

THE MARK O. HATFIELD CLINICAL RESEARCH CENTER  
NATIONAL INSTITUTES OF HEALTH



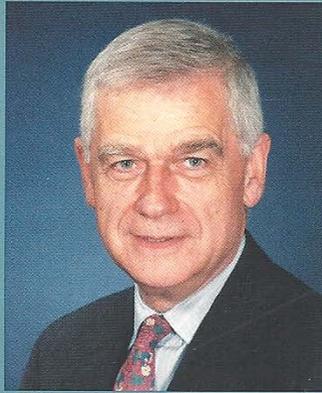
Dedicated to better health through research...there's no other hospital like it.



## SENATOR MARK O. HATFIELD

A life in public service

A student, teacher, and practitioner of American politics, Mark O. Hatfield has devoted himself to improving the human condition through a lifetime of public service. Elected to the Oregon legislature in 1950, when he was teaching political science and serving as dean of students at Willamette University, Hatfield served two terms in the Oregon House of Representatives and two years in the Oregon Senate. When he became



the youngest secretary of state in Oregon history he was only 34. Elected governor in 1958, he was re-elected in 1962. In 1966, while serving as Oregon's governor, Hatfield was elected to the U.S. Senate. In 1993 he became the longest-serving U.S. senator from Oregon. His distinguished public service career ended in January 1997 with his retirement from the United States Senate. He never lost an election.

During his long career in Washington, Senator Hatfield provided strong support for biomedical research and the National Institutes of Health. Under his leadership as chair of the Senate Committee on Appropriations, NIH funding increased by more than \$2.5 billion. Determined to find ways to fund NIH above and beyond the federal budget appropriations process, he worked closely with Senator Tom Harkin of Iowa to introduce a National Fund for Health Research—to generate research funds through a 1 percent set-aside of health insurance premiums and a voluntary federal income tax check-off. He often reminded his Senate colleagues of “the desperate human needs in our midst.” To researchers in search of funding, he counseled: “Tell Congress that you have found a gene, and they’re interested. But tell Congress that you’ve found a way to cure a genetic disease, and watch the budget grow.” He is proud to be associated with the hope placed in the Clinical Research Center, saying, “We all have good reasons for that hope. This new building represents the new frontier in medical science.”

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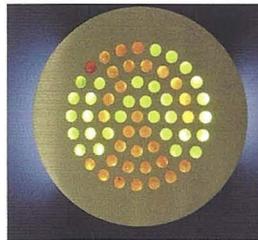
Dedicated to better health through research....there's no other hospital like it.

As a special hospital for the nation, the NIH Clinical Center provides a new chance at life for people from every state in the union. Many patients with poor prognoses—patients told they had just weeks or months to live—are alive today because of their participation in research studies at the Clinical Center. The largest hospital in the world dedicated totally to clinical research, the Clinical Center provides hope when there is none—not just for the patients who come to the facility as volunteer partners in research, but for citizens around the world, whose lives are changed when that research advances medical knowledge.

The Mark O. Hatfield Clinical Research Center (the Clinical Research Center, for short) is the NIH Clinical Center's new hospital. A physical extension of a facility built 50 years ago (now known as the Warren Grant Magnuson Clinical Center, and informally known as Building 10), the Hatfield Clinical Research Center is located strategically on the

Bethesda, Maryland, campus of the nation's most prominent health research organization, the National Institutes of Health. The proximity of patient care units to basic science laboratories within and around the Hatfield Center enables the rapid translation of scientific observations and discoveries into new approaches for diagnosing, treating, and preventing disease.

Every patient in the Clinical Center is admitted as part of a clinical research protocol (a research plan). Patients pay no hospital bills, nor are they selected to participate in research because of financial considerations. The U.S. Congress funds the NIH Clinical Center through budgets appropriated for the institutes. The institutes that use the Clinical Center sponsor research protocols here. As investigators work to develop new treatments for diseases, they form unique relationships with patients as partners in discovery.



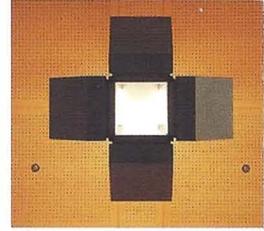
(c) Alan Karchmer



Hospitality staff will welcome patients and visitors at the reception desk.

