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LATEST ON LOSING WEIGHT**

**HE'S GOOD, HE'S BAD—THE TWO  
SIDES OF MORT ZUCKERMAN**

# WASHINGTONIAN

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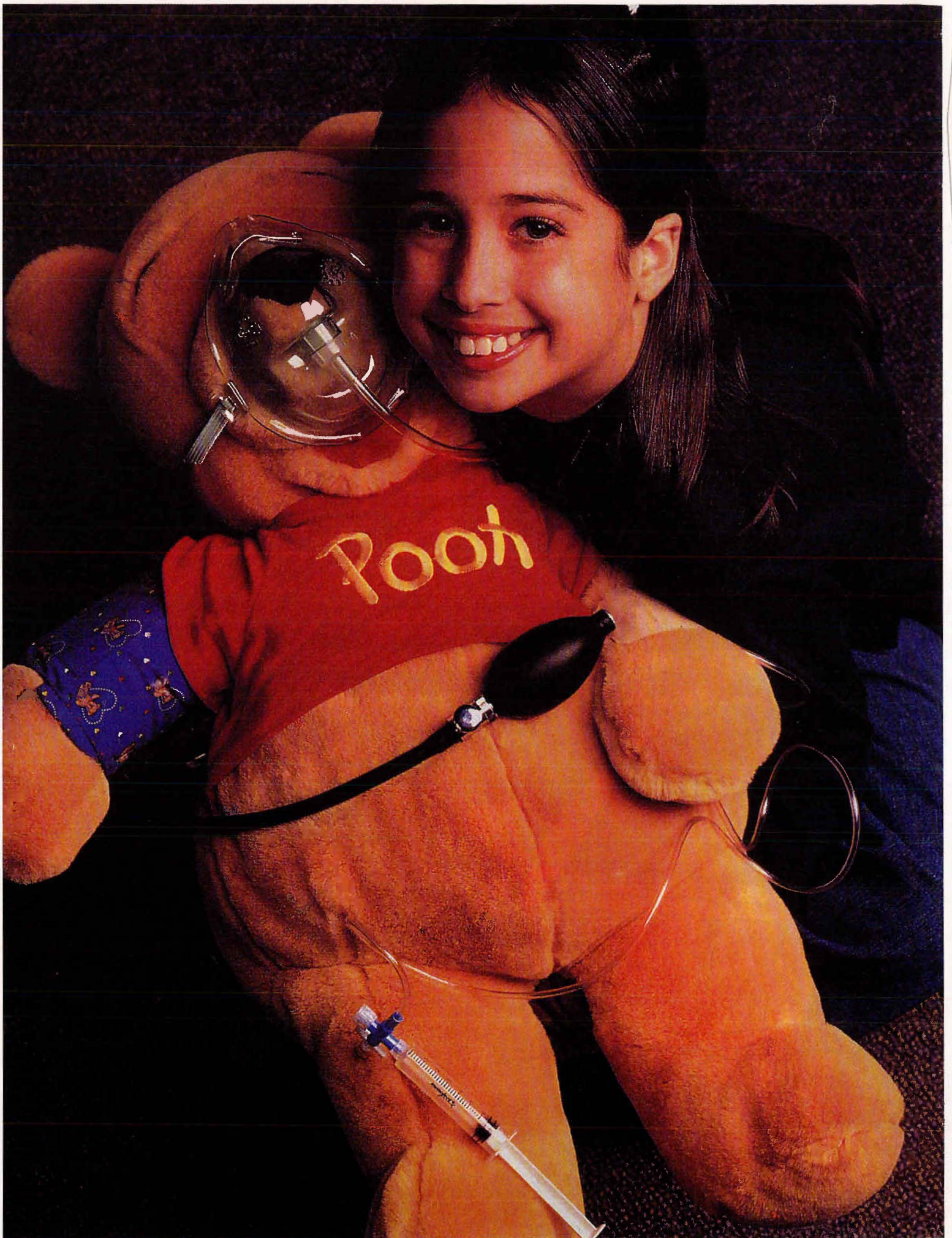
## GREAT WEEKENDS

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# What's Wrong With Jessica?

DOCTORS AT THE  
NATIONAL INSTITUTES  
OF HEALTH IN BETHESDA  
HAD NEVER SEEN  
HUMAN BLOOD QUITE  
LIKE THAT OF THIS SICK  
LITTLE GIRL. HERE'S  
WHAT IT TOOK TO  
CRACK THE CASE.

**BY LARRY VAN DYNE**

PHOTOGRAPHS BY  
ROBERT SEVERI

**When Jessica Chancellor arrived at NIH as a three-year-old, her mother asked the doctors how long she might survive. They had no good answer because her disease was so unusual and mysterious.**

**E**IGHT YEARS AGO A LITTLE girl from Oklahoma named Jessica Chancellor was admitted to the Clinical Center of the National Institutes of Health with the hope that doctors there could unravel the mystery of why she was so sick. Though she was just three years old, her medical record was filled with page after page of notes from doctors at other medical centers describing what her little body and spirit had endured. Her kidneys had once begun to fail, and she'd been hooked up to a dialysis machine. Surgeons had removed her spleen when it swelled to the size of a grapefruit. She'd been through multiple biopsies, blood transfusions, and drug treatments. She'd suffered from abdominal pains, rashes, and fevers. Swollen lymph nodes bulged along the sides of her neck.

At NIH, the federal government's premier medical-research facility, doctors were accustomed to encountering rare diseases, but even they were astonished at what they discovered during Jessica's first visit. The composition of her blood was so abnormal that no one had ever seen or read about anything like it in human beings. She was suffering from something so rare and so puzzling that doctors felt compelled to try sorting out its mysteries. Thirty-seven times they have asked Jessica—accompanied by her mother, Norma—to come back to Bethesda from their home in Oklahoma for tests and treatments.

The search for what was wrong with Jessica has been filled with odd twists and close calls, involving everything from a strain of diseased laboratory mice to a Catholic priest called to administer last rites. For the doctors at NIH, led by a virologist named Dr. Stephen Straus, her case has offered a window on cutting-edge questions in molecular biology. But

it also has given Straus and his colleagues a chance to answer the plea in a note from Jessica that he keeps pinned to his bulletin board: "Please, Dr. Straus, make me better."

