St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

Promise

Winter 2006

Amazing Grace

page 4

St. Jude Children's Research Hospital was founded by the late entertainer Danny Thomas. It opened February 4, 1962. The institution was created because of a promise Thomas made during the depression era to St. Jude Thaddeus, the patron saint of the hopeless.

"Show me my way in life," Thomas prayed. In return, Thomas promised to build St. Jude Thaddeus a shrine. That shrine became a world-class research institution that treats children regardless of race, color, creed or their ability to pay. This remarkable event also inspired the name of this magazine,

Promise.

St. Jude Children's Research Hospital, Memphis, Tennessee

Promise
is a quarterly publication of the
Department of Public Relations
St. Jude Children's Research Hospital
332 N. Lauderdale St.
Memphis, Tennessee 38105

St. Jude Children's Research Hospital's mission is to find cures for children with catastrophic diseases through research and treatment.

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A publication of St. Jude Children's Research Hospital Winter 2006

Features

Highlights

Perspective

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On the cover: Anna Grace Davis. Photo by Laura Hajar.

Highlights

Snappy synapses

The brain's ability to transmit and process information requires a lifelong commitment to maintaining the integrity of synapses—the special connections that permit the passage of nerve impulses from one nerve cell to another, according to investigators at St. Jude and Hokkaido University School of Medicine, Japan.

This long-term commitment requires proteins called synaptotrophins to maintain millions of synapses in good working order. In the absence of such proteins, the synapses weaken and eventually fall apart. This compromises nerve transmission and provides the opportunity for other nerves to extend their axons toward these faltering synapses and make inappropriate connections that further disrupt brain function.

James Morgan, PhD, of Developmental Neurobiology was senior author of a paper on this topic, which appeared in *Nature Neuroscience* in November 2005.

Critical collaboration

The *Ink4c* and *Ptch1* genes work together to suppress development of the brain tumor medulloblastoma, according to St. Jude researchers and their colleagues at three other institutions. The genetic teamwork occurs independently of another tumor suppressor, the *p53* gene.

The discovery sheds light on how cells in the cerebellum called granule neuronal precursor cells give rise to medulloblastoma when certain genes are absent or functioning abnormally. A report on this work appeared in *Genes & Development* in November 2005.

Based on these findings, the St. Jude Pediatric Brain Tumor Program will try to determine if the absence or presence of the *Ink4c* RNA or protein in medulloblastoma cells can help doctors predict patient outcomes, said Martine Roussel, PhD, of Genetics and Tumor Biology, the paper's senior author.

Clever combination

In the lab, St. Jude investigators have found a new treatment for the pediatric eye cancer retinoblastoma that appears to be more effective than the current standard therapy and more likely to prevent recurrence of this cancer. A report on this work appeared in *Clinical Cancer Research* in October 2005.

The study showed that combination therapy with topotecan and carboplatin is superior to the standard therapy using vincristine, carboplatin and etoposide. The study suggests a new approach to treatment that could save both lives and vision, said Michael A. Dyer, PhD, of Developmental Neurobiology, the report's senior author. The new treatment might also prevent recurrence of retinoblastoma in children whose cancer is advanced.

Construction of the hospital's Integrated Patient Care and Research Building (IPCRB) continues to progress. The facility will house the Department of Radiological Sciences, provide space for new research laboratories and accommodate the expansion of inpatient activities. The 300,000-square-foot facility is scheduled for completion in June 2007.

Stem cells and brain tumors

Brain tumors called ependymomas that occur in different parts of the central nervous system appear to arise from subpopulations of stem cells called radial glia cells (RGCs), according to St. Jude investigators. The discovery explains why some identical-looking ependymomas are actually distinctly different diseases.

The study found that when rare populations of RGCs acquire mutations that disrupt the cell signaling pathways controlling growth and differentiation, these cells reproduce continually and give rise to an ependymoma.

The findings suggest that treatments should be designed to kill cancer stem cells instead of the tumor itself, said Richard Gilbertson, MD, PhD, of Developmental Neurobiology and Hematology-Oncology. He was senior author of a report on this work, which appeared in *Cancer Cell* in October 2005.

Stress reliever

St. Jude researchers have discovered a previously unrecognized mechanism that controls a key protein linked to the cell's stress response. This finding holds promise for new ways to enhance cancer therapies or protect cells from dying after exposure to damaging chemicals or radiation.

The gene for this protein, called *p53*, is the most commonly mutated gene in human cancer; *p53* plays a critical role in helping cells respond to stresses that damage DNA.

The St. Jude study showed that the level of p53 protein synthesis increases following DNA damage. Scientists may be able to use this mechanism to modulate p53 function in order to control whether cells in the body mutate, and whether cells live or die after DNA damage. A report on this work appeared in the journal *Cell* in October 2005. Michael Kastan, MD, PhD, of Hematology-Oncology, was the paper's senior author.

St. Jude takes care of children. That care can mean chemotherapy treatment for cancer, tutoring help so a child doesn't fall behind in school, a hug on a bad day or tending to the needs of pediatric cancer patients displaced because of Hurricane Katrina. More than 125 children whose cancer treatment was disrupted because of the catastrophe received care at St. Jude affiliates in Louisiana or, like the mother and child below, were flown to Memphis for treatment. Reporter Lisa Ling (at left) interviewed St. Jude National Outreach Director Marlo Thomas and several patients whose care was disrupted by Katrina. The segment was aired on *The Oprah Winfrey Show.*

Research with muscle

The loss of function of the *FOXO1a* gene plays an important role in development of the most common soft tissue cancers in children; restoring that gene's function in cancer cells suppresses the cancer, according to St. Jude researchers. The cancer, called alveolar rhabdomyosarcoma (ARMS), arises from immature skeletal muscle cells.

Researchers found that the expression of *FOXO1a* is suppressed in ARMS and that the gene potently suppresses tumor activity when re-introduced into ARMS tumor cells in the laboratory. Thus, the investigators theorize that the observed loss of FOXO1a activity is a pivotal step in ARMS development.

Gerard Grosveld, PhD, of Genetics and Tumor Cell Biology is senior author of a report on these findings, which appeared in *Journal of Cell Biology* in September 2005.

Transplants and teeth

Many children who undergo bone marrow transplantation (BMT) as part of cancer treatment already have dental abnormalities that leave them vulnerable to potentially life-threatening bacterial infections, according to St. Jude investigators.

Researchers found that the most common dental problem in children about to undergo BMT was tooth decay, often resulting from neglected oral hygiene and poor nutrition. Tooth decay is especially dangerous in children undergoing BMTs because physicians must first suppress patients' immune systems to reduce the chance of transplant rejection. Therefore, these children should have dental checkups. Sue Kaste, DO, of Radiological Sciences and Christopher Rowland, DDS, of Surgery co-authored a report on this study, which appeared in *Bone Marrow Transplantation* in October 2005.

Amazing *Grace*

FROM A ROADSIDE IN RURAL CHINA TO THE HEART OF A MISSISSIPPI FAMILY, THE JOURNEY OF ANNA GRACE DAVIS IS JUST BEGINNING.

By Ruth Ann Hensley

Draped in a luxurious feather boa, crowned with a silver jeweled tiara and daintily sipping tea as if the Queen Mother herself had instructed her, a young girl charms her admiring subjects. With a dramatic sweep of her hand and a prim toss of her head, she brushes back the regal, dark locks that cascade to her waist and instructs her court to "Drink more tea!" Her guests might assume that they're in the company of the heir apparent to a throne. Except that the boa is made from chicken feathers dyed purple, the crown is plastic, and the 5-year-old sipping imaginary tea has already won more battles than most royals have fought in a lifetime.

Anna Grace Davis was abandoned on the roadside of a rural community in southern China when she was only a day old. What may seem like a cruel deed may in fact have been the very act of kindness that set off a miraculous chain of events that has inspired, delighted and amazed people from Memphis to Malaysia. The kindness, divine coincidence and incredible family support that have guided her life are proof that true princesses are made, not born. Anna Grace doesn't require sovereign rights to a kingdom because her feisty charm has free reign over the hearts of everyone she meets.

The long and winding road

"We bonded immediately," says her dad, Greg Davis, as he recalls holding Anna Grace in his arms the evening he and his wife, Nancy, stood in the Chinese consulate's office to finalize the adoption that had taken 22 months to complete. "There were seven couples with seven new babies in that office; six of the seven babies were screaming at the top of their lungs, and Anna had her head nuzzled right here in my neck," he says, tilting his head to the side.

A rare blood disease that nearly took Nancy's life in 1994 had led the couple to consider adoption when they decided to enlarge their family. Their biological son, Colton, was 8 years old when Anna Grace was adopted from an orphanage in Le Chang, China, where she was taken after being found on the roadside. In addition to dealing with the blood disorder, the family has dealt with a heart disease that has subjected Colton to four open-heart surgeries.

After weathering life-threatening storms of poor health and enduring months of frustrating international adoption delays, Greg and Nancy were ready to begin a new chapter in their lives the day they walked out of the consulate's office.

