grade magnet specially designed for rodents, Towner works to develop new, non-invasive techniques for studying cells at microscopic levels. These methods do not harm the animals, and OMRF's work provides clinicians like Brewer—a neurologist—with blueprints for using MRI to diagnose and treat disease in human patients.

With a bore (the hole in the center of the magnet) less than a foot in diameter, OMRF's MRI cannot accommodate human subjects. But it is this small bore that makes OMRF's magnet so powerful, four times stronger than those found in most hospitals. Brewer's research-grade magnet, which is twice as strong as a standard hospital MRI but still only half as powerful as OMRF's, represents the gold standard for human scanners. It is on magnets like Brewer's that scientists have seen dizzying progress in understanding in the human brain and in diagnosing and treating the diseases that afflict it.

The work done at OMRF and similar facilities has given neurologists like Brewer the tools to assess tumors and help develop surgical plans for patients with brain cancers. To understand how people learn, make memories, tell lies and fall in love. And, in a potentially groundbreaking study, to diagnose Alzheimer's disease at an earlier stage than currently is possible.

No, I decide, I'm not going back to Oklahoma just yet.

Our waiter offers Brewer some coffee. He opts for decaf. "I'll need a steady hand," he says. He's joking, I think.

If something goes wrong, I ask him a few minutes later, how will we know?

"Oh, you'll feel it." With magnetic fields tens of thousands times stronger than the earth's magnetic field, explains Brewer, "MRIs have been known to pull nails right out of floors." And Brewer's $5 million machine is no average MRI. "I was planning on running some really aggressive scans, so we'll just take it slow and see how things go."

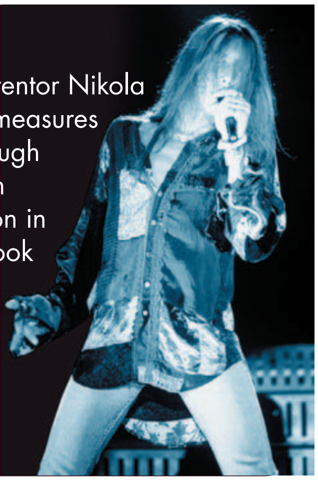
I don't finish my dessert; I seem to have lost my appetite.

MRI WORKS BY MEASURING the behavior of molecules in a magnetic field. Because molecules behave differently in different tissues, MRI can create highly detailed images of the body's internal organs. Using more powerful magnets (like Brewer's), researchers also can perform what's known as "functional" scans, which detect changes in the natural magnetic properties of the blood cells that carry oxygen.

With functional MRI, scientists can measure brain activity as well as structure. Researchers place subjects in the center of a powerful magnet, then use different electromagnetic pulses to perturb the magnetic field. These pulses measure temporary changes in the blood's hemoglobin concentration caused by neural activity, and MRI captures these changes with a series of snapshots of what's going on inside the body. For instance, when Brewer scans my brain to see how it functions when I perform basic motor tasks, a protocol lasting about 6 minutes, he will take 5,520 different shots of the space between my ears.

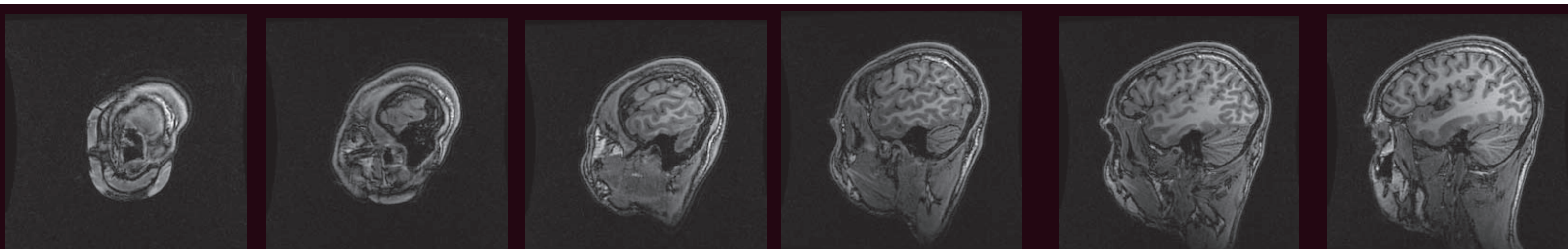
What's a Tesla?