"FOR MORE THAN 50 YEARS, WORK AT THE NIH CLINICAL CENTER HAS ENABLED THE RAPID TRANSLATION OF SCIENTIFIC OBSERVATIONS AND DISCOVERIES INTO NEW APPROACHES FOR DIAGNOSING, TREATING, AND PREVENTING DISEASE. THE MARK O. HATFIELD CLINICAL RESEARCH CENTER PROVIDES A WONDERFUL VENUE TO CONTINUE THE NIH'S REMARKABLE TRADITION OF LEARNING, HEALING, AND DISCOVERY FOR GENERATIONS TO COME."

John I. Gallin, M.D.  
Director, NIH Clinical Center



No organization in the world sees more patients with orphan (rare) diseases, but in the Clinical Center's rich history, NIH researchers have also pioneered treatments for common diseases, such as diabetes and cardiac conditions. A short list of the many notable research advances made in the Clinical Center includes:

- The first cure of a solid tumor with chemotherapy
- The first chemotherapeutic cures for childhood leukemia and Hodgkin's disease
- The first use of immunotherapy to treat cancer
- The first use of AZT to treat AIDS
- The first controlled trials of lithium's effect on depression
- The first successful replacement of a mitral heart valve with an artificial valve
- Analysis of the disorders of lipid metabolism and the pathogenesis of arteriosclerosis
- The first use of chemotherapeutic agents to treat such nonmalignant diseases as lupus and Wegener's granulomatosis

- The first gene therapy (for adenosine deaminase deficiency)
- The development of screening tests for AIDS and hepatitis (which reduced the transmission rate of transfusion-transmitted hepatitis from 30 percent to near zero).

The Clinical Center has also led the nation in developing rigorous standards for the safe and ethical practice of clinical research. When it opened in 1953, the Clinical Center produced the first written federal policy for protecting human research subjects, integrating existing policies into a clear process of informed consent. This early policy was a precedent for the country's institutional review boards (IRBs), which review research protocols for patient safety and for the informed consent required before patients can participate in any clinical trial.



Research and patient care require a high staff-to-patient ratio.

The Clinical Center's research over five decades has produced many medical breakthroughs for the treatment of diseases. The future offers unprecedented opportunities in disease prevention and in the management of chronic diseases such as cancers and Alzheimer's disease. Among other things, researchers are striving to develop various forms of gene therapy; to develop therapies using adult stem cells to restore function to diseased

organs and to treat cancer and other diseases, ranging from immune deficiencies to diabetes; to develop effective vaccines to treat cancer and to prevent infectious diseases; and to learn how to manipulate the immune system so that organs from unmatched donors can be used for organ transplants.

## A SPECIAL HOSPITAL



Patient rooms are large and flexible in design.

As the most technologically advanced clinical research facility ever constructed, the Hatfield Clinical Research Center was designed to facilitate such medical advances. Built for flexibility, the seven-story facility can easily adapt to changing research agendas. To control infection, for example, special air-handling units will be able to shift the direction of airflow in patients' rooms—blowing air out of some (to protect patients with severe immune deficiencies from exposure to infectious diseases) and preventing air from exiting others (to shield staff and other patients from exposure to highly infectious diseases such as SARS). Day-hospital stations will allow outpatients to participate in research studies such as new therapeutic approaches using gene therapy without requiring admission to a patient-care unit. A special pharmacy will be able to make small amounts of new drugs for initial evaluation in patients.

In addition to CT scan and MRI technologies (which provide different kinds of computer-read images of a patient's anatomy and body processes), the hospital will have three cyclotrons, machines that generate radioactive isotopes used for PET scanning to study cellular pathways in the body. Nanotechnology (seeing and manipulating materials at the molecular and atomic level) will permit new approaches to the diagnosis and treatment of diseases.

Patients will receive their treatment in a hospital designed to deliver the highest quality care in the best environment possible, ensuring that they will complete the full course of research and evaluation. The Clinical Center nurses—among the best educated in the world—say “there is no other hospital like it” because at the Clinical Center they can practice medicine the way they learned it should be practiced in a clinical research setting.

Inviting facilities will help to create a healing environment. Large windows and skylights bring natural light to patient rooms, the intensive care unit, and even the patient parking area, providing a warm and welcoming first impression. Beautifully landscaped courtyards will help relieve stress in patients and their families. Special medicinal plant displays, developed in collaboration with the National Arboretum, will adorn areas that encourage patients, care providers and scientists to meet and talk.