But less than a week after their arrival home, the couple began to notice a change in Anna Grace. "We thought she had an ear infection," Greg says. It turns out she did have an infection in both ears. But Anna was also losing the ability to sit up on her own, and one of her eyes had begun wandering inward. "Even though her ears were getting better, she was not," Nancy says.

A pediatric ophthalmologist who examined Anna Grace indicated the eye problem might correct itself. But when the baby became less steady and began vomiting, the couple rushed her back to the pediatrician. This time the pediatrician ordered a CAT scan. By that point, Anna Grace couldn't sit up at all.

"We were driving home after the CAT scan and the pediatrician called us," Nancy recalls. "The pediatrician said, 'Where are you right now?' Greg said, 'We're driving down the interstate.' And he said, 'Well, you'd better pull over.'"

The faith factor

The CAT scan had revealed an orange-sized medulloblastoma tumor on Anna Grace's brain stem. The Davis family didn't go home that day; they immediately turned around and went back to the hospital, where Anna Grace underwent surgery to remove the malignant brain tumor.

LAURA HAJAR

Every queen has her loyal subjects, and Anna Grace is no different. Today, her entourage consists of her baby doll and her parents, Nancy and Greg Davis.

"The first words out of the neurosurgeon's mouth were, 'This is every parent's worst nightmare,'" Nancy says. It wasn't a line they expected to read in the new chapter of their life, but the family pulled together.

"We've faced challenges before, and we've learned that what happens inside of you is far more important than what happens to you," Greg says. "The greatest expression of faith is to keep on going when you don't have all the answers, when you don't understand God's plan."

"We have a saying in our family," Nancy says. "You can get bitter, or you can get better." So the Davises decided they were going to get better.

Anna Grace survived the complex, life-threatening brain surgery and was referred to St. Jude Children's Research Hospital, where the 13-month-old began 16 months of chemotherapy and a procedure called conformal radiation. This form of radiation is a precise treatment that sends radiation beams from several directions directly onto the brain tumor, killing it and sparing the rest of the brain from most of the harmful effects of radiation. St. Jude pioneered the use of this therapy in protocols for children with brain tumors.

"There were pages, typewritten pages, of the possible negative side effects of the treatment," Greg says, "ranging from mild to don't-even-talk-about-it."

Saving grace

Not only did Anna Grace survive, but she thrived. She gained 12 pounds while she was in treatment. And most amazing of all, outside of hair loss, she suffered no ill side effects.

"And she did bald really well," Nancy says of her fashion-conscious daughter.

"Yeah, she had about a hundred hats," Greg says with a laugh.

For an infant to survive brain surgery and such an aggressive round of treatments with virtually no side effects such as loss of motor skills, hearing loss and speech impediments, is extremely rare.

"She really is the poster child for our treatment efforts," says Maryam Fouladi, MD, of St. Jude Hematology-Oncology, who monitored Anna's case throughout her treatments and sees her every six months for checkups.

"Anna is the best of both worlds—she is cured of her disease, and she's functionally normal," Fouladi says. "Not only does that give faith and hope to other families, but it gives us, as doctors, hope that we're making some strides in moving toward that goal."

"It's been a joy to watch her grow up," says Jana Freeman, a clinical research associate in Hematology-Oncology. Freeman and the Davis family maintain a friendship that formed during Anna's treatments. "We are so grateful for stories like this," Freeman says.

The Davises are grateful, too, for the support of the St. Jude staff. "I can't imagine going through what we went through with our daughter anywhere else," Nancy says. "It's an amazing place."

Greg agrees. "These doctors are here for way more than a paycheck," he says. "It's a life mission. It's a calling for them to be here."

Greg would know about that sort of thing, since he's the pastor of a church. He says prayers from around the world, the decision to take things one day at a time and faith in God's plan brought their family together and made them stronger.

"I don't know what Anna Grace is going to do in life. But I do know that God went to an extreme amount of trouble to get her out of China, to get her here and to get her well," he says.

Anna Grace's physician says that if the child had not been left on the roadside and adopted by the Davis family, she would not have survived her cancer.

"She wouldn't have lasted another month," says Fouladi, who describes the Davis family as phenomenal. "It's interesting that her middle name should be Grace," Fouladi continues, "because that's what she is."●

LAURA HAJAR

Even as a toddler undergoing treatment, Anna Grace stole the hearts of St. Jude staff. "Truly, she's precious," says Maryam Fouladi, MD, of St. Jude Hematology-Oncology. "Everyone in the clinic is so thrilled when Anna Grace comes because she's always got a new act or a new cheer to share with us. She's such an inspiration."

Daytime TV Salutes St. Jude

By Joe Hanna

The stars and fans of daytime television embrace the St. Jude mission.

RON GUBERMAN

St. Jude patient Cody Bigos pauses with actress Martha Byrne of *As the World Turns* at the Daytime Television Salutes St. Jude fund-raising event. The second-largest gathering of daytime TV stars has raised more than $1 million since its inception.

Following his famous vow to St. Jude Thaddeus ("Help me find my place in life and I will build you a shrine"), Danny Thomas found employment in radio dramas—precursors to the modern day soap opera, or as it is called today, daytime television.

Daytime television has not forgotten Danny Thomas or St. Jude. For more than a decade, the stars of *As the World Turns*, *All My Children*, *One Life to Live*, *The Young and the Restless*, *General Hospital*, *Guiding Light*, *Another World*, *The Bold and the Beautiful*, *Days of Our Lives* and other programs have supported the institution through an event called Daytime Television Salutes St. Jude Children's Research Hospital.

The event was the idea of Emmy-award winning actress Martha Byrne, who plays Lily on *As the World Turns*. Byrne has been a supporter of St. Jude since, at the age of 10, she appeared in *Annie* on Broadway. "My mom always donated a portion of my earnings to St. Jude," Byrne says. "She loved the hospital and felt that when you are given an opportunity you should give back."

In 1993, Byrne literally knocked on the door of the St. Jude fund-raising offices in New York, told them she was on a daytime TV drama and that she wanted to help introduce fans to the hospital. From that encounter, the fund-raising event was born. It's a night where loyal fans can mix and mingle with stars, participate in silent and live auctions and support St. Jude in the process.

"That first year we only had about 100 guests and we raised about $15,000," Byrne says. The event is now the second largest gathering of daytime TV stars, and has raised more than $1 million since its inception.

"It has become a staple in the industry, which is what I wanted it to be," Byrne says. "I wanted it to be huge, and I knew it had the potential to do so. I knew there was a niche there, because our fans are so loyal."

That loyal fan base, Byrne feels, sparked the event's growth. "I feel like it's more a testimony—not to me, but to the fans and the daytime TV community," she says.

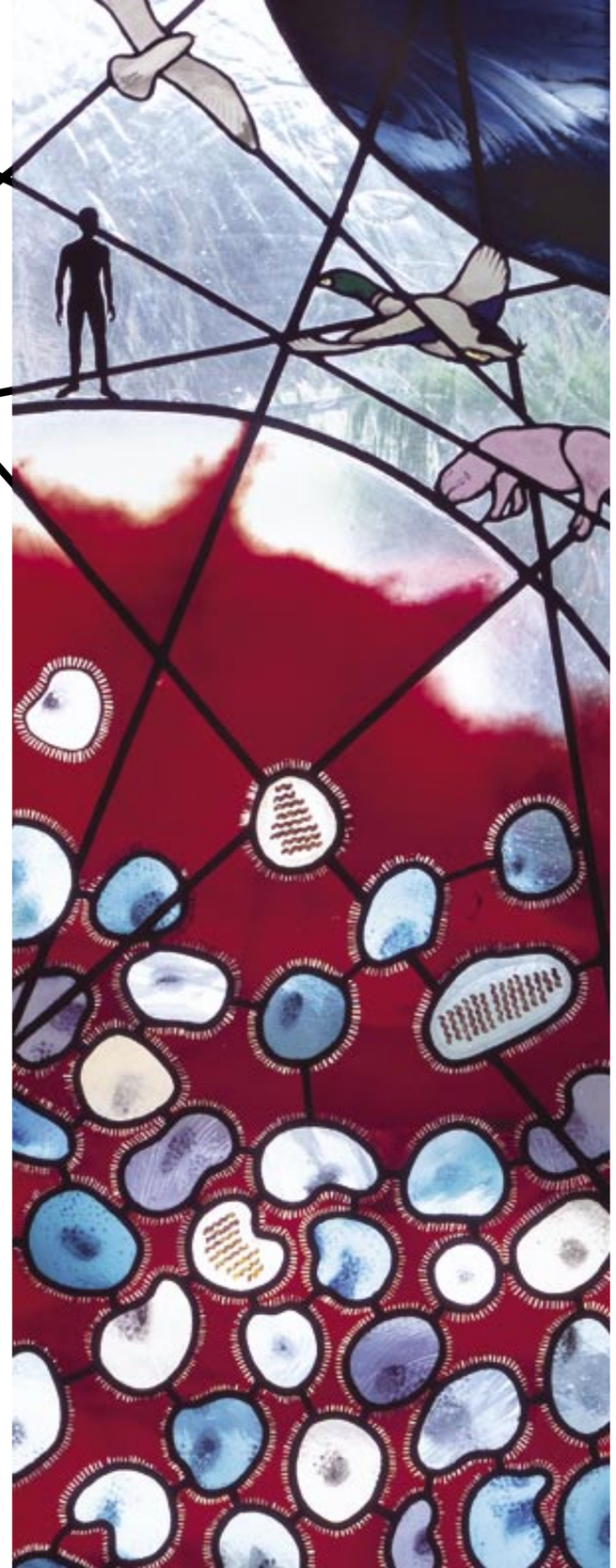
"St. Jude is so fortunate to have the support of people such as Martha Byrne and the entire daytime TV community—from its stars to its fans," said David L. McKee, chief operating officer of ALSAC, the fund-raising arm of St. Jude. "Our mission of finding cures and saving children is a universal one. The success St. Jude has had in saving the lives of children could not have happened without this kind of support."