*If you saw pictures of me when I was sick, it looks like I have those cheek pouches that hamsters have, and my stomach is sticking out of my shirt."*

—Jessica Chancellor, in an essay called "My Story on Health," written at age nine

**O**NE DAY IN FEBRUARY 1989, when Jessica was about 20 months old, Norma Chancellor noticed that her daughter was not feeling well and that both sides of her neck appeared swollen. Norma was not alarmed, thinking it was a case of strep throat that is so common among toddlers—a diagnosis confirmed by Jessica's pediatrician, a Tulsa doctor named David Jubelirer. He prescribed antibiotics, and Jessica perked up for a few days but soon was not feeling well again. Over the next three months, Norma took Jessica back to the pediatrician several times, each time getting more antibiotics and each time worrying more and more about the puffiness in her neck.

During one of these visits, in the middle of May, the pediatrician began to think that Norma might be justified in worrying that Jessica was suffering from something serious. As he massaged the little girl's neck and then moved his fingers down to her abdomen, Norma detected in his face an expression of deep concern.

"What do you think?" she asked.

"I really don't know," the doctor said, "but the lymph nodes on her neck are enlarged and so are her liver and spleen. I think we need to get some lab work."

This was a familiar routine for Norma,



**Jessica's mother, Norma, took her to specialists in Oklahoma, Minnesota, and California before coming to NIH: "I've been with her for every prick and poke."**

who had worked as a registered nurse since finishing training in her native Texas. She had grown up on a cotton-and-cattle spread near San Angelo and trained at a nursing school in Austin, where she met Jon Chancellor, a young doctor. They had married and settled in Tulsa, where he established a practice in anesthesiology and she joined the Springer Clinic, the same place where Jessica's pediatrician had his office. The couple had two children—Jessica and an older girl named Jennifer—but the marriage had ended in divorce and the girls lived with their mother, a stylish woman in her mid-thirties.

Routine blood tests indicated that Jessica was anemic, and the pediatrician was concerned enough to recommend that Norma take her to see a specialist across the street at Saint Francis Hospital. Norma was terrified that Jessica had cancer, probably leukemia or lymphoma. They were going to see Dr. Michael Hensley, a pediatric hematologist oncologist. He recommended biopsies on Jessica's lymph nodes and bone marrow.

The result of these procedures was both reassuring and frustrating. There was no clear evidence of lymphoma or leukemia. But there also was no clear explanation for her anemia or for an excess of cells found in her lymph nodes.

Relieved that Jessica didn't have cancer,

Norma tried to carry on a normal life. She continued dating Tom Jones, a Tulsa native who had been a four-time All-American golfer at Oklahoma State University and was now the pro at one of Tulsa's top country clubs. She kept working as a nurse at the Springer Clinic, leaving Jessica with a babysitter who was careful to call her to report any change in the girl's health. There were moments when Jessica was not a well child; she had skin rashes, she cried with pain in her tummy, and her abdomen protruded. Norma continued to search for answers to Jessica's problems, looking back at some of her old books from nursing school and pressing the doctors in Tulsa about

where to find a specialist who might offer some insight.

They suggested that Norma take Jessica for an evaluation at the Mayo Clinic, the renowned medical center in Minnesota. The two flew up there near the end of October 1989. Norma took along Jessica's bunny costume so she wouldn't miss Halloween, and they celebrated by trick-or-treating at a shopping mall near their hotel. The doctor at Mayo ran more tests—including one for HIV that proved negative—but he too seemed baffled by Jessica's case.

*I've had a lot of blood tests and a lot of surgery, but I've made it through it all because I'm tough.*

**S**HORTLY AFTER RETURNING from the Mayo Clinic, Norma noticed that Jessica's urinary output was decreasing—enough to warrant a trip to the pediatrician. After some tests, he concluded that her kidneys were failing and recommended she be taken to a children's hospital in Oklahoma City that had the only pediatric kidney specialist in the state. Tom Jones drove them the 110 miles to the hospital in his big white Chevrolet Suburban, Jessica resting in Norma's arms in the back seat. The mood was somber, with Jessica asleep and Tom and Norma talking about how frightened they were that she might die.

The hospital began treating Jessica under the direction of Dr. James Wenzl, the kidney specialist, who was out of town

at a meeting but was in touch by phone. The girl got a diuretic and lots of fluid in hopes that her kidneys would function, but that had little effect. She puffed up in a way that reminded Norma of a toad. She was very ill, lying there in a little crib, with Norma and Tom staying in the room at night and celebrating Thanksgiving with a meal from the hospital cafeteria.

Though Norma feared Jessica might need a kidney transplant, Dr. Wenzl reassured her when he returned from his trip that dialysis ought to be enough. So Jessica was hooked up to the machine, and several treatments later her kidneys were functioning normally. She was released in mid-December after a 23-day stay and given some restrictions on sodium in her diet.

As New Year's approached, Jessica's spleen was becoming so enlarged that the issue of what to do about it had to be confronted. The spleen, which is a lymphatic tissue similar to that in the lymph nodes, plays an important role in cleansing the blood and in protecting the body from infection. Humans can live without it, but doctors much prefer to save it. Jessica's spleen, which should have been the size of a walnut, was now as big as a grapefruit and was causing pain by pinching nerves in her abdomen.

Jessica entered Saint Francis Hospital in early January, and surgeons removed her spleen. To compensate for the loss of its infection-fighting capacity, she would have to take an antibiotic each day for the rest of her life. And she came away with a scar on her stomach, just to the left of her bellybutton.

**W**ITH HER SPLEEN REMOVED, Jessica's health improved. But the swelling of the lymph nodes in her neck did not recede, and Norma remained exasperated that doctors weren't able to give her a solid diagnosis. She kept pestering the doctors in Oklahoma for ideas about other medical centers to visit—to the point where one physician turned to her one day and suggested that she just "give up." Norma thought of it as a slap in the face—and it only made her more determined to keep looking for answers.

The doctor did have one name to offer—Dr. E. Richard Stiehm, an immunologist at the medical center of UCLA. So in May 1990, with Jessica just past her third birthday, Norma packed their bags and the two flew to Los Angeles. There were more tests as well as side trips to the beach and to Disneyland. This time the diagnosis was unambiguous: Jessica was suffering from a herpesvirus known as chronic Epstein-Barr.