Several patient care units will support long-term studies of patients with behavioral-health diseases such as schizophrenia, depression, alcoholism and obesity. The study and treatment of these diseases often requires patients to stay longer, so these units contain special areas for dining, exercise, interaction, and group therapy—and other resources to help patients leave their homes and communities. The unique combination of special staff and facilities—and enough patient time in the

hospital—provides a spectacular opportunity for breakthrough observations.

Children who participate in clinical research at NIH will not have to miss school, because a special school for children (K–12) will bring learning to their bedside. And if their treatment does not necessitate spending the night at the Hatfield Clinical Research Center, they will be able to stay with their families in the recently expanded Children's Inn, where they can escape from the challenges of the hospital. Adult patients requiring long hospital stays, and their families, can take midday breaks or spend the night at the new Edmond J. Safra Family Lodge.

## BEYOND CLINICAL RESEARCH

The Hatfield Clinical Research Center is a hospital for both doing and studying clinical research. New tools for information technology are being developed to help clinical investigators write research protocols, monitor studies, and report study results to monitoring agencies such as the FDA, as required to protect patient research volunteers. New approaches to tracking a patient's care will reduce medical errors. Computers at every bedside will help patients learn about their diseases, making them better partners in research.

As a special home for conducting research, the Hatfield Clinical Research Center will continue to train tomorrow's clinical investigators. From the start, young researchers at the NIH Clinical Center have gone on to launch and lead clinical research programs all over the country. Through new distance teaching classrooms, the NIH Clinical Center can now export its clinical research training programs throughout the United States and the world.

The remarkable Mark O. Hatfield Clinical Research Center will be a national home for great minds dedicated to discovering new approaches to preventing disease and treating chronic disease. It will continue the Clinical Center's long tradition of being the last, best hope for patients. For many more patients, who will never visit the NIH, the Hatfield Clinical Research Center promises to be the incubator of science that will produce some of tomorrow's greatest advances in medicine.



Bright and airy labs provide an ideal environment for staff.



Wide doors in the intensive care unit fold open so that beds and large equipment can pass through easily.



PATIENTS,  
THE CLINICAL  
CENTER'S  
PARTNERS  
IN DISCOVERY

**BRIANNE SCHWANTES**

## OVERCOMING BRITTLE BONE DISEASE



**Lynn Gerber**, chief of rehabilitation medicine in the Clinical Center since 1977, has a mission: to add life to years, not just years to life. She and her colleagues have made an enormous difference with young patients with osteogenesis imperfecta (OI), a rare genetic disorder often called brittle bone disease. Because of an inborn error of synthesis of collagen (a component of connective tissue), children with OI don't grow normally. They are born with bones so fragile that a hiccup can cause them to break.

Brianne Schwantes, a 24-year-old from Wisconsin who has been coming to the Clinical Center since she was three months old, recalls, "Up until I was about six, I'd break the longest bones in my legs every 6 weeks or so." Wearing a plaster cast from her toes to armpits was awful—especially when she had chicken pox.

Some children with OI never become upright. Gerber and Joan Marini, a senior investigator in the National Institute of

Child Health and Human Development, wanted to know whether helping children to stand early in life would be helpful. Their randomized trial of long-leg bracing showed that braces from waist to toes are most useful when children are suffering from severe muscle weakness. Braces enable them to get up, possibly protect them from fracture, and allow them to be more active.

Brianne, the first patient with OI at the Clinical Center, loved the long-legged braces she wore in the study. "They were my best friends when I was growing up," she says. "They were with me everywhere—in the sandbox, on the playground. When I was 8 years old I carried a crescent wrench in my backpack to fix them. Nowadays kids who have OI are told that braces are one of the main ways that they can improve their condition and that was because of the research they did on me. I'm so proud of that." She no longer needs to wear the braces. Another recent study in rehab medicine showed strong links

"THEY HELPED ME TO WALK WHEN NOBODY THOUGHT IT WAS POSSIBLE, TO BE INDEPENDENT WHEN NOBODY THOUGHT IT WOULD HAPPEN."

between patients' temperaments, family support, and their physical progress. Brianne took an active part in her own rehabilitation and had as much say in what was going to happen as the doctors did. But she also gives the rehab department credit: "They helped me to walk when nobody thought it was possible, to be independent when nobody thought it would happen. Because I grew up saying 'I can achieve any goal I set for myself,' I'm living a life I never expected."

In the spring of 2003 Brianne Schwantes graduated from American University in Washington, D.C., and spent a year working in communications with a foundation that helps children with chronic and life-threatening diseases.