For more information about the Daytime Television Salutes St. Jude event, visit *www.stjude.org/daytimetv.*●

Flu Fighters

Researchers at St. Jude help the world prepare for an avian flu outbreak.

By Victoria Tilney McDonough



BIOMEDICAL COMMUNICATIONS

When sunlight shines through the stained glass window in Robert Webster's home, colors dapple the floor and walls. But this is not your average stained glass window. There are no saints or prophets, no historical or biblical scenes. Instead, there are ducks and migratory birds, pigs, humans and many colorful particles depicting 16 different subtypes of influenza viruses. Commissioned by Webster and his wife, Marjorie, this window was created by an English artist to depict the natural history of influenza viruses and the exchange among species. Its design is based on the life's work of Webster, PhD, of Infectious Diseases, who holds the Rose Marie Thomas Chair at St. Jude Children's Research Hospital.

"Ducks are like the Trojan horse of this virus," says Robert Webster, PhD. "They can be infected—spreading this disease around—and look perfectly healthy and unaffected." This stained glass window, which hangs in Webster's house, illustrates the natural history of the influenza virus.

The window is art at its best, but the situation it reflects is nothing short of terrifying. Building like uncontrollable anger, the threat of a worldwide avian flu pandemic is rising toward its snapping point.

Not your average flu

Ready or not, every winter a new strain of the human influenza virus makes its rounds, killing approximately 36,000 people in the United States, usually children and the elderly. Since the virus mutates so quickly, no one ever becomes fully immune. International experts create a new vaccine each year targeted to that year's strain. That is the ordinary flu.

The most virulent form of the flu virus, known as H5N1, consists of eight segments of RNA, enclosed in protein capsules, surrounded by a globular envelope of proteins. The virus looks like a microscopic hedgehog. Aquatic birds of the world, ducks in particular, serve as the flu's "reservoir," the place where the virus naturally exists between outbreaks. In the last several years, however, H5N1 has learned to hop among other species.

"The H5N1 virus has taken on some nasty characteristics since it was first seen in 1996 in southern China. Human-to-human transmission is the only thing that it has yet to learn," says Webster, who directs the World Health Organization (WHO) Collaborating Laboratory on the Ecology of Influenza Viruses in Lower Animals and Birds. Located at St. Jude, it's the world's only lab designed to study flu at the animal-human interface. And why is such a lab situated in the middle of a children's hospital? "Because influenza kills kids," Webster says.

Like all viruses, H5N1 needs to take over a host cell to reproduce. The more hosts it can grow in, the more chances it has to spread. The H5N1 virus has become expert at jumping from host to host. The more the virus multiplies—the more opportunities it gets to make a genetic "mistake"—the greater chance it has to mutate into a strain that has the capability to transmit human to human.

For Webster, who has been studying flu viruses for more than 40 years, the current H5N1 in Asia is the most deadly virus he has seen. "There has never been anything like it," he says. Not only is it frighteningly lethal to chickens—killing them within hours of exposure and making them endure a hideous death—it has, over the last few years, killed mammals like cats and tigers with equal prowess. "A human-to-human version of this virus would be catastrophic," he adds.

At press time, strains of H5N1 had been detected in Cambodia, China, Croatia, Greece, Hong Kong, Indonesia, Japan, Kuwait, Lao, Mongolia, South Korea, Thailand, Vietnam, Romania, Russia and Turkey.

Since it appeared in 1997, H5N1 has been responsible for hundreds of millions of poultry deaths in Asia alone. Although it has appeared mostly in birds and some mammals, it has also killed 68 humans who came in contact with infected birds. The virus has killed more than half of the humans it has infected. The recent spread to Europe seems to be a result of infection in wild migratory birds. For many flu experts like Webster, a worldwide epidemic, or pandemic, is more a matter of *when* than *if*.

Looking back for clues

As the threat of a pandemic from the avian flu becomes more vivid, people are looking back in history at other flu epidemics for clues, comparisons, warnings.

In 1918, in the wake of the devastating trench battles of World War I, the Spanish flu killed at least 50 million people worldwide in 18 months. Recently, scientists completed the sequence of the genome of that virus, providing clues and patterns to its deadly bent. In 1957, an Asian flu, in which bird and human viruses mixed, caused 1 million human deaths; another such outbreak in 1968 in Hong Kong killed about 750,000.

In 1997, the H5N1 virus leapt to humans. When several people died and more fell terribly sick, the source of the virus was traced to Hong Kong's live-poultry markets. Officials wasted no time, killing all poultry (chickens, ducks, geese, quail, pheasants and guinea fowl) in local farms and markets—1.5 million of them.

"I was there that day," says Webster, who is well aware of the maelstrom such a pandemic could cause. "We went to the big central market and all the scientists were scrambling to get samples for study while behind us all the chickens were being killed as fast as possible. Then the

DAVID WALKER

In the summer of 2005, Webster (at left) and his team set up a surveillance site in Lao, one of the least developed countries in Asia. Many flu experts like Webster say that a worldwide epidemic, or pandemic, is inevitable.

“You can’t be prepared for every rare event, but we do know that there is a history of influenza, a pattern of recurrence. It behooves us to put our ducks in a row, as it were.”

press arrived—hundreds and hundreds of microphones outside the market gates. I was nominated to be the spokesperson and was placed on top of a great big yellow Jeep to give a statement. I was pounded with questions. Finally, the guy driving quickly took me away. But the paparazzi followed on motorcycles. The Jeep was driven into a garage, and I jumped into another car so I could escape to get more samples at another place where they were killing the chickens.”

Hong Kong was successful in its culling efforts; that particular genetic strain of H5N1 has never been seen again. Since then, improved sanitation, poultry vaccination and stricter rules have kept the live-poultry markets of Hong Kong virus free. But in each of the nearby countries, such precautions have not been taken, and a viral outbreak would be almost impossible to control.

Prevention: vaccines

Erich Hoffmann, PhD, Infectious Diseases, developed a process called reverse genetics. By tinkering with a virus’ genes, it is possible to create a new strain that can be used as a “master seed” for vaccine manufacturing.

“Basically, we created a benign virus like the ones found in nature,” says Hoffmann. “Using reverse genetics, we were able to make a genetically modified harmless strain that grows well in chicken eggs and is an optimal vaccine strain.”

“Quickly” has been a key word lately. With the virus spreading across Asia and most recently to Europe, governments are starting to sweat.

The seed stock developed at St. Jude against the H5N1 virus is currently in clinical trials. Although the jury is not yet in, the message so far is that the vaccine is effective but will be more difficult to manufacture than ordinary vaccine and will require more doses. “Instead of producing 10 doses of vaccine from a chicken embryo [the way all flu vaccine is produced], you will only produce one dose of vaccine per egg. So that means it’s going to take millions more eggs to produce enough vaccine for the United States alone,” explains Richard Webby, PhD, Infectious Diseases. “If a pandemic were to break out today, we would not be prepared. But we are far more prepared than we were five years ago.”

And the United States does not have the infrastructure to produce vaccine. “Whether it’s your tea cups or motor cars or dresses, so many things we have in this country are now made off shore,” Webster says. “We are dependent on foreign countries for our goods. That includes vaccine. We used to have eight manufacturing companies in the U.S. making vaccine; now we have only two. This is a severe problem.

“Governments need to step up and take responsibility,” continues Webster, now an American citizen, though a New Zealander by birth. “No company is going to take on the problem of liability, and there is always risk involved with the manufacturing of vaccine. Hurricane Katrina has changed our attitude; we realize we are not prepared. You can’t be prepared for every rare event, but we do know that there is a history of influenza, a pattern of recurrence. It behooves us to put our ducks in a row, as it were.”

Prevention: antiviral drugs

Down the hall from the labs where Webster’s team develops seed virus strains for pandemic preparedness and studies the molecular basis of disease-causing influenza viruses, other scientists combine antiviral drugs that may work against a potential avian flu outbreak.