Named for physicist, engineer and inventor Nikola Tesla, the tesla is a scientific unit that measures the intensity of a magnetic field. Although Tesla died in 1943, the so-called "man who invented the 20th century" lives on in popular culture: A 1980s rock band took his name, a graphic novel imagines him teaming up with Mark Twain to battle Thomas Edison, and, most recently, David Bowie played him in the 2006 film *The Prestige*.

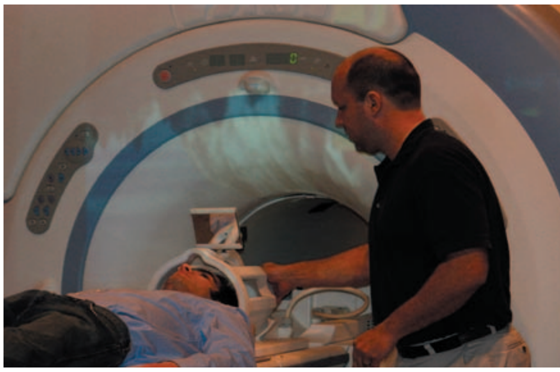


The technology of MRI, which came into clinical use in the 1980s and has undergone constant refinement since, provides a non-invasive way of seeing what's going on inside a person (or a rodent). As the magnets have grown more powerful, the images they capture have grown more resolute. At OMRF, with a magnet 140,000 times stronger than the earth's magnetic field, Towner and his colleagues can examine cellular structure and activity at microscopic levels, without surgery or any tissue samples.

Scientists and physicians sometimes inject contrast agents—essentially dyes—to enhance visualization of certain structures.



But, according to Towner, the evolving technology is decreasing the need for these compounds. He cites his own work as an example.



"There recently was a study of premature infants who were deficient in particular nutrients like zinc," he says. Towner decided to dig deeper by using MRI to study the brains of young rats with similar nutritional deficiencies that, like their premature human counterparts, had spent time in an incubator in a 100-percent-oxygen environment. "We wanted to see if there were any neurological developmental changes caused by incubators and poor diet. And one way to do that is to use a contrast agent to see if there's damage to the blood-brain barrier", which separates brain tissue from blood vessels.

But through the use of certain biological markers already found in the brain, Towner devised a method of gauging neurological development in the rodents without contrast agents. "We can measure the animals' neuronal development at a very early stage in a completely noninvasive way," says Towner. The next step will be to adapt these protocols to people. "In humans, premature children with nutritional deficiencies often suffer from learning deficits. If we had a way to test at-risk infants using MRI, we could intervene much earlier with behavioral therapies to help stem the developmental problems they'll face."

Towner's study has multiple clinical applications. First, it provides valuable pre-natal information about the importance of nutrients like zinc in pregnant mothers' diets. His findings also caution against using pure oxygen on preemies. And, most importantly, they offer a way to identify and improve the lives of children facing substantial learning deficiencies.

"If you think of the technology as the starting point and human application as the end goal, researchers like Dr. Towner build bridges that connect the two," says Brewer. "Clinicians need people like Dr. Towner."

THE W.M. KECK BUILDING SITS NEAR A ROW OF eucalyptus trees at the University of California, San Diego. A low-slung, boxy building, its austere façade is broken only by a riot of pink flowers and a small, glass pyramid that crowns it.