Back home a couple of weeks later,

when Jessica developed a bad case of hives, Norma took her to a Tulsa dermatologist, Dr. Bernard Robinowitz. As Robinowitz took down her medical history and examined her—the big lymph nodes, the kidney problems, the missing spleen, the Epstein-Barr diagnosis—he realized he was up against something extraordinary. After telling Norma he thought he'd better read up on some of Jessica's problems, he drove to the library at the Tulsa branch of the University of Oklahoma's medical school and looked in the *Index Medicus* for articles on Epstein-Barr.

Robinowitz called Norma back to say that he had located a doctor at NIH who was a leading authority on Epstein-Barr and that it was worth exploring the possibility of taking Jessica to Washington to see him. His name was Dr. Stephen Straus, and several days later Straus himself called Norma. After looking at Jessica's medical record, he was willing to examine her and consider enrolling her in an ongoing research study of chronic Epstein-Barr.

*If you ask how many doctors I have, I just wouldn't answer. I don't know how many doctors I have, there are so many.*

**J**ESSICA AND NORMA flew in to National Airport in the early evening of August 7, 1990, and took a taxi to Bethesda. Making their way onto the NIH campus off Wisconsin Avenue, they passed the Clinical Center, the 14-story hospital where Jessica was to begin her evaluation the next morning, then went down the hill to the Children's Inn. The new inn was designed to offer families with sick children a homey alternative to a hotel, and Jessica and Norma went up to their room hoping to get a good night's sleep.

But Jessica was too sick. She screamed late into the night with abdominal pain, and nothing Norma did could make it go away. On the phone back home to Tulsa,

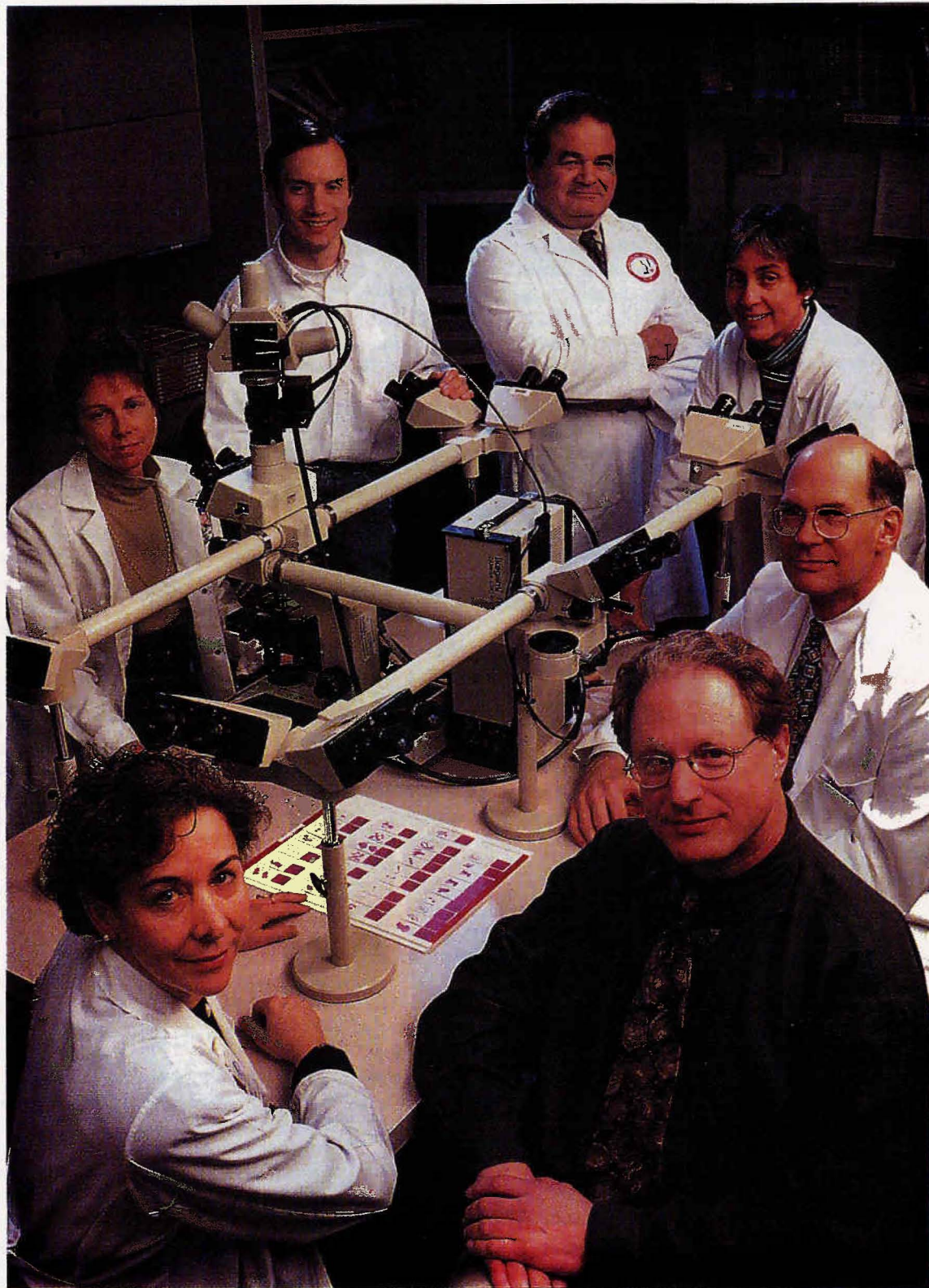
Norma poured out her frustration to Tom, whom she'd married earlier that summer: "We've been fighting this for a long time. We've been through a lot, and she can take a lot. But I am exhausted. I think I may lose it."

Norma's instinct was to get Jessica admitted right away to the Clinical Center, just a couple of hundred yards up the hill. But the inn's manager explained that it was not that simple. Because the Clinical Center is devoted to research, it does not have

**Stephen Straus, lower right, has had lots of help solving the mystery of Jessica's illness. The NIH team, clockwise from lower left, included Janet Dale, Elaine Jaffe, Michael Lenardo, Warren Strober, Jennifer Puck, and Thomas Fleisher.**

some of the facilities available in an ordinary hospital—like an emergency room to comfort a sick little girl at two o'clock in the morning. The nearest emergency room

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## What's Wrong With Jessica?