Suiting up and showering twice daily to work with dangerous viruses, Elena Govorkova, MD, PhD, Infectious Diseases, tests combinations of two classes of antiviral drugs—oseltamivir (Tamiflu) and zanamirvir (Relenza), and amantadine and rimantadine. Some of these antiviral drugs work best at the beginning of the flu; others are more effective as the flu progresses. “We have already found that these drugs work synergistically, increasing the effect of each other,” she says. “However, initiation of antiviral treatment within 48 hours after infection is crucial for the most beneficial effect.”

Resistance to amantadine has spread significantly among the H5N1 virus subtypes because chickens in China may have been given the drug to prevent an outbreak. The St. Jude team reached this conclusion by evaluating the frequency of drug-resistant strains and by studying mutations in one protein of different flu viruses found in North America and Southeast Asia during 1991–2004.

“We were able to determine how frequently amantadine resistance occurs in avian influenza A subtypes isolated in various parts of the world—especially among those subtypes that had the potential to cause a pandemic,” explains Natalia Ilyushina, PhD, Infectious Diseases.

The media has touted Tamiflu as the drug to stockpile, along with the vaccine when it is ready. Unfortunately, there is not enough antiviral medication to support the millions of people worldwide who could become infected if a full-blown pandemic unfolds. And in some Asian regions, the virus may also be building up resistance to this drug.

Traditions are hard to break

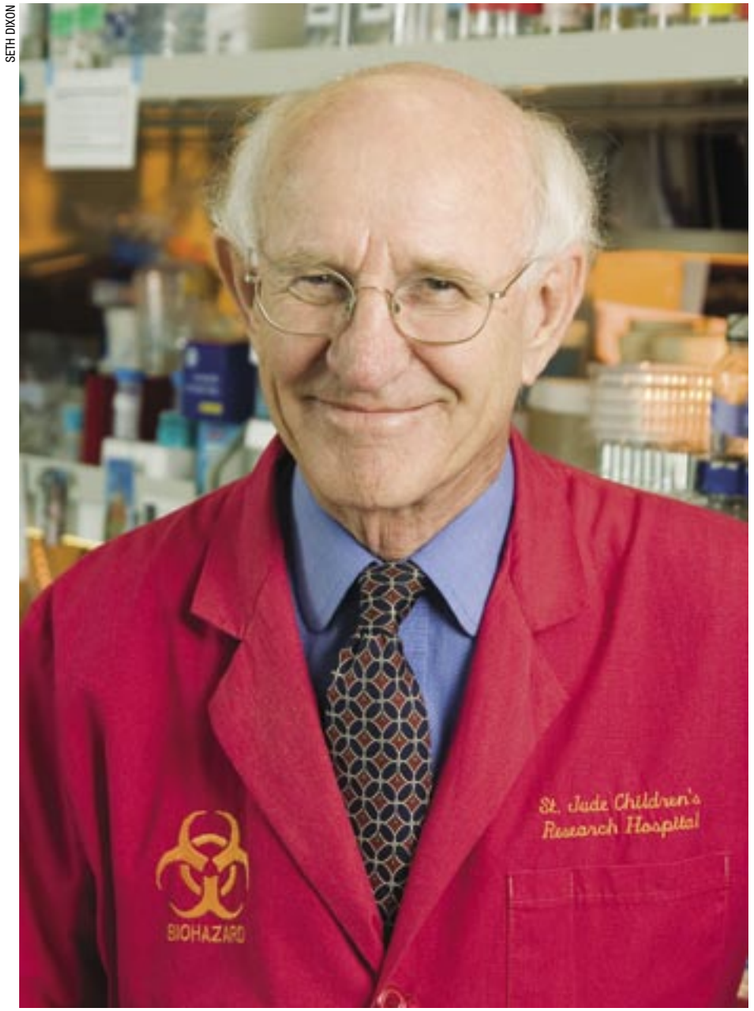
In the summer of 2005, Webster’s team set up a surveillance site in Lao, one of the least developed countries in Asia, bordering the Mekong River east of Thailand. “We went to help initiate a study on the ecology of influenza in collaboration with the National Animal Health Centre,” says David Walker, Infectious Diseases. The team organized twice-a-week collections of feces from poultry in local markets, from small flocks that people raise behind their homes and from birds in the town’s environs. “We collected primarily from ducks but also from chickens, turkey, geese, quail and sometimes ornamental birds. We arranged a collection schedule and virus isolation practices with the Lao staff, coordinating the acquisition of supplies and helping train the staff.”

Traditions in this part of the world play a key role in the avian flu’s potential to jump from human to human. Ducks and chickens are an inextricable facet in the culture and cuisine. They can also be a family’s livelihood—whether for a farmer or a cockfighter.

A cock can bring in a great deal of money and prestige. So much so that cock owners do not hesitate to risk their health by sucking the blood from the wounds of their champions after matches, or the mucous from the birds’ tracheas to ensure better breathing.

The tradition of eating blood pudding is also prevalent in Lao and Vietnam. “It’s a special treat for the young men in these areas after they go drinking. They go and eat this fresh, uncooked duck blood, clotted with some bits and pieces of vegetable and meat,” says Walker. Recently, two brothers died from the H5N1 virus after indulging in this delicacy in Vietnam.

SETH DIXON



Webster directs the World Health Organization (WHO) Collaborating Laboratory on the Ecology of Influenza Viruses in Lower Animals and Birds. Located at St. Jude, it’s the world’s only lab designed to study flu at the animal-human interface.

The science of art

In the last year alone, Webster, a feisty 73-year-old, has logged more than a half-a-million miles worldwide in his relentless study of the baneful H5N1 virus.

“The difficulty that I am having at this moment is that the things I have been afraid might happen are happening; I am watching my predictions unfold before me,” he says. “I guess that is why I am still working and not retired like most people my age.”

When asked if the stained glass window in his house makes him nervous, reminding him of what could be right around the corner, he smiles, sips his tea, and says, matter-of-factly, “No. It’s just a piece of art.”●

The WEIGHT Trait

By Bonnie Kourvelas

Are you fated to be fat? The loss of one gene may tip the scales toward obesity.

We've all heard the advice: to avoid obesity, eat less and exercise. Watch your portion control. Eat the right foods. Hit the gym.

That's still good advice, but now researchers at St. Jude Children's Research Hospital have come across intriguing evidence that at least some cases of adult-onset obesity may not be caused solely by overeating. In this study, scientists discovered that when one copy of the *Prox1* gene is missing, normal development of the lymphatic system is disrupted. Lymph can then leak out of ruptured lymphatic vessels and fat cells nearby—often in the abdomen—become significantly enlarged, accumulating extra fatty acids provided by the lymph.

The system of capillaries and vessels that drains lymph is essential for the immune response in inflammation, and it is the main route for the spread of tumors to the lymph nodes. This study indicates that lymphatic system disruption, caused by loss of a specific gene, might allow lymph fluid to leak into the body and then stimulate fat cells in that area to grow larger. Researchers also discovered that when lymph is mixed with cultured cells, those cells are stimulated to develop into fat cells.

"This is the first *in vivo* evidence showing that defects in the integrity of the lymphatic vasculature could lead to adult obesity," says Guillermo Oliver, PhD, of Genetics and Tumor Cell Biology. "Our findings might encourage physicians to consider that at least some of their obese patients might be suffering from a problem that can't be solved by eating less and exercising more.

"This form of obesity is interesting because we thought most of the time, obesity follows certain rules; for example, in general, an obese person will develop diabetes. That's common in most forms of obesity. But now we've discovered a type that doesn't follow some of those rules."

A growing problem

Excess weight has become a major health concern in the United States. According to the latest statistics, at least two-thirds of American adults are overweight, and one-third of them are obese. It's a trend that cuts across ages, genders, racial and ethnic groups, educational levels, smokers and non-smokers alike. Between 1960 and 2000, obesity more than doubled from 13.3 percent to 30.9 percent of American adults. Many obese adults also develop diabetes, with an estimated 70 percent of diabetes in the United States attributed to obesity. If these trends continue, obesity will cause billions of dollars in health care costs in upcoming decades. It is a problem that is being researched on many levels in many institutions.

SETH DIXON

Why is Guillermo Oliver, PhD, studying adult-onset obesity? Occasionally, investigations conducted at St. Jude lead to revolutionary discoveries in other areas.

But why, you may ask, is a hospital devoted to curing childhood diseases presenting research that addresses adult-onset obesity? Occasionally, research conducted at St. Jude leads to discoveries that have little or nothing to do with catastrophic childhood illnesses. Oliver says this study illustrates the importance of all the research done at St. Jude.

"Although this is a place that focuses mostly on pediatric cancers, we also have a huge commitment to basic research: studying how things work normally in the body," he explains. "In order to understand how something in the body works wrong, first we must study how it works right."

Why weight?