Brianne with Lynn Gerber, above, and as a Cherry Festival princess, below.



AL COHEN

## TAKING HIS VITAMINS



**Al Cohen** came from Illinois for a 2-week stay as a high school senior in 1959, left 12 years later, and still comes for follow-up visits. His body is such a beautiful experiment in nature that NIH investigators in various institutes—including Arthritis and Metabolic Diseases, Child Health and Human Development, and Heart, Lung, and Blood—have been studying Al for more than 40 years. At 63, he is still benefiting from, and contributing to, cutting-edge medical research.

In his first 6 months at the Clinical Center, Al was afraid to be seen in public, because of his tremor and equilibrium problems. Finally, he attended a movie in the auditorium in a wheelchair, saw patients worse off than he was, and stopped feeling sorry for himself. He took over the place, becoming “Peck’s bad boy.” Free in the evenings, he became a master bridge player and socialized. In the mornings he did tests. Al and a normal volunteer followed every diet the scientists could devise, including a quart

of carrot juice a day, a dozen eggs, and once, a pound of butter a day (with saltines). Researchers measured everything that went in and everything that came out.

His original symptoms were neurological, the indirect result

of his body producing no measurable levels of LDL in his blood (LDL being a low-density lipoprotein, the major cholesterol-carrying particle in human blood). But it took NIH a while to diagnose the problem. The complications from his unusual disease, abetalipoproteinemia,

arose because he produced too few lipoproteins to carry fat-soluble vitamins. Once Clinical Center staff figured out what the core problem was, they began giving him megadoses of vitamins A, E, and K. These vitamins have doubled his life expectancy.

## STUDYING PATIENTS WITH RARE DISORDERS

**Experiences with patients** at the Clinical Center often affect young physician-scientists long after they complete their training. As clinical fellows from 1968 to 1970, for example, Michael S. Brown and Joseph L. Goldstein were intrigued by several patients of Donald Frederickson, a Heart Institute researcher who later served as NIH director. Brown saw Al Cohen as a patient in the Arthritis Institute and with Goldstein saw a brother-sister pair with excessive levels of LDL in the Heart Institute. Their condition had produced severe atherosclerosis, so they were having heart attacks in childhood.

“Dr. Goldstein and I became fascinated with these patients,” says Michael Brown, “and we decided that we would figure out how genes control the LDL level in blood, and why some people have no LDL and others have enormous levels. These patients are very rare—they are only one in a

million—so the chance that we would ever see a patient like that again was extremely small. But we remembered those children, and we set up a research program to try to figure out how the body normally controls the level of cholesterol in the blood and why the level should have been so high in those children. If we hadn’t seen those patients at NIH, we would have never known about this illness and we would have never worked on the problem.”

In their later collaboration on studies of familial hypercholesterolemia at the University of Texas Southwestern Medical School, they made use of Al Cohen’s plasma and of cells from patients with familial hypercholesterolemia. In 1985 they won the Lasker Award and the Nobel Prize for their discovery of mechanisms regulating cholesterol metabolism.

DINORA HERNANDEZ

## TARGETING HER CANCER CELLS



**When Margarita Dinora Hernandez** began having stomach pains in April 2003, she assumed the cause was stress (she had plenty) or something she ate. The pains persisted, her normally high energy flagged, and a client for whom she cleaned house urged her to see a doctor. A hard-working Salvadorean immigrant—a healthy woman who took care of herself—Dinora had counted on getting through life without medical insurance. Concerned clients persuaded her to see a specialist. He recommended an endoscopy, which showed a possible ulcer or stomach cancer. A biopsy followed by a CT scan revealed that she had advanced lymphoma, a cancer of the circulatory system, which had spread beyond the system where it originated. Dinora was stunned.

Then another client told Dinora that the National Cancer Institute was running a clinical trial for treatment of diffuse large B-cell lymphoma, the kind she had. Within a week, Dinora was enrolled in the study.

Four decades earlier such a diagnosis would have been a death sentence. Neither surgery nor radiation—the only treatments known to be effective against cancer in those days—worked in a cancer that spread through the lymph system. And the cancer researchers who had pioneered in combination chemotherapy in the Clinical Center in the 1960s had been vilified as “poison doctors,” for offering fatally ill patients a combination of toxins that produced terrible side effects. But one of combination chemo’s first successes had been cures in patients with non-Hodgkins lymphoma, and Dinora’s lymphoma, though aggressive, usually responded well to chemotherapy.