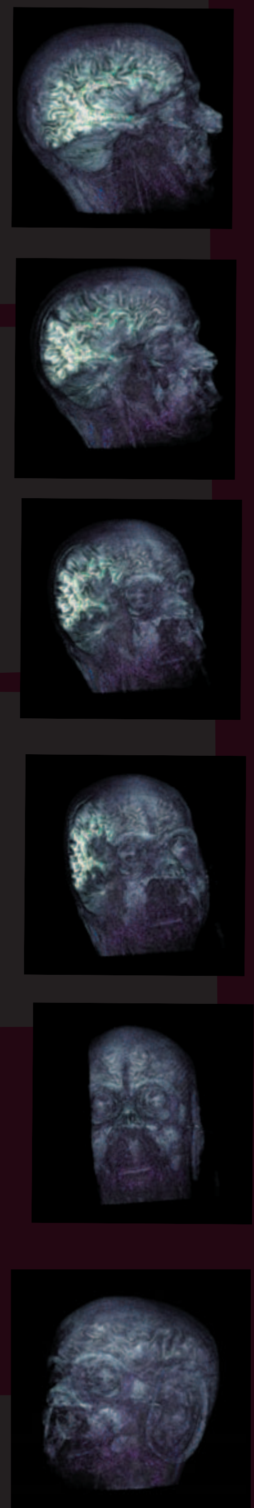
Brewer leads me into a laboratory suite, where I fill out a series of forms. I consent to participate in a research project that, according to the form, will involve "lying quietly inside the center of a large doughnut-shaped magnet for approximately 75 minutes." The potential risks, the form instructs me, are manifold: claustrophobia, anxiety, dizziness, nausea and, worst of all, "the possibility of an abnormal finding." I attest that I do not have a pacemaker, heart valve replacement, brain clips or dentures, am not pregnant, and do not have permanent eyeliner. Then I jettison all items containing any metal: Keys, change, cell phone, belt, money clip, shoes. Even my wedding ring.

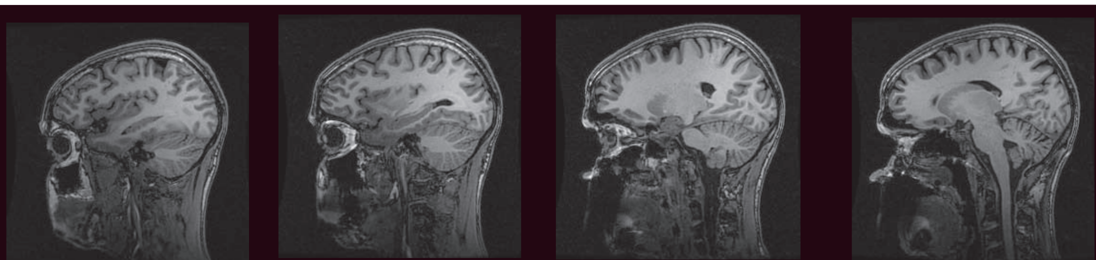
Still, when Brewer waves his metal-detecting wand over me, a disturbing thing happens: It beeps. By my upper jaw. Hello, surgical pins.

Brewer frowns. The magnet sits in the next room, its field blocked by copper sheathing that lines the chamber's walls. "I want you to approach the MRI very carefully," he says to me. "And tell me if you feel anything. Anything."