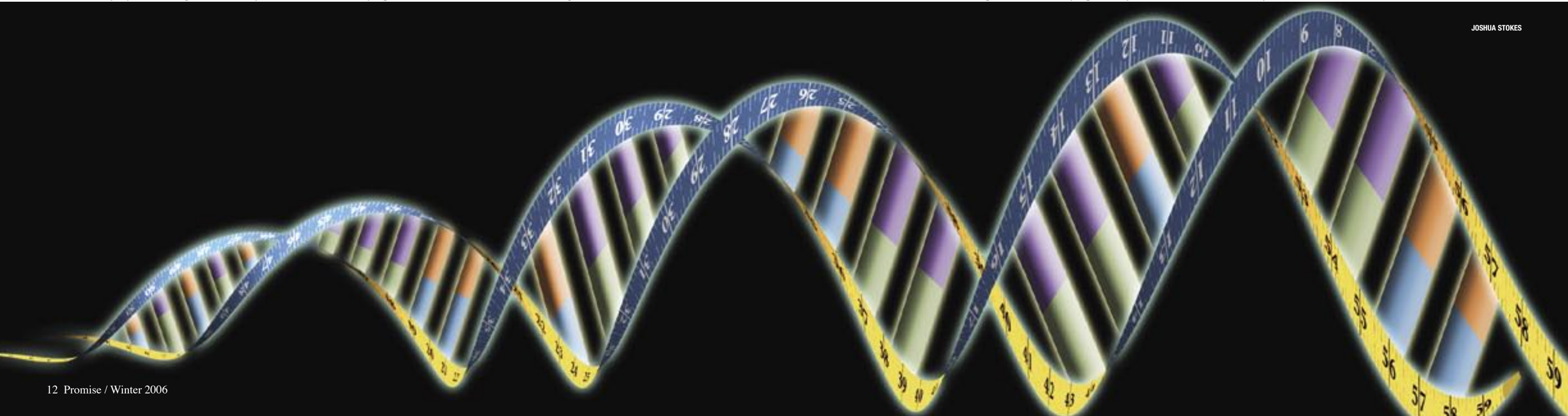
The obesity research began as basic study of the *Prox1* gene. Several years ago, Oliver's lab discovered that *Prox1* is necessary for normal development of the lymphatic system. Scientists knew the lymphatic system would be affected by manipulating this gene, but the resulting obesity connection was unexpected and extreme. This form of obesity didn't follow the usual rules, because it was not linked to diabetes or defects in the liver or pancreas, which can be factors in obesity.

But, Oliver asks, can we make individuals who lack the *Prox1* gene leaner? And how can we keep them from becoming obese in the first place?

"We don't know—this is just the first step in this particular research," he says. "Now, more work must be done, studying the lymphatic system as well as the genes that affect it. One important question: What exactly is in the lymphatic fluid that stimulates cells to turn into fat cells? This will be extremely valuable to know. We are just scratching the surface here."

He laughs at the notion of the "Oliver Diet" hitting the bookstores one day. Before anyone can assume that a weight problem is caused by leaky lymph, researchers must dig deeper to learn more about the lymphatic system and its general functional role in health and disease. "Now, we need to learn more about the exact mechanisms of how the lymphatics become leaky and promote weight gain," Oliver says. "Then, maybe in the future, we will figure out how to ameliorate this."●

JOSHUA STOKES



Safety from the Storm

Hurricane evacuee Mason King finds safe harbor at St. Jude.

By Victoria Tilney McDonough

The day Mason King entered the world, he was about the size of a paperback dictionary and weighed little more. At 1 lb., 13 oz., he could almost fit in his mother's palm.

Until that day, a paperback dictionary was just another book for D'Anna Holmes, a studious and driven sophomore at Dillard University in New Orleans.

When she discovered she was pregnant, D'Anna was sick with worry that her parents would be disappointed. They were strict, and in her family, life was supposed to follow a certain order: college, career, marriage, children. There were consequences to making choices that disrupted that order. But sometimes life's unexpected surprises become blessings—ones that spread their gentle fingers, touching the hearts of more people than can be counted. Mason is one of those blessings. Born premature at 26 weeks, he immediately rose to No. 1 on everyone's list. One look at the tiny baby and his family promptly fell in love.

The first hug

Unlike most parents, who are able to take their baby home after a few days in the hospital, D'Anna and Mason's dad, Ronnie King, had to say good-bye to their son each day for almost five months. Within days of his birth in July 2004, the young parents quickly learned that life is rarely neat and predictable; ironically, the best of life is often lived outside those tidy lines.

"I didn't get to hold him until he was a month old," says D'Anna. "Everything was so surreal. It took me a while to realize that this was my life, but looking in Mason's eyes, especially that day when I finally got to hold him to me, I knew I wouldn't trade it for anything."

Like many preemies, Mason faced multiple health issues. He had a small seepage of blood in his brain, and before he even weighed 2 lbs., he had to have surgery to clip the vein above his heart, something that closes naturally for a full-term baby. Severe respiratory problems and a collapsed trachea forced doctors to perform a tracheotomy, something Mason will have until he can breathe easily on his own.

For a college student striding confidently toward graduation, having a premature baby became a crash course in medicine and health care. More importantly, D'Anna's vision focused, her priorities shifted and her heart suddenly grew several sizes.

Dark clouds

That vision would become even more vivid in the following months.

In August 2005, D'Anna and Ronnie found out Mason had hepatoblastoma, a tumor in the liver. His abdomen had become distended, and soon he was barely taking any formula. After a battery of scans and tests, a liver biopsy came back positive for cancer. The tumor comprised almost half of his body weight.

Almost immediately, Mason started his first round of chemotherapy at Children's Hospital in New Orleans. Hepatoblastoma is rare and accounts for only 1 percent of pediatric cancers worldwide. The standard treatment includes four rounds of chemotherapy to shrink the tumor followed by surgery to remove the tumor and then two more rounds of chemotherapy. Because the liver has the capacity to regenerate, up to three-quarters of it can be safely removed.

D'Anna and Ronnie were so busy tending to Mason, overseeing his treatment, giving him love and comfort—and still going to school full time—that they barely had time to tune in to the news. As they entertained Mason with his favorite stuffed monkey, Alfred, clouds gathered, winds accelerated, and then, just like that, Hurricane Katrina changed the landscape of their lives.

"We had been in the hospital, sort of sealed from the outside world," says D'Anna. Sure, they knew something big was going on when the lights went out, generators were put in place and patients were moved up several floors and to the side of the hospital most protected from the wind. But it wasn't until they drove in a convoy to Baton Rouge with ambulances

ANN-MARGARET HEDGES

"Mason just makes your day when he lights up with that little smile," says speech-language pathologist Sarah Zoerink (at left), Rehabilitation Services, who is working with Mason to improve his feeding and language skills. Mason's mother, D'Anna is pictured in the background.

ANN-MARGARET HEDGES

By the time Katrina hit New Orleans, tiny Mason King had already faced one hurricane—a diagnosis of hepatoblastoma, a liver tumor. Nevertheless, he has retained his sunny disposition. "One of my favorite things to tell people about Mason is that, even this little, he's a morning person," says his mom, D'Anna. "I'll wake up and say, 'Good morning, Mason.' He'll roll over and have this smile on his face like, 'Good morning, I'm ready to start some trouble!'"

and other cars crammed with doctors, nurses, hospital staff and other families that they realized what havoc Katrina wreaked.

There hadn't been much flooding near the hospital, but as they circled the city, they stared, open-mouthed. "We had to cross the Westbank Bridge, and we saw families just walking across—mothers and little babies, old people, anyone, everyone, and it was so hot outside," says D'Anna. "There was nothing but water everywhere. I couldn't believe it. It looked like something out of a movie. The expressions on people's faces—so lost, distraught. It was heartbreaking. We didn't have any room in the car; I felt so bad. We were in a horrible situation, but my heart really went out to those people."

Another hurricane

From Baton Rouge, D'Anna and Mason flew to St. Jude Children's Research Hospital while Ronnie drove. "I was nervous—flying in a small plane and thinking about what would happen next," says D'Anna. "I sat next to a nurse practitioner from St. Jude and she gave me great comfort. She had had leukemia as a kid, and here she was in the seat next to me assuring me that we'd be taken care of at St. Jude."

"It was an honor to be in that situation and to be able to help," says Cindy Burleson, RN, director, Domestic Affiliates. "I was very impressed with D'Anna—how knowledgeable she already was about Mason's condition and how loving she was with her beautiful son. She had been through one hurricane and was facing another; I tried to keep her distracted and comforted."

"We felt comfortable here from the first minute," says Ronnie. "St. Jude is one of the most wonderful places, and the staff makes this time as easy as possible. They think of everything. It's a place where nothing matters but you and your child."

Since starting treatment, Mason has made noticeable progress. His tumor is no longer visible and has shrunk substantially. His energy level has also increased, much to the joy of his parents.