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was at Suburban Hospital, just across Old Georgetown Road from the NIH campus. Norma decided to tough it out and wait for daylight.

Though the original plan called for Jessica to visit the Clinical Center as an outpatient, she was in enough pain the next morning to be admitted to one of its pediatric units. She was given intravenous morphine to control her pain and was soon asleep.

**Dr. Straus was perplexed: "I was stuck with a little girl who did not have what she was billed to have. But I hadn't the foggiest idea of what she did have."**

**T**HE MAN THEY WERE THERE to see, Dr. Stephen Straus, had been doing medical research for more than two decades. He had grown up in New York City, studied life sciences at the Massachusetts Institute of Technology, received his medical degree from Columbia, and spent time working on infectious diseases at Washington University in St. Louis. He had been at NIH since 1979 and was just months short of moving up to become chief of the Laboratory of Clinical Investigation in the National Institute of Allergy and Infectious Diseases. His curriculum vitae listed him as author or coauthor of 143 scientific papers (it's now 272) and as a member of dozens of medical organizations and committees.

Most of Straus's career had been devoted to studying the prevention and treatment of human viral and immunological disorders, particularly various types of herpesviruses. In the early 1980s, he conducted some of the first studies proving that genital herpes could be effectively treated by the drug acyclovir. He'd also studied another type of herpesvirus called Epstein-Barr. It is the cause of infectious mononucleosis, which is fairly common, but there's also a chronic form of EBV that is rare. He had studied only about a dozen patients suffering from chronic Epstein-Barr virus in 15 years and knew it to be a debilitating, often fatal illness.

Straus stayed at NIH because it was the best place to do the kind of research he loved. Its labs were filled with experts on every imaginable aspect of modern medicine, colleagues to whom he could turn for advice if he confronted a problem he did

not understand. It was a place where he could both do laboratory work in molecular biology and have face-to-face contact with patients—a circumstance reflected in the fact that his office and laboratory were just a few feet from the rooms where his patients stayed. And it offered the intellectual freedom and financial support to pursue basic questions about the human body.

**W**HEN STRAUS WALKED into a pediatric unit at the Clinical Center to meet Jessica Chancellor, the question of what was

wrong with her was not among the most intriguing mysteries he faced. After all, she had been referred to him because a blood test at UCLA had picked up the chronic Epstein-Barr virus.

But it was standard procedure at NIH to start from scratch with each new patient, which meant that most of Jessica's first visit there was taken up by a physical examination and lab tests. It was obvious that she was small for her age, below the fifth percentile in height and weight, and that she still had bulging lymph nodes in her neck. But other aspects of her condition depended on laboratory analyses whose results would come back over the next several weeks—including a rerun of the Epstein-Barr test.

One sample of Jessica's blood went down to the second-floor pathology department to Dr. Thomas Fleisher, who had helped with evaluations on many of Straus's patients over the years. Fleisher was an expert in analyzing the blood's lymphocytes, a kind of white blood cell that plays a pivotal role in fighting infection. Using a technology known as flow cytometry, Fleisher was skilled at sorting and quantifying the various types of lymphocytes, which had become an important bit of knowledge in the fight against AIDS.

As Fleisher examined Jessica's blood, his eye caught something that a technician in an ordinary lab might never have noticed. It had to do with certain kinds of lymphocytes called CD4 T cells and CD8 T cells. Fleisher saw that Jessica's blood did not possess these cells in the right numbers or proportions. Something was out of order.

That led Fleisher to realize that there were far too many of another type of lymphocyte known as "double negative" CD4/CD8 T cells. These cells are normally such a minor population in human blood that most labs don't bother to count them. In adult humans they normally range from 9 to 122 in a standard volume (one millionth of a milliliter) of blood, but in Jessica's blood the count was 6,416. Fleisher had never seen anything like that, and he sent a report to Straus characterizing Jessica's lymphocyte profile as "extremely abnormal."

Jessica and Norma prepared to return to Tulsa to await word from Straus on a diagnosis. Before they left he prescribed a steroid called prednisone in hopes of relieving the pain in Jessica's abdomen, which was thought to come from swollen lymph nodes pressing on her nerves and organs. The effect was dramatic—the lymph nodes on her neck began to shrink, her abdominal pain ceased, and Norma thought they had found a miracle drug. But prednisone had such serious side effects that it could not be taken over long stretches, and the lymph node swelling returned when she tapered off it.

Norma brought Jessica back to NIH three times in that fall of 1990—in September, November, and December—as Straus and his colleagues struggled to understand what was wrong. The treatment was free—a longstanding policy at NIH that applies to all patients because they are volunteers for scientific studies.

Team members repeated the blood test in case the odd result noticed by Tom Fleisher had been a mistake, but the second test only confirmed the first.

They performed a new lymph-node biopsy and sent the tissue to a NIH pathologist named Dr. Elaine Jaffe, who confirmed that Jessica's lymph nodes also contained an elevated level of those negative T cells Fleisher had seen in her blood.

Finally, when results from NIH's Epstein-Barr test came back, they were negative—evidence that the positive test at UCLA had been mistaken.

Straus was perplexed: "I was stuck with a little girl who did not have what she was billed to have. But I hadn't the foggiest idea of what she did have."

*It's not always fun being sick, but it can be interesting.*

**O**NE OF THE MOST PROMISING leads in Jessica's case came from a couple of Straus's colleagues on the Clinical Center's 11th floor—a senior researcher named Dr. Warren Strober and a younger clinician, Dr. Michael Sneller. Straus took them to meet Jessica, showed

# It Was Blake's Best Day

**B**LAKE RENFROE, WHO LIVED in a small Texas town near Houston, had been so sick for so long that his mother, Joyce, had never been sure how long the little boy might live.

At six weeks he had begun vomiting and running a high fever. A few months later he developed swelling in the lymph nodes along his neck. And by age two, his spleen was so enlarged that it had to be removed, along with his swollen tonsils.

By the time Blake was six he'd been through dozens of tests and biopsies as well as several long hospital stays. He'd been to medical centers in Fort Worth, Houston, Galveston, Little Rock, and Minneapolis, and doctors had thought at various times that he had Castleman's disease or lymphoma. Among his treatments had been one experimental chemotherapy that made him throw up again and again, caused his hair to fall out, and destroyed the enamel on his teeth.