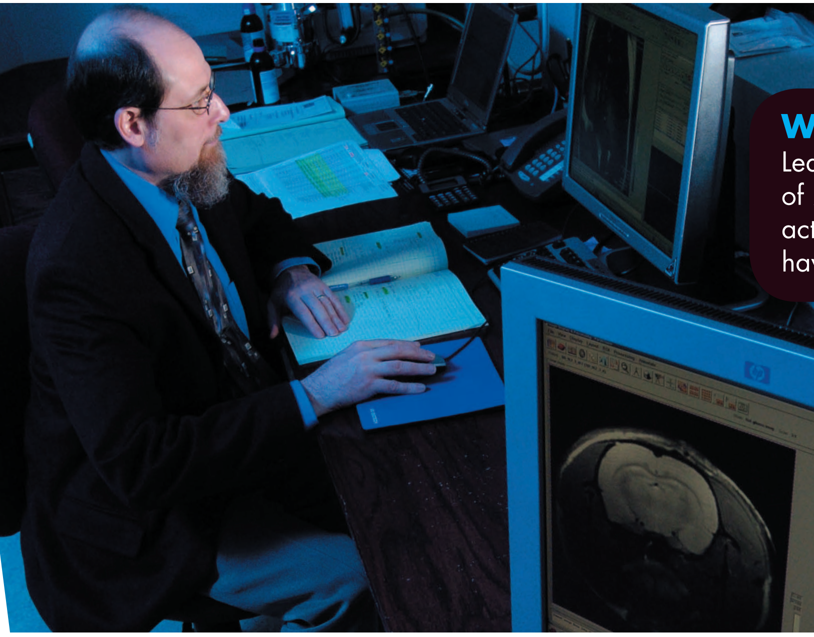
We step through the doorway, Brewer clutching my bicep to ensure that I take only baby steps. The magnet greets us with a steady, canary-like chirping (the by-product of hundreds of liters of liquid helium re-circulating through its coils). With each step, I anticipate a searing in my jaw, but the burn never comes. Eventually, our promenade delivers me to the doughnut hole of the MRI, where I lie flat on my back and squeeze my head inside a birdcage-like apparatus. Brewer hands me a small, rubber sphere. "Hold onto this. This is your panic button. Squeeze it if you feel any pain. Or if you just feel like you need to get out." Then he pushes something, and I slide headfirst into the MRI's belly.

Brewer retreats to the next room, where he operates the scanner from a computer while watching me through a plate-glass window. "Just rest comfortably and try to keep your head still," he says through a microphone. "This is going to be a high-





Head Case
Dr. Jim Brewer prepares the author for his MRI (top), which produced cross-sectional (left) and three-dimensional (above) images of his brain and its surrounding anatomy.



Working Overtime

Led by Dr. Rheal Towner, OMRF's MRI facility now is in use an average of 20-plus hours a day, 7 days a week. There currently are 30 different active projects, and since the facility opened in October 2004, scientists have run MRI studies on more than 3,000 subjects.

resolution structural scan of your brain. Are you ready to go?"

I am.

For the next hour or so, the magnet bangs and whirs and squeaks while Brewer runs sequence after sequence to capture different aspects of my brain's architecture. Toward the tail end of the session, he runs a functional scan. A small mirror mounted on my birdcage lets me see a computer screen positioned by my feet, and the screen instructs me to perform a simple finger-tapping routine, alternating between my left and right hands.

Left index, middle, ring, pinkie. Rest. Right index, middle, ring, pinkie. Repeat. For six minutes I continue, tapping my fingers precisely as instructed. And then the screen goes black. "All done," pipes in Brewer's voice. "Now let's get you out of the scanner and take a look at your brain."

MRI CAPTURES REMARKABLY DETAILED PICTURES of subjects' brains, and the images also can be pieced together to create three-dimensional models. At OMRF, scientists have tapped this technology to study neurodegenerative diseases like Alzheimer's, Huntington's and ALS (Lou Gehrig's disease). They're also employing MRI to understand cancers of the brain and lesions that form in the brains of multiple sclerosis patients. Yet the utility of MRI is not limited to studies of the brain: Towner also counts current research projects involving liver and colon cancers, lupus, anthrax, diabetes and heart disease.

More at omrf.org

Hear an interview from Dr. Brewer and take a look at movies of the author's brain at **omrf.org/braingames**

OMRF opened its facility in the fall of 2004; contributions and grants from the Presbyterian Health Foundation, Henry Zarrow, the National Institutes of Health and the Oklahoma Center for the Advancement of Science Technology helped foot the nearly $4 million bill for building and equipping the facility, purchasing the magnet and recruiting the scientific personnel to operate it. In less than three years, Towner and his staff already have run more than 3,000 scans. The projects have involved scientists not only from OMRF but also from other institutions across the state and around the world (Towner now is working on a pair of studies with Japanese scientists).