"Mason's parents are incredibly dedicated to him. They're always by his bed. They are on top of his medical care, and their recounting of what happened in Louisiana helped immeasurably since we didn't have his full medical records immediately," says Jeffrey Dome, MD, Hematology-Oncology. "I asked them how they weathered the hurricane, and what was striking was that they didn't care about what had happened to their possessions. It was all about their son and taking care of him."

Morning people

D'Anna Holmes doesn't know exactly how life will unfold in the next six to 12 months. Like Mason, who is taking baby steps toward getting better and catching up to his age developmentally, she is also taking life day by day. Although enrolled in online college courses, she yearns to get back to her beloved great-aunt's home in New Orleans where she has lived since Mason was born.

"I know a lot of people will read this, and I don't want them to get sad or cry when they hear Mason's story because it's not sad. Yes, he has been through a lot; we all have," says D'Anna.

"One of my favorite things to tell people about Mason is that, even this little, he's a morning person," she continues. "I'll wake up and say, 'Good morning, Mason.' He'll roll over and have this smile on his face like, 'Good morning, I'm ready to start some trouble!' Our son's story is a hopeful one. After all, it's Mason's story so far."●

Never Forget

BY JOE HANNA

His life was saved by people he didn't know. Now Elias Skovron helps save the lives of children he has never met.

Elias Skovron was 22 years old when two people he had never met saved his life.

In 1938 he was desperately trying to leave war-torn Poland. His aunt applied for him to receive an American visa. But the visa was turned down—a death sentence for a young Jewish man in Nazi-occupied Poland. But Skovron's aunt did not give up.

She talked to John J. Gore, a federal judge who knew U.S. Secretary of State Cordell Hull. Gore wrote to Hull, and Skovron's visa was approved. It was an act of kindness that Skovron never forgot.

After coming to America, Skovron served in the army. During World War II, he lost all of his immediate family except for his oldest brother. Later, Skovron became a furrier in a local fur specialty shop. He married his love, Rachel, and enjoyed a life that he felt fortunate to have, thanks to people he had not known.

Now 90 years old, Skovron is helping save the lives of children he has never met. Since 1970, he has helped fund research that allows St. Jude Children's Research Hospital to find cures for deadly diseases that strike children.

Skovron became a Danny Thomas fan after meeting the comedian in a night club in the 1940s. Years later, he saw Thomas on television talking about his vow to St. Jude Thaddeus and his plan to build a hospital for children with deadly diseases. "The idea struck me, and I was very much interested in it," Skovron says.

In 1996 he visited St. Jude for the first time since the 1960s. It was an emotional period, as he was mourning the loss of Rachel.

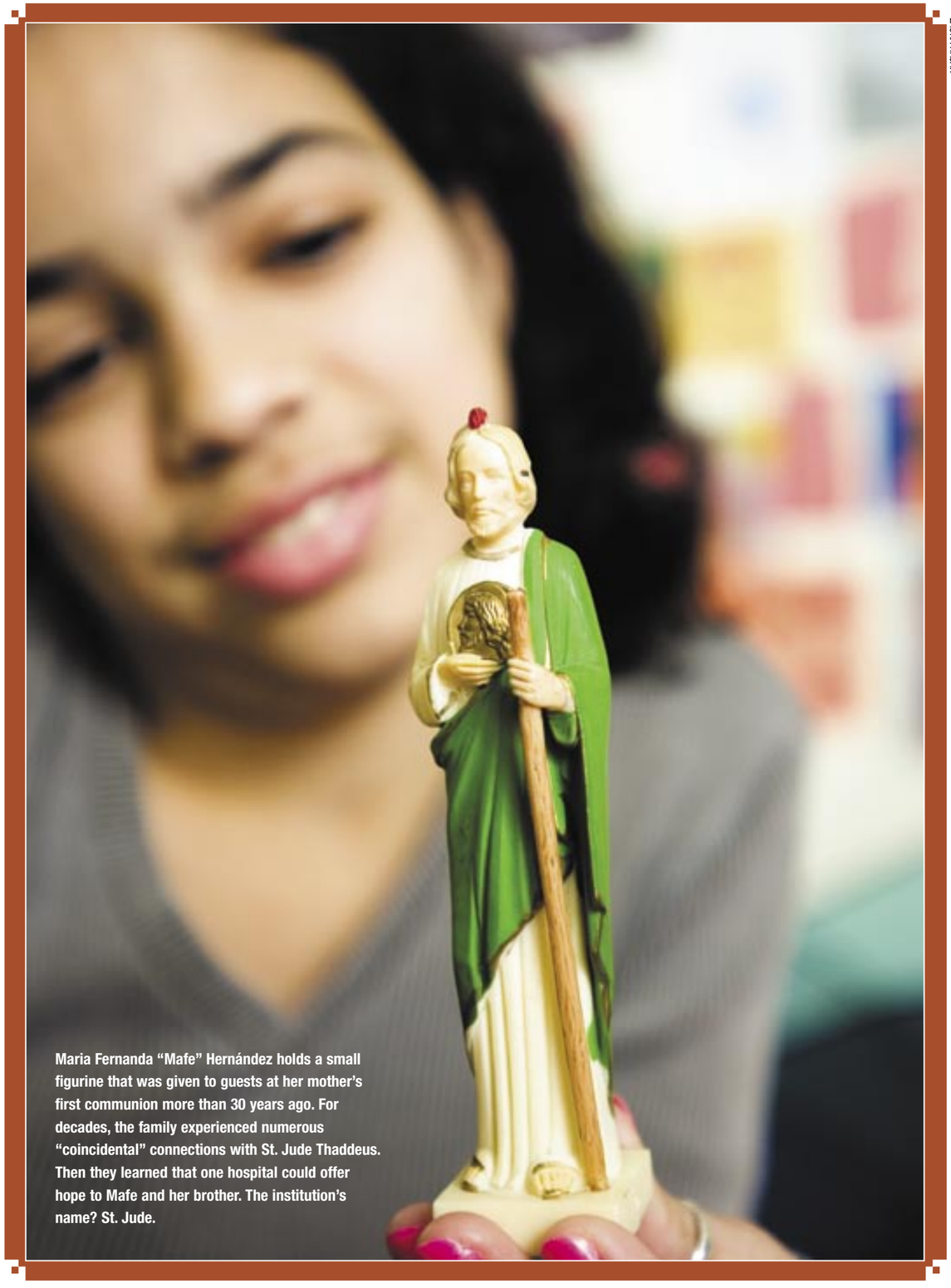
"I am still convinced that my visit to the hospital at that time did a lot more for me than anything I could have contributed to the hospital," Skovron says. "You are so depressed, and you think the world is coming to an end when you lose someone you have been married to for 45 years. But the visit did a lot for me. I was ashamed about being depressed. It seems like I was there just at the right time."

Re-energized, Skovron again counted his blessings and has sought to enjoy life to its fullest. One way he does that is by skiing. Skovron takes an annual ski trip to an area near Aspen, Colorado. For his 90th birthday, his favorite ski resort held a celebration for him. "They gave me a birthday party I will never forget as long as I live, and I hope it's going to be a long time," Skovron laughs.

Skovron has put St. Jude in his estate plans and has established gift annuities with ALSAC, the hospital's fund-raising arm. He knows his gifts are helping to save the lives of children and families from a lifetime of heartache.

"It gives me more pleasure than you can imagine," Skovron says about giving to St. Jude. "It is really helping to give someone a gift of life."●

To learn about more ways to give, call ALSAC Gift Planning at (901) 578-2425 or toll free at (800) 830-8119, ext. 2425.



LAURA HAJAR

Maria Fernanda "Mafe" Hernández holds a small figurine that was given to guests at her mother's first communion more than 30 years ago. For decades, the family experienced numerous "coincidental" connections with St. Jude Thaddeus. Then they learned that one hospital could offer hope to Mafe and her brother. The institution's name? St. Jude.

TWO MORE *Miracles*

ONE OF THEIR CHILDREN HAD DIED OF SICKLE CELL DISEASE. THE OTHER TWO WERE DESPERATELY ILL WITH THE SAME DISORDER. TO WHOM COULD THE HERNÁNDEZ FAMILY TURN FOR HELP?

By Elizabeth Jane Walker

Her footsteps echoing in the empty church, a solitary woman approached the statue of St. Jude Thaddeus. In the holy silence, the dim tranquility, Mary Carmen Hernández placed her hand on the saint's cool, marble foot. As the young woman began to pray, the baby moved within her womb. Hours later, Mary Carmen felt her first contractions; the next day, Enrique José was born.

Mary Carmen and her husband, Epaminondas, delighted in the birth of their first child. But soon they discovered that Enrique had inherited a terrible blood disorder. The disease ravaged his small body and took his life after only seven years and eight months. Burdened with sorrow, the couple from Venezuela nevertheless drew upon deep reserves of faith as they contemplated their loss.

"It hurt very, very much," Mary Carmen confides. "If a child is healthy and is safe, that is good; this is a miracle. Some children need to go to heaven, and this is another miracle. Heaven is a different kind of miracle. Enrique no longer feels pain. My husband and I are parents of an angel, and this is something special that God sent us."