Blake's mother remembered that as one of the worst moments: "He just lay there, didn't move, and would say, 'Mom, please make the hurting stop. I can't take it anymore. Please, just let me die.'"

Joyce Renfroe, just 18 when Blake was born, would do anything to protect him—at one point becoming obsessed with assuring that everything in their mobile home was sterile. She washed the walls every other day with bleach.

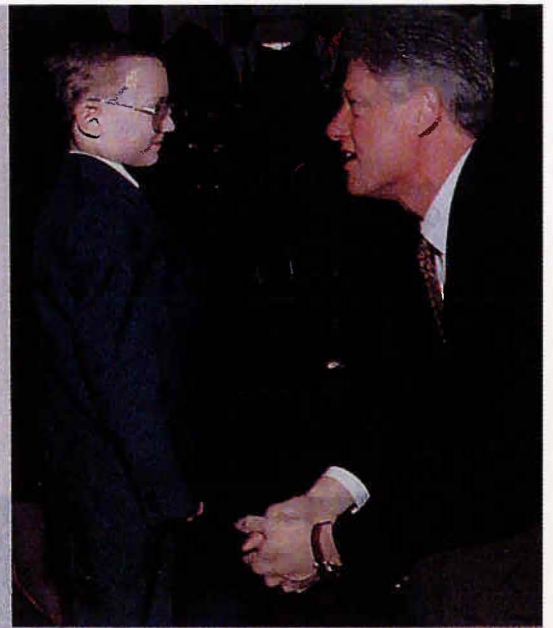
Joyce was persistent in other ways. She tracked down the name of a doctor at the National Institutes of Health in Bethesda and kept calling until he referred her to someone there for an evaluation. Once, when frustrated about losing health insurance for Blake, she fired off a letter to Bill Clinton at the White House, complaining that it wasn't fair that an American citizen with a sick child should be treated this way.

Shortly after sending that letter, in February 1995, Joyce got a call from the White House. A presidential aide wondered if she would like to bring Blake to Washington to sit in the Oval Office and watch Clinton deliver his Saturday morning radio address. Although Blake's chances of long-term survival were still in doubt, he was feeling well enough to make the trip, so Joyce accepted the offer—partly because it would allow them also to visit NIH.

Blake's day in the Oval Office included a bonus. Among the other guests were members of his favorite team, the Houston Rockets, which had won the National Basketball Association championship the previous season. Blake got to sit near his favorite player, Hakeem Olajuwon.

After the address Blake stood in line to shake hands with the President and have his picture taken. Noticing that the boy's double-breasted blazer was buttoned

**Blake, after a fateful visit to NIH, is back home in Texas, strong enough to play ball.**



**Blake's visit to the White House led to a talk with the President and a visit with his favorite basketball player.**

crookedly, Clinton got down on his knees to rebutton it and ask how he was feeling. The *Houston Post* covered the event and ran a story under the headline DYING BOY'S VISIT TO WHITE HOUSE WAS A DREAM COME TRUE.

Two days later Blake and his mother went to NIH, where a research team headed by Dr. Stephen Straus examined him and drew blood. A few weeks later, when the test results were in, Joyce got a call saying that Blake did not have a fatal disease. He was suffering from a new disease called ALPS, which meant he might have some continuing bouts of illness but ought to survive. Joyce broke down and cried.

Now, three years later, Blake is doing remarkably well, despite some troubles with arthritis. He goes to school and is able to play baseball, ride his bike, and run around outdoors. He's well enough now to allow Joyce to hold a job as a prison guard.

"It's been great to finally get the answer I needed about what was wrong with him," she says. "I've even calmed down on the cleaning. I'm glad, because I hate cleaning."



them Fleisher's report on her abnormal blood, and asked for their opinions. Because they were immunologists who kept up with the scientific literature in that field, they recognized that Jessica's blood and some of her symptoms were similar to those of a widely researched group of laboratory mice.

These mice had been identified in the early 1980s at Jackson Laboratory, a facility in Maine that specializes in breeding "mouse models" that mimic human diseases. They had been used mainly in studying systemic lupus erythematosus, a

disease that affects the kidneys, joints, and skin.

Straus was interested in the possible connection between Jessica and the mice, but there was one problem: Nobody had yet figured out the origin of the disease in the mice.

But the connection between Jessica and the mice, they all figured, was strong enough and interesting enough that they could write a paper for submission to a scientific journal. Michael Sneller, who did most of the hands-on laboratory work, was listed as the lead author, along with Straus,

Strober, Fleisher, Jaffe, and a couple of others. The paper was conservative in its claims, simply describing the symptoms and blood profile of an anonymous patient and pointing out her similarities to the mice. In effect, as the office talk had it, all they could claim was that Jessica seemed to be "a kid with a mouse disease."

They submitted the paper to the *New England Journal of Medicine*, the most prestigious medical journal in the country, hoping the editors would be as interested as they were. But a few weeks later the journal sent back a rejection letter, accompa-

nied by the opinions of a couple of anonymous scientists who had been asked to review the work. The rejection was disappointing, and the NIH team was miffed by one reviewer's judgment that Jessica had simply been misdiagnosed.

"Our juices were flowing here. We were convinced we had something interesting. But our *aha!* was not appreciated," says Straus. "One reviewer was basically laughing at us. He thought this child clearly had juvenile lupus and sort of implied that we would have known that too if we were in any way competent. He didn't think our work merited any kind of public attention. It was old news."

**W**HILE THE GROUP AWAITED word from the *New England Journal*, there had been another development. One day Straus got a phone call from a doctor at the University of Michigan, who explained that he was seeing an eight-year-old girl with a set of symptoms he thought might be attributable to the chronic Epstein-Barr virus. Knowing of Straus's reputation in that field, the doctor wondered if he was interested in seeing her.

The answer was yes, but the more the Michigan doctor described the little girl—she had enlarged lymph nodes and had undergone a splenectomy—the more Straus thought she sounded like Jessica. Straus had always heard that "chance favors the prepared mind," and here was an example. When a sample of the little girl's blood was sent off to Tom Fleisher, it looked much the same as Jessica's.