With one of only a dozen or so 7-tesla magnets in the U.S., OMRF's facility has been popular among researchers from the get-go. But it has become so busy lately that the magnet can no longer meet demand. "We're operating seven days a week, and on most days, we run for 24 hours," says Towner. To keep up, OMRF will purchase a second MRI later this year. That magnet will have a field strength of 11.7 tesla—roughly eight times stronger than MRIs found in most hospitals. According to Towner, OMRF's new magnet will be in elite company: "There are only a handful of 11.7's out there."

Like OMRF's 7-tesla magnet, the new one will be small-bore, large enough only to accommodate small animals. Keeping the bore small improves magnetic field strength. And that stronger field, says Towner, "will give us higher resolution, so that we can study changes that are occurring in even smaller groups of cells."

A FEW DAYS AFTER MY SCAN, BREWER E-MAILS me the results. "Good news, Adam! You do not appear to have Alzheimer's disease. The size of your hippocampus falls right on the norm for a 66-year-old."

Um, I'm 39.

"Don't worry, that norm also applies for young folks."

Brewer explains that my brain appears "fairly symmetrical" (good news) and that my functional MRI shows activity in all of the right places during the finger-tapping drill. He doesn't see any signs of unwanted brain masses (again, good).

Besides helping me sleep better, the data gathered from my scans will become a part of an ongoing clinical research project Brewer is conducting. Researchers have known for some time that the hippocampus, a seahorse-shaped region of the brain, shrinks rapidly with Alzheimer's disease. Using MRI, La Jolla's Cortechs Labs have developed a method of measuring hippocampal volume with a single mouse click. Brewer now has scanned more than 200 subjects—including me—using this "volumetric imaging" system, and he is optimistic about its potential. "This could revolutionize the diagnosis of Alzheimer's disease. Right now, there's no definitive diagnostic test. But with volumetric imaging, we can catch it before a person is overly impaired. And that will be critical as new treatments come down the pike."