Reason for hope

Enrique suffered from sickle cell disease, an inherited disorder of the red blood cells. The disorder causes round, soft cells to become sickle-shaped. The misshapen cells hook together, forming long rods that clog small blood vessels and deprive organs and tissues of oxygen-carrying blood. The bottleneck leads to episodes of severe pain, strokes, pneumonia, organ damage and even death. Millions of people worldwide suffer from sickle cell disease. In the United States, it affects about 72,000 people, mostly African Americans and Latino Americans.

Researchers at St. Jude Children's Research Hospital have been investigating treatments for sickle cell disease since the institution opened in 1962. In fact, the hospital's first ALSAC grant recipient was a scientist studying this genetic disorder. Regular blood transfusions are a common treatment physicians use to combat the severe symptoms of sickle cell disease, but long-term transfusion therapy carries a risk of iron overload and other life-threatening reactions. For some patients, St. Jude physicians use hydroxyurea, a form of chemotherapy, to decrease pain crises and lung problems.

More than 20 years ago, a St. Jude patient was the world's first patient to be cured of sickle cell disease by undergoing a bone marrow transplant. Since that time, hundreds of patients worldwide have been cured by obtaining stem cell transplants from matched donors, usually siblings who have the correct tissue type and who do not have the disease themselves.

Unfortunately, only a small percentage of patients with sickle cell disease have matched siblings who are disease free. That's why St. Jude began exploring ways to use parents as stem cell donors. The procedure, called a haploidentical stem cell transplant, uses a special machine to magnetize and isolate donor stem cells. This process reduces the chance that donor T-cells will attack the patient and cause a potentially life-threatening condition called graft-versus-host disease.

T-cells are white blood cells that recognize cells that do not belong in the

“To my knowledge, we’re the only place in the world that’s doing haploidentical transplants for sickle cell disease.”

body. Transplanted T-cells can perceive the patient’s organs and tissues as the enemy and can mount a war to destroy them.

“A transplant is the only cure that’s available for children with sickle cell disease, but not many of our patients have a suitable match,” explains Russell Ware, MD, PhD, director of the St. Jude Hematology Division. “In an attempt to provide this opportunity to more families, we needed to find a different donor. Nearly everyone has a parent who’s available, even if they don’t have matched brothers or sisters. Haploidentical stem cell transplantation provides that curative option, so we’re very excited about it.”

Although the new treatment was discovered after Enrique’s death, Mary Carmen and Epaminondas had two reasons to be excited about it: their other children, Maria Fernanda “Mafe” and Fernando José “Nano” had also been born with severe cases of sickle cell disease.

Coming full circle

In the early 1960s, a priest in Caracas, Venezuela, suggested to his parishioners that they raise money to build a church in honor of St. Jude Thaddeus, the patron saint of hopeless causes. Every Sunday, Mafe and Nano’s grandmother gave a weekly donation to the fund. When the priest asked his flock to give more money to support a children’s hospital that had just been built in the United States, the family’s matriarch again answered the call. For more than 30 years, she donated money for that purpose.

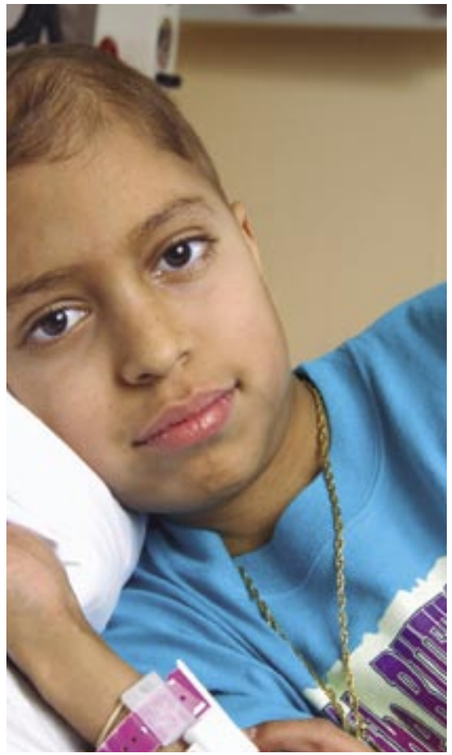
Little did she know that she was helping to fund a fledgling hospital that would one day treat her grandchildren.

In Venezuela, regular chronic blood transfusions were not available for Nano and Mafe. Both children became sicker and sicker, suffering frequent pain crises and even strokes. During one particularly frightening period, fluid accumulated around Nano’s heart.

Then St. Jude Children’s Research Hospital opened a protocol that offered hope. Nano would be the second child with sickle cell disease in the world to receive a stem cell transplant using a partially matched parent as a donor.

In June 2003, Mary Carmen’s sister stepped forward as the family was leaving for Memphis. “This is for you,” she said, as she pressed an object into Mary Carmen’s palm. Opening her hand, Mary Carmen gazed at a figurine that had been given to guests at her first communion many years before. Clinging to the small statue of St. Jude Thaddeus, she boarded the plane.

When she arrived in Memphis and saw the statue of St. Jude in front of the hospital, she suddenly realized this was the same institution her mother-in-law had been supporting since the 1960s. “My family said, ‘This is a miracle!’” Mary Carmen recalls.



LAURA HAJAR

ANN-MARGARET HEDGES

Expertise and resources

In Memphis, Nano immediately began preparations for his transplant. Three months later, he underwent the procedure, with his dad serving as the stem cell donor. Unfortunately, Nano’s body rejected that transplant and he underwent a second procedure in October of that year. This time, the stem cells engrafted successfully.

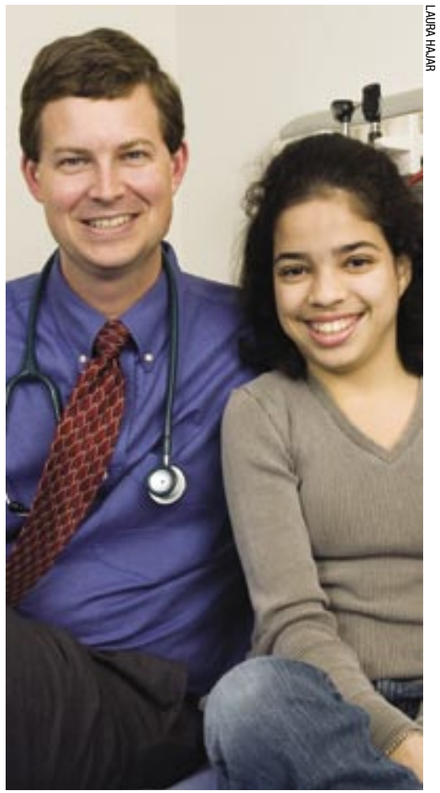
“It was hard,” admits Nano, who suffered three strokes before arriving at St. Jude. “I wouldn’t like for anybody to have to go through two transplants, but this hospital saved my life, and it will save my sister’s life.”

Now 15 years old, Nano attends high school near Target House while awaiting his sister’s transplant. “I want to be an NBA player when I grow up,” says the young athlete, who also plays the guitar and trumpet. His dislikes? “Algebra!” he says.

Paul Woodard, MD, asserts that the success of the hospital’s stem cell transplant program can be attributed to expertise and resources. “To my knowledge, we’re the only place in the world that’s doing haploidentical transplants for sickle cell disease,” he says. “There’s a high learning curve to doing these transplants. You have to learn how to do them well. We have a team who understands how to do it—from the doctors and nurse practitioners to the lab workers and support staff. It took several years to get that in place.

“Haploidentical transplants are also labor intensive compared to other kinds of transplants,” he continues. “You have to have a lot of support services. For instance, we have to do molecular monitoring every week to monitor for donor cells and viruses, and that’s expensive.”

Although Mafe will be the fifth patient in the world to undergo the procedure, her protocol is a little different than the one that was used to treat Nano. The new version of the study has been tweaked to make the engraftment process even better. “We’re doing these studies very slowly on purpose,” Woodard explains. We treat two patients at a time, and we don’t enroll subsequent patients until one of those two is at least 100 days post-transplant.” This process helps the team provide the best treatment as safely as possible.



LAURA HAJAR

(Above) Paul Woodard, MD, helps Mafe prepare for her transplant.

(Facing page, top) In 2003 Fernando José Hernández, known as “Nano,” was the second child with sickle cell disease at St. Jude and in the world to receive a stem cell transplant using a partially matched parent as a donor.

(Facing page, bottom) “This hospital saved my life, and it will save my sister’s life,” says Nano, pictured with his 17-year-old sister. Mafe will be the fifth patient in the world to undergo a haploidentical transplant for sickle cell disease.

“The protocol is being conducted carefully with small numbers of patients and extremely close follow up,” Ware comments. “It has the potential to change dramatically the way we consider treatment options for children with sickle cell disease.”