The discovery of this second patient allowed Michael Sneller to add a new example to the paper rejected by the *New England Journal*, and the revised version was soon shipped off to another journal with hopes of a better hearing. The *Journal of Clinical Investigation* was oriented more to research types than ordinary practitioners, which meant that it would not reach as many doctors who might be able to refer patients to NIH. But it still was a high-quality journal and a place where the NIH team could claim credit for discovering Jessica's disease—an important consideration in the competitive realm of world-class science.

Already there was evidence that somebody else had picked up the trail. While the NIH manuscript was being considered by the *Journal of Clinical Investigation*, Elaine Jaffe noticed a paper by Danish researchers in the *Scandinavian Journal of Immunology*. They described a patient similar to Jessica, but they had not yet made the connection to the mice.

The *Journal of Clinical Investigation*, to

the surprise of Straus and the NIH team, rejected their paper. Again a reviewer thought they'd missed the lupus diagnosis. This time they decided to fight back. Warren Strober called up an editor he knew at the journal and argued that he ought to reconsider: "I said, 'Wait a minute, this is a new disease. You have to put this in.' I was trading on my reputation for honesty and integrity."

It worked. The journal published the eight-page article in August 1992, two years after Jessica Chancellor's first visit to Bethesda.

**Straus developed a layperson's version of the story and briefed Jessica and her family. She spent her time doodling, but she did manage to get down some pictures of cells.**

*Sometimes I have to go to boring meetings. I write everything down the doctor says, but it still doesn't make sense to me.*

**A**S RESEARCH ON JESSICA'S illness evolved, Steve Straus organized a team meeting every other Friday to take stock of progress and decide what to do next. Usually it was held in a conference room next to his office that had just enough space for a large table, ten chairs, and a wall of bookshelves filled with medical journals. Most of those who'd taken an interest in the case in the beginning continued to be involved—Straus, Warren Strober, Michael Sneller, Elaine Jaffe, and Tom Fleisher—but other researchers and assistants helped out. Always there, too, was an efficient nurse named Janet Dale who kept track of patients and dozens of other details.

Although these meetings continued after the appearance of the paper in the *Journal of Clinical Investigation*, the team did not make much progress in its search for the disease's root causes. Ideas were floated and checked out in the lab, but nothing panned out.

Frustrating as that was, Straus knew from experience that it was important to be patient and keep an ear to the ground: "In science you sometimes have to wait for new opportunities—new technology or a new piece of information—that allows you to move ahead. In the background noise of science, your ear has to be tuned to what is relevant."

The clue they were listening for came from halfway around the world. In 1992, a group of Japanese scientists published a paper in the British journal *Nature* that ex-

plained for the first time what was wrong with those mice whose disease so resembled Jessica's. The answer was a genetic flaw. They were missing a protein called *Fas* that was important in triggering the death of certain lymphocytes when their bodies no longer needed them to fight infection.

To follow this lead, Straus had to recruit other experts at NIH with relevant specialties—and he knew just the two he wanted. One was Dr. Jennifer Puck, a specialist in genetic immunological diseases who had

recently joined NIH's National Human Genome Research Institute. And the other was Dr. Michael Lenardo, an expert in programmed cell death in both humans and laboratory mice.

Straus knew both doctors, having met them years before at Washington University in St. Louis when they all were just beginning their careers. He also thought he could convince them that the questions posed by Jessica's disease were intellectually interesting and potentially answerable. But his secret weapon was Jessica herself, whom he brought them to see during one of her visits; she put a human face on the disease. Both Puck and Lenardo, whose career researching mice had rarely before put him in direct touch with human patients, soon were coming to the team's meetings.

Their contributions, using the most advanced techniques available in molecular biology, allowed the project to move forward. Puck found that Jessica did have a subtle flaw in her *Fas* gene. And Lenardo determined that this flaw prevented the elimination of lymphocytes in the blood that no longer were needed to fight infection.

These conclusions made their way eventually into scientific journals in language so specialized that it was beyond the comprehension of most nonscientists. But Straus also developed a layperson's version of the story behind the disease—a briefing that he first delivered for Jessica and her family in one of those meetings she found so boring. Jessica spent her time doodling, but she did manage to get down some pictures of cells and a few of the concepts.

In healthy human beings, Straus ex-



plained, there is an ongoing process that works like this: White blood cells called lymphocytes serve as the soldiers of the immune system, expanding in number to attack infections that threaten the body. When the infection is conquered and these cells are no longer needed, the body is equipped to destroy them through a process called "apoptosis." A key part of the biochemical control mechanism that triggers this "programmed cell death" is a protein produced by the *Fas* gene.

Straus explained that Jessica suffers from a glitch in this process. Her lymphocytes—including those double-negative T cells Tom Fleisher had found in such abnormally large numbers—do not die as they should but build up in her body to levels 30 to 50 times normal. They collect in lymph nodes and other parts of the body with lymph-like tissue, including the spleen. The reason is that the protein made by her *Fas* gene, which is supposed to trigger cell death through apoptosis, has a subtle mutation that renders it ineffectual. One upshot of this is that she is prone to attacks of "autoimmune disease," in which her immune system attacks her body's own tissues.

When it became clear to the NIH team that Jessica's disease was genetic in origin, it was important to determine who she had gotten it from. So in the summer of 1995, tests were done on blood samples taken from both her mother, Norma, and her father, Dr. Jon Chancellor. It was not apparent which one had passed the flawed gene to Jessica because neither parent had swollen lymph nodes or any of the other symptoms of the illness plaguing their daughter.

A few weeks later, Norma picked up the phone at her home in Tulsa to find Steve Straus on the line. Stepping into the master bedroom, she closed the door so she could be away from the two girls. The lab results were back, Straus said. Although Norma showed no outward signs of the disease, the tests revealed that she carried the same genetic defect as Jessica.

It was difficult news for Norma to take: "Having seen all the illness she had been through, I was pretty sad at first to know that she got the gene from me. I talked to Tom about it, and I realized that I had no way of knowing. Eventually I came to grips with the reality."

Other parents whose children suffered this disease would be confronted with similar revelations. It was always a difficult moment, which Straus tried to handle with sensitivity. "It's tough news to deliver to a parent. There is always a sense of guilt. I just try to explain that it's an accident of nature, that no one is to blame. I tell them

we all have mutations. That's what makes us unique." Sometimes Straus points to his own right eye, which has been crossed from birth, and explains that one of his uncles had the same.