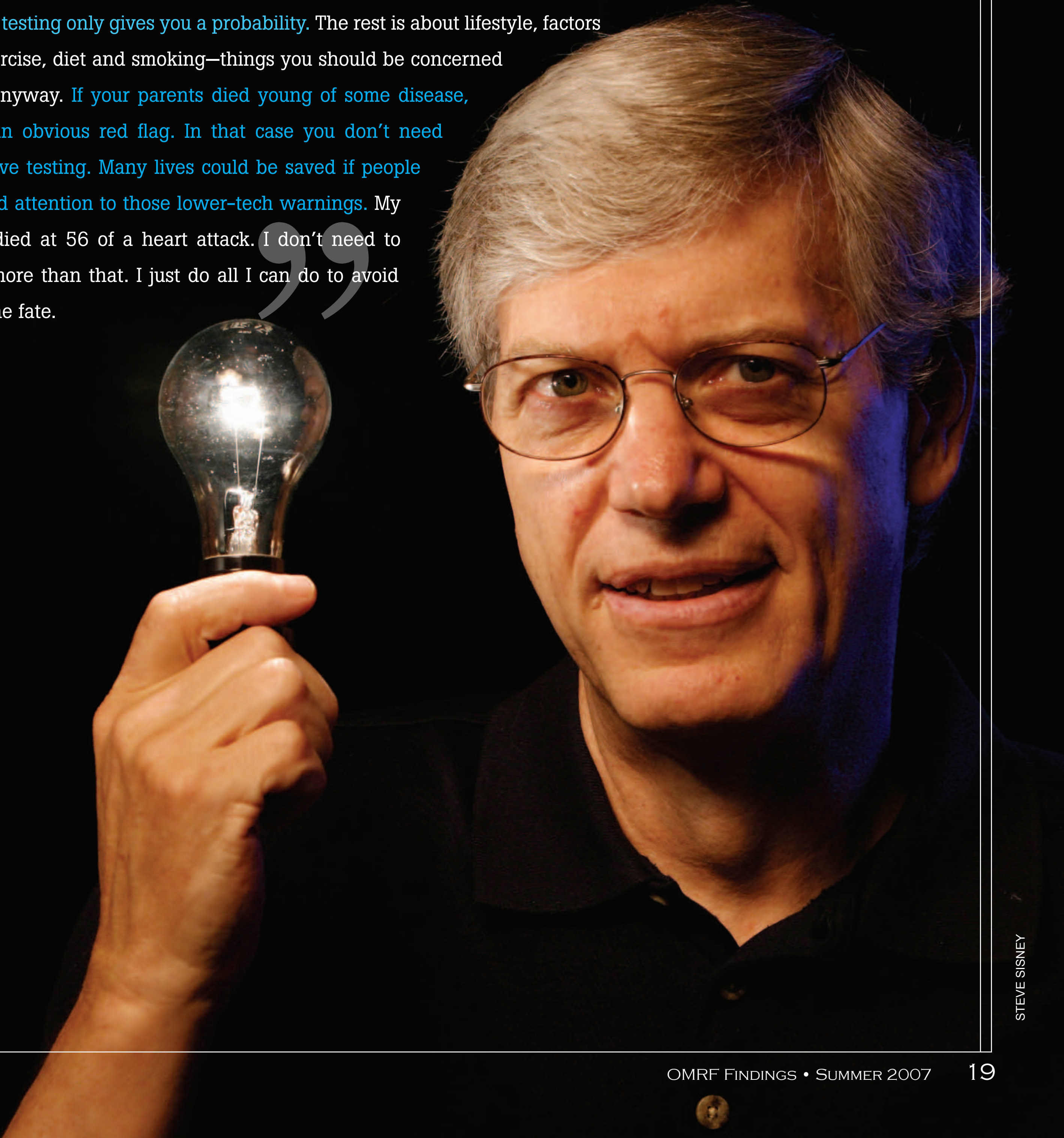
To Brewer, Alzheimer's is but the tip of the iceberg when it comes to the potential of MRI. "We have this amazing technology, and from it we get these beautiful images of the brain that are rich with information." The problem, he says, is that physicians and scientists aren't mining all the data. "We send the images to a radiologist, who looks at them and then dictates a little paragraph about what he saw. It's like a game of telephone; there's so much information lost. If we can devise a way to squeeze out all that information, I believe MRI will be the way to detect almost every neurological disease."

And with earlier detection will come more effective treatments for human disease. Even, perhaps, ways to prevent the onset of symptoms in the first place. Talk about a powerful magnet.

Shedding Light on Genetic Testing

Dr. Philip Silverman • Majorie Nichlos Chair in Medical Research

"Learning your genetic "secrets" can be a deeply emotional issue. Can you live happily without knowing? Or not? You need to sort out how you'll deal with it beforehand, because once you have the results, the "gene's" out of the bottle. Some diseases—sickle cell anemia, Huntington's disease, cystic fibrosis—are the result of a single gene. We can test for those diseases. But we can't stop them. At least not yet. Would you want to know you were going to get sick if there was little doctors could do to help you? Employers can require drug testing. Can genetic testing be far behind? Would it be constitutional? The majority of diseases arise from the interplay of many genes. That's the way it is with cancer and heart disease. So most of the time, genetic testing only gives you a probability. The rest is about lifestyle, factors like exercise, diet and smoking—things you should be concerned about anyway. If your parents died young of some disease, that's an obvious red flag. In that case you don't need predictive testing. Many lives could be saved if people just paid attention to those lower-tech warnings. My father died at 56 of a heart attack. I don't need to know more than that. I just do all I can do to avoid the same fate."