Two more miracles

Like the other kids in the study, Mafe has had multiple strokes. “I couldn’t see very well, and I couldn’t walk very well,” she says, recalling one such incident, which was accompanied by a horrific headache. “I knew immediately what it was. It was scary.”

As she prepares for her upcoming transplant, Mafe continues to concentrate on the future. A bright girl who enjoys the challenge of languages—she speaks Spanish, English and French—Mafe is also an artist, musician and expert volleyball player. Her vocational dreams fall into yet another category. “I want to be a plastic surgeon someday,” proclaims Mafe, who keeps in touch with her friends in Venezuela via telephone and e-mail. She and her family have not returned home since 2003, and they expect to be at St. Jude for a year past her transplant.

Mary Carmen says the separation from family and friends is difficult, but that she and Epaminondas try to keep everything in perspective. “Our focus is Mafe and Nano—and God, who is most important,” she says. “We miss our family, but the really, really important things are here. We can do this with faith. We have love for our children and love for life.

We need to give our children hope, and this is the place to do that. St. Jude is wonderful. In this place we have seen many, many miracles—in many ways, in many situations.

“This is a big miracle for us,” she continues. “Nano is a miracle, and Mafe will be another miracle. It will happen because of God and St. Jude.”●

Hitting the Target

By Carrie L. Strehlau

The best dose of a chemotherapy drug for one child is not necessarily the best dose for another. St. Jude scientists are simplifying individualized therapy for children with cancer.

Getting the right dosage of a drug is important for treatment of any disease. Researchers at St. Jude Children's Research Hospital know that finding the best dosage of the drug topotecan offers hope to children with neuroblastoma. This tumor usually arises in the tissues of the adrenal glands but is also seen in the nerve tissues of the neck, chest, abdomen and pelvis. Pinpointing the optimum dosage to treat neuroblastoma can be tricky.

"Topotecan is a fascinating drug," says Clinton Stewart, PharmD, of St. Jude Pharmaceutical Sciences. "It interacts with a critical enzyme in the body called topoisomerase. This enzyme helps DNA unwind so it can replicate, and topotecan inhibits its function, leading to cell death."

From the results of a number of earlier studies, St. Jude researchers found that giving a low topotecan dosage on an extended schedule was the best way to kill tumors. More recently scientists found that if they closely monitored and fine tuned topotecan drug levels for each child—a technique called pharmacokinetic-based (PK-based) dosing—children with neuroblastoma responded very well.

"PK-based dosing is a promising tool that reduces variability in the amount of topotecan in the body, leading to improvements in response and ultimately improving the odds of survival," Stewart says. "Basically, what we're trying to do is get the right dosage of topotecan in the kids to get a good anti-tumor effect and to minimize toxicity."

One of those studies was in collaboration with Victor Santana, MD, director of the Solid Tumor division and co-leader of the Solid Malignancies Program.

"The study with Dr. Santana showed that by obtaining plasma samples from children with neuroblastoma, then adjusting the topotecan dosage, we could attain the concentrations in the blood we needed," Stewart says. "It showed that we could do this and that it would be safe in children."

A recent study addressed the problem posed by the different rates at which children eliminate or clear topotecan from their bodies. Such differences mean that the standard topotecan dosage might help some children, but in others the drug levels might

LAURA HAJAR

Children eliminate the chemotherapy drug topotecan from their bodies at different rates. A standard dose might help some kids, but in other children, that same dose might be too low to kill cancer cells or so high that it produces unacceptable side effects. Clinton Stewart, PharmD, of St. Jude Pharmaceutical Sciences is trying to pinpoint the best dosage of topotecan for kids with neuroblastoma, a tumor of the peripheral nervous tissue.

be either too low to kill cancer cells or so high that it produces unacceptable side effects.

According to researchers, this study was critical. "Those children were newly diagnosed; they received topotecan as one agent, and they got two courses on the dosage individualization schedule," Stewart explains.

In the study, children received topotecan before undergoing standard treatment. The aim of this initial treatment was to quickly reduce the size of the tumor that must be surgically removed. Reducing tumor size with topotecan and surgery also reduces the risk that the cancer will develop resistance to standard chemotherapy drugs that are administered afterward. The children did exceedingly well and tolerated the therapy with few ill effects.

"Topotecan was the first drug Bryce got," says Kristi Cherry, whose son was found to have stage IV neuroblastoma when he was 10 months old. "After only two rounds of chemotherapy, his softball-sized primary tumor shrank 25 percent. The doctors were very pleased at how well it worked."

Bryce also had mild side effects that were on par with other drugs he was taking. "But I didn't realize how great topotecan was until I started speaking to other families who had children on the same drug," Kristi says. "They were raving."

Those rave reviews are what doctors like to hear.

"Our results are a proof-of-principle that children who receive topotecan may have an earlier reduction of their tumor size if treated according to the PK-guided dosing strategy," says Santana. "Our findings also suggest that children who receive topotecan according to a PK-guided dosing strategy may have a better initial response and reduction in the size of the tumor."

St. Jude researchers have also used PK-based topotecan dosing for the brain tumor medulloblastoma and are starting the same type of studies with the eye cancer retinoblastoma. Results of the neuroblastoma study are being sent to the Children's Oncology Group (COG) for another PK-based dosing pilot study. COG is a National Cancer Institute-supported clinical trials cooperative group devoted to childhood and adolescent cancer research.

"If there is success in the pilot study, we hope to propose some form of dosage individualization for topotecan in a Phase III study for the entire Children's Oncology Group," Stewart says. "In addition, we are working on a method where we could tell pediatric oncologists that if their patient has certain characteristics they could adjust the topotecan dosage to get a better anti-tumor effect and not even need to check blood levels."

Six-year-old Bryce is thriving, says his mother.

"He reacted so well to topotecan," she says. "He plays T-ball and is an active child. You would never know he had cancer."●

Perspective

A Mother's Vantage Point

"We as a family will recognize St. Jude as a place of miracles where our daughter was given a second chance—not only at life, but as a walking, dancing symbol of hope."

LAURA HAJAR

When Micah Grace was a baby, a tumor called neuroblastoma wound around her tiny spinal column. Physicians feared that she would be paralyzed from the waist down. But thanks to the care she received at St. Jude, Micah Grace walks, runs and dances her way through life.

By Sarah Barker

As the mother of a St. Jude child, I can only imagine what it really means to go through the traumatic experience of having childhood cancer. However, through the eyes and feelings of my daughter, Micah Grace, I can *almost* imagine.

When Micah arrived at St. Jude, she was only 11 months old. Several signs had led us to believe something was wrong with our little girl's body, but in October of 2001, it was confirmed: Micah had cancer.

A tumor called neuroblastoma, stage IV, had wrapped around Micah's tiny little spinal column and had done so much damage that she would likely be paralyzed from the waist down, a condition which the doctors said was probably permanent.

As a mother, my head was spinning: Cancer? Paralysis? Life-threatening? I could quote other parents here by saying, "Our worst fears had just come true." But cancer? This hadn't even registered in my paranoid, first-time-mom mind. My imagination had been swarming with worries about a childhood of broken bones, chicken pox and common colds. But Micah's prognosis gave her just above a 50 percent chance of survival. In reference to your child's life-or-death ratio, 50 percent sounds devastating.

However, from the moment we entered St. Jude, we were embraced by an unbelievable sense of family. Everything was taken care of financially, emotionally, physically and medically. After all of Micah's chemotherapy, surgeries, therapy, medicines and shots, our view of St. Jude is not of painful, traumatic memories, but of a wonderful place, full of hope.

After months of chemotherapy and four operations, news came that was music to our ears: Micah was in remission! Last September, we celebrated her third year in remission. Since the end of treatment, Micah not only walks, but is our beautiful, dancing ballerina.

Although Micah's memories of St. Jude may only be through photos and stories, we as a family will recognize St. Jude as a place of miracles where our daughter was given a second chance—not only at life, but as a walking, dancing symbol of hope.

We thank the doctors and nurses at St. Jude for their awesome devotion to our children. We thank God for his healing powers. And we thank the hospital's many financial donors and supporters for making sure that St. Jude kids have the best treatment possible. When it comes to our children, St. Jude really does try to make sure that, in the words of founder Danny Thomas, "no child dies in the dawn of life." I am so thankful I am blessed to watch Micah experience the dawn of her life.●

Today, 5-year-old Micah Grace enjoys coloring and drawing, riding her bike, playing T-ball, dancing and singing. She has flown to several states to share her story. Her goal is to raise "lots of money for St. Jude so that kids won't die, like I didn't." She is well on her way to fulfilling that dream.

PHOTOS BY LAURA HAJAR

Oscar-winning actor Morgan Freeman hangs out with St. Jude kids during the filming of TV spots for the hospital's recent *Thanks and Giving* campaign. In its second year, the program asked Americans to show thanks for the healthy children in their lives and give to those who are not. Marlo Thomas, Antonio Banderas, Faith Hill, Sarah Jessica Parker, Ray Romano and Robin Williams also filmed TV spots and movie trailers as part of the fund-raising campaign.

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