**I**N JUNE 1995—WITH THE NEW knowledge from Puck, Lenardo, and other contributors in hand—the group published a second paper in a journal called *Cell*. The team was now ready to give Jessica's disease a name.

One possibility was to name it after

**"Having seen all the illness she had been through, I was pretty sad at first to know that she got the gene from me. Eventually I came to grips with the reality."**

Straus or several senior members of the group. The practice had a long history in medicine, resulting in such well-known names as Tay-Sachs, Epstein-Barr, and Alzheimer's as well as dozens of rare-disease names like Klippel-Trenaunay-Weber Syndrome, the affliction of pro golfer Casey Martin. But this custom, which many people thought arrogant, had fallen out of favor.

Something more descriptive was in order. But it would be helpful to have an acronym that was memorable. The choice turned out to be ALPS, which stood for Autoimmune Lymphoproliferative Syndrome. Within the research team, though, there was an inside joke: ALPS also might stand for A-Lenardo-Puck-Straus.

*I was one of the first ones to get it.*

**T**HE DOCTORS AND OTHER scientists who do research on the NIH campus see lots of patients with illnesses that afflict millions of people, from breast cancer and heart disease to diabetes and arthritis. But they're also attuned to diseases like Jessica's that are so unusual that only a few cases may exist. "We're a place," says Janet Dale, the nurse on the Straus team, "that specializes in unicorns."

But Steve Straus and his team also were aware that finding more patients with ALPS was necessary to move their research along. That would offer them more blood samples and biopsy tissues to examine—a necessity in research medicine that had been limited so far by ethical considerations and Jessica's small size. More patients also would allow the team to study

patterns of variation in the disease, to discover what they had in common and what they did not. And they could accumulate experience with treatments, seeing how different patients responded to different drugs.

It was reasonable to assume that there were other people with ALPS out there. And as word of the disease spread—as doctors read the NIH researchers' papers or heard them speak at medical conferences—these patients began to find their way to Bethesda. More and more doctors

called up to describe patients they thought might have the disease, and Straus got so he could almost predict before the blood test which ones fit the pattern.

At the moment—nearly eight years after Jessica's first appointment in Bethesda—the ALPS team has found and is studying 26 people with the disease. They come from all over the United States, male and female, black and white, and from all economic circumstances. Many are young, because the disease usually shows up early in life, at a median age of nine months.

Although most of these patients have come from physician referrals, a few were located by detective work involving computer searches of old medical journals. Four or five articles turned up people with symptoms that in retrospect seemed similar to ALPS, and Straus has written to the authors seeking leads. Already enrolled in the NIH study are five patients from a Midwestern family originally described in an article by University of Wisconsin doctors in 1974.

*If you think I have a weird life, here are some of my favorite things to do. I like swimming, art, and playing outside. I really have a good life besides being sick.*

**F**OR THE PAST FOUR YEARS, Jessica has lived with her family just outside Stillwater, Oklahoma, a town west of Tulsa that is the home of Oklahoma State University. Her stepfather, Tom, the former OSU golfer, is pro and manager of the new Karsten Creek Golf Club as well as project director of the surrounding residential development. The family's house, one of the first built on

the 1,000-acre property, is a spacious four-bedroom of the sort you might find in McLean or Potomac. Besides Jessica and her parents, the household also includes her sister, Jennifer, who is now 15, and a half-sister, five-year-old Tommye Raye.

Jessica's health is good enough much of the time for her to enjoy all that comes with being a normal 11-year-old. She's in the fifth grade—at a point in life where it's still possible to be attached to both a stuffed Pooh bear and Hanson, the pop singing group. She also has regular visits in Tulsa with her biological father, Dr.

a screened-in porch where Jessica can play without being exposed to insect bites. Inside the pantry is a four-foot-by-four-foot medicine cabinet crammed with vials of pills, swabs, syringes, and special soaps.

**J**ESSICA GOES TO NIH FOR REGULAR checkups every six months, more often if her health deteriorates. She's made 37 trips over the past eight years—most recently in early April—each one described in Norma's delicate handwriting on the pages of a worn legal pad. That's

sica's skin. A new combination of drugs managed to halt the attack on her liver, and she is again doing well—another example of NIH's ingenuity and Jessica's resilience. "Sometimes she seems to have nine lives," says Steve Straus.

Several weeks ago, when he had to tell her that one of the drugs he was prescribing might make her hair fall out, he was worried how she might react. "Oh well," Jessica shrugged, "nobody's ever died of a bald head."

*One good thing when I'm in the hospital is that I get a lot of presents. So it kind of pays off going to the hospital.*

**Doctors gave her only a 10-percent chance of surviving the night. A Catholic priest administered last rites. But by morning Jessica's condition improved.**

Jon Chancellor.

ALPS has affected her physical appearance. She is short for her age, just four feet, partly because of the growth-stunting side effects of the prednisone she has taken on several occasions. And she still has those bulging lymph nodes in her neck.

There was a time, back in Tulsa, when kids at school teased Jessica about her appearance—calling her "leprechaun" and making fun of her swollen neck. That's been less of a problem in Stillwater, but it used to send Norma into a protective mode whose ferocity only a parent could comprehend.

Once, when Jessica was in first grade and Norma was volunteering as a playground monitor, she found herself grabbing one of Jessica's tormentors by the collar and warning him to lay off. Another time, when a boy teased Jessica about having "fat cheeks," the girl took some advice from her sister Jennifer and got back at him in a way she found most satisfying: "I told him he had a 'fat butt.' It was really funny to see that kid's face."

Because Jessica has suffered several crises that required hospitalization, everyone at home is vigilant about possible dangers. They worry she will get too hot when she runs or have a bad reaction to a bug bite. She's trained to take her medicines on time, to turn away when someone sneezes, and to wash her hands thoroughly.

The custom-built house where Jessica lives, which is set in woods overlooking the cove of a lake, has a couple of architectural features designed with her illness in mind. The open deck attached to the back of the house is accompanied by

enough visits to have made Washington almost a second home—to have mastered Metro, toured the monuments, tested the restaurants of Bethesda, taken a tour of the White House, and celebrated Fourth of July on the Mall. And it's enough to have put Jessica on a first-name basis with a host of NIH doctors, nurses, and technicians, including a lab employee who once came to her room to see her because he "wanted to put a face with the blood."