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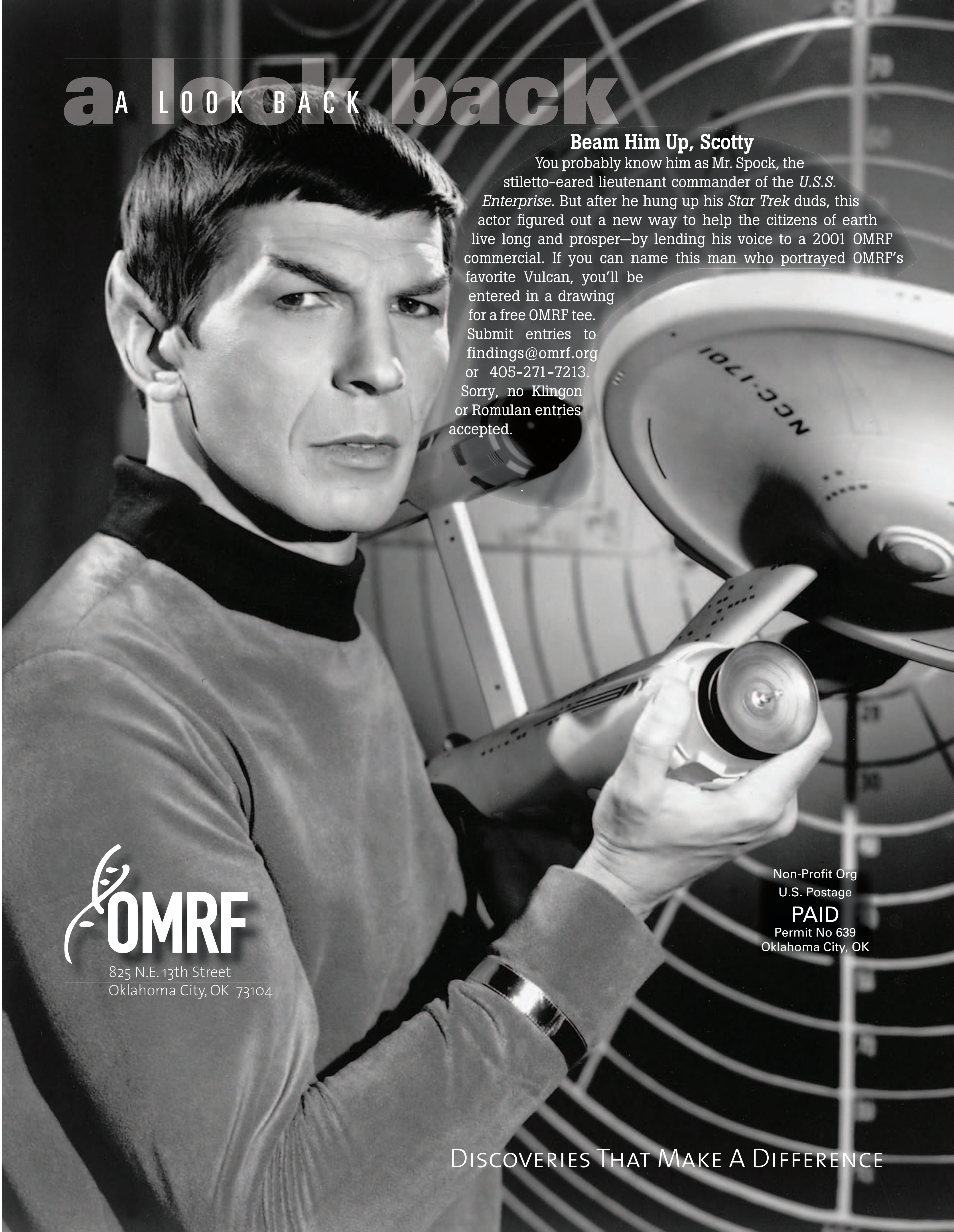

A LOOK BACK

Beam Him Up, Scotty

You probably know him as Mr. Spock, the stiletto-eared lieutenant commander of the *U.S.S. Enterprise*. But after he hung up his *Star Trek* duds, this actor figured out a new way to help the citizens of earth live long and prosper—by lending his voice to a 2001 OMRF commercial. If you can name this man who portrayed OMRF's favorite Vulcan, you'll be entered in a drawing for a free OMRF tee. Submit entries to findings@omrf.org or 405-271-7213. Sorry, no Klingon or Romulan entries accepted.

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