During the years she's been coming to NIH, Jessica has gone through several episodes of severe illness, forcing Steve Straus and her doctors in Oklahoma to work together to save her. One of the worst was in February 1993 when she developed a pneumococcal infection and had to be rushed to Saint Francis Hospital in Tulsa and placed in the intensive care unit. Her father, Dr. Chancellor, spent long hours at the hospital monitoring her condition and helping with her treatment, while Norma and Tom rushed back from a vacation in Florida to be at her bedside.

At one point it appeared that antibiotics were having little effect, and her condition deteriorated so much that doctors gave her only a 10-percent chance of surviving the night. A Catholic priest administered last rites. But by morning Jessica's condition improved, and she returned home after a 12-day stay.

Just last fall she experienced her latest siege, this one when her body's immune system began trying to destroy her liver. One function of the liver is to clear cholesterol from the system, and Norma first noticed something was wrong when little fatty pockets began to show up under Jes-

**O**NCE THE NIH RESEARCHERS confirmed the genetic basis of ALPS, one of their next steps was to begin examining entire families. Blood tests were performed on mothers and fathers, sisters and brothers, grandfathers and grandmothers. And pedigree charts were drawn up showing which family members had the flawed gene and which did not, who showed symptoms of ALPS and who did not. In one case an NIH team was dispatched to San Antonio to do tests on four generations of a family there because its members were unable to take time off to come to Bethesda.

These family portraits are surprisingly complex. It has become clear that some people with a flawed *Fas* gene go on to develop ALPS, while others in the same family with the same defect do not—the situation that prevails in the case of Jessica and Norma. It also turns out that parents like Norma who have the defective gene may pass it on to some of their children but not to others. Neither Jennifer, from Norma's first marriage, nor Tommye Raye, from her second, inherited the gene that has led to their sister Jessica's illness. Finally, the complications that arise from the disease cover a wide spectrum—with some patients, including Jessica, far more severely affected than others.

Discovering why these differences occur has been among the NIH team's priorities. Is it possible that a parent without the genetic defect contributes something at conception that interacts with the other parent's defect to affect an offspring's chances of developing ALPS? Could it be that those who have the defect but have not developed ALPS have "compensatory pathways" that allow their bodies to dispose of unneeded cells in a normal way?

The hope is that unlocking the secrets of this one rare disease—this one "experiment of nature," as Straus calls it—will reveal answers to some of the most basic

questions about how the body works. These insights, in turn, might one day be applied to a cure for autoimmune diseases affecting millions of people, including rheumatoid arthritis, lupus, and sclerodema.

**E**VERY STEP FORWARD IN THIS journey of discovery results in a paper in another scientific journal. So far the team has turned out half a dozen of these treatises. The most recent have appeared in the *Journal of Immunology*, the *Journal of Experimental Medicine*, and *Blood*—this last with a photo of an unidentified patient who happens to be Jessica, her head tossed back to show her swollen neck. The sixth paper, concerning that family near San Antonio and written in connection with doctors there, has been accepted by the *Journal of Pediatrics*.

As this string of papers has emerged from NIH, researchers elsewhere have begun trying to understand the disease. Teams in France and Italy have published papers, and another research effort is under way at the Cornell University Medical Center in New York City. All of which has set up a competitive situation that is fairly common in scientific circles and has resulted in some tension between the teams at NIH and Cornell.

This conflict came to a head a couple of years ago when both teams submitted papers simultaneously to the *New England Journal of Medicine*. The NIH paper focused specifically on new findings about ALPS, assuming no need to repeat in detail the revelations in the team's first two papers. The paper from Cornell, while mostly reiterating the story of the *Fas* mutation's effect on cell death, made a startling claim about the four patients its own team examined. A couple of them had been identified 30 years earlier, in 1967, by two Cornell doctors, who had published a paper about their disease and named it Canale-Smith in their own honor.

To the chagrin of the scientists at NIH, the *New England Journal* rejected their paper and published the one from Cornell. That prompted a chilly letter to the editor from Steve Straus, Michael Lenardo, and Jennifer Puck, arguing that their own work on the disease extended "well beyond" anything the doctors at Cornell had achieved. What's more, they said, NIH's name for the disease—"Autoimmune Lymphoproliferative Syndrome"—was "more informative . . . than the eponymous Canale-Smith syndrome."

**A**FTER EIGHT YEARS, NIH cannot offer Jessica Chancellor or its other ALPS patients a cure for

their disease. There's no miracle drug that reverses its symptoms and restores perfect health. Gene therapy, while much ballyhooed as a promising new technique, is only a long-range possibility, given the complicated and subtle nature of the genetic defect.

But there has been enough progress to offer ALPS patients and their families considerable comfort. The disease can now be diagnosed with certainty, which in itself is a great relief to people who once searched for years to find anyone who could correctly identify their affliction.

There's also some solace in knowing that one is not the only one in the world with this rare illness. Straus remembers seeing this powerful affinity at work once when Jessica and another little girl with ALPS happened to be in a Clinical Center's pediatric unit at the same time. Seeing each other in a corridor, they stopped in their tracks and stared. "As if seeing for the first time another human being who looked like themselves," says Straus, "they ran up and gave each other a big hug."

As Straus and his team have seen more patients, they also have accumulated lots of experience in using various drugs to manage the autoimmune attacks that arise from the disease. Most of these attacks now appear survivable, and some ALPS patients now go months or years without hospitalization.

There is one other bit of encouraging news. When Jessica arrived at NIH as a sick little three-year-old in 1990, Norma was eager to know from Steve Straus how long her daughter might live. He had no answer because he had seen no other cases. But as his team has found and studied other patients—someone age five, someone in his teens, then someone in her twenties—evidence has mounted that people can live with ALPS for many years and that their symptoms may lessen with age.

There is special excitement now with the discovery of that family near San Antonio in which ALPS is spread across four generations. One member of the family, a man in his mid-fifties, apparently has lived with the disease since he was a baby; his enlarged spleen was removed back in 1945. At the time his parents were told he had leukemia, and he now takes pride in having outlived many of the doctors who made the misdiagnosis.

Even for someone as young as Jessica, the implication of this man's survival is not lost. "That's really good," she says, "because it means you can live a long time." □

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