Luckily for Dinora, knowledge of cancer has deepened and cancer researchers today can target a treatment to a specific type of cancer. They can identify, for example, several distinct types of B-cell lymphoma, whose tumor cells might look similar but whose “molecular engines” work differently—which is why one lymphoma patient might

“FOR THE FIRST TIME IN MY LIFE I SAW DOCTORS WHO ACTUALLY LISTENED TO ME AND TOOK THE TIME TO ANSWER ALL MY QUESTIONS—AND I HAD A LOT OF THEM.”

respond differently to one treatment than another.

Wyndham Wilson, the doctor in charge of Dinora’s protocol, explained that the regimen prescribed for Dinora represents a new generation of treatment for aggressive B-cell lymphomas. Dinora went through 6 months of intensive combination chemotherapy—most of it on an outpatient basis, with occasional stays in the Clinical Center hospital to monitor such procedures as the initial administration of monoclonal antibodies. Three months after Dinora’s final treatment, scans showed her body to be clear of cancer.

She is a textbook case of how, given enough information, someone who is seriously ill can get access to some of the finest, most sophisticated medical care in the country—if she qualifies for an active research protocol.

“I thank God for this miracle,” says Dinora. “For the first time in my life I saw doctors who actually listened to me and took the time to answer all my questions—and I had a lot of them. I trust the NIH. When other cancer patients ask me about it, whether they have insurance or not, I tell them that they will get the best possible care there.”

MAUREEN SCHULTZ

## WARDING OFF INFECTIONS



**Most of us coexist** with billions of bacteria daily and are exposed to millions of fungal spores a year that rarely cause problems. A rare genetic condition called Job's syndrome makes 34-year-old Maureen Schultz highly susceptible to bacterial infections (especially boils) and fungal infections on her skin and in her lungs. She is also susceptible to problems with her teeth, sinuses, and bones—including scoliosis and osteoporosis. Maureen can break a rib fairly easily just swinging a golf club, and she's lucky—those with more severe bone damage can break a leg just carrying the groceries. Like Job, patients with this disease battle one problem after another.

Job's syndrome is not easy to diagnose, but Maureen knew she had it from the age of 3, thanks to an informed immunologist in Cleveland, Ohio. Maureen had all the cardinal signs of the disease, losing part of one lung to surgery when an abscess developed there. Through high school and college she did pretty well,

but after college she developed one infection she could not kick. Tired of feeling unwell, in 1994 she got in touch with physician-scientists John Gallin, who is now director of the NIH Clinical Center, and Steve Holland at the National Institute of Allergies and Infectious Diseases. Holland invited her to participate in first one, then several, studies of the disease.

"Job's syndrome is an absolutely remarkable disease," says Holland. He studies patients who get bacterial or fungal infections spontaneously—to understand why they do, how to treat them, and from that to extrapolate fundamental principles. "This is work that has gone on in one shape or another here for decades," he says. "What makes the NIAID approach to infectious disease distinct is the focus on host defense: If exposure to these organisms is relatively broad but disease is relatively rare, the problem must be something about the host, or the environment in which the host is being exposed."

"WITHOUT THE NIH I DON'T KNOW THAT I WOULD BE HERE TODAY."

She has been studied and treated by Holland in collaboration with experts in other institutes, including genetics, dermatology, neurology, dentistry, and ear, nose and throat. In July, Clinical Center surgeons successfully removed a fungus from her sinuses. This August, while on vacation in the West, she began coughing up blood. At 3 a.m. she paged Vickey Anderson, the

nurse practitioner who runs Holland's clinics, so Anderson could advise the doctors in an Idaho emergency room about what to look for and what medications to give her, to stabilize her enough to get her to Bethesda.

"Without the NIH I don't know that I would be here today," says Maureen.

Built long and low, the new hospital contains 4.6 miles of corridors.



(c) Alan Karchmer

CARMEN SIMPSON

## PREMATURE OVARIAN FAILURE



**“Imagine how insane** you feel when you seem to be going through menopause at the age of 22—especially when you go to professionals and they don’t believe you,” says Carmen Simpson, who was in the military when she experienced her first symptoms. “I knew there was something really wrong, but I was misdiagnosed for years. It got so bad that my doctors sent me to a psychiatrist. They thought I was a hypochondriac.” Finally a blood test revealed that she had Premature Ovarian Failure, or POF. Her doctors referred her to the NIH, where physician Larry Nelson told her she was not alone—more than half of the women with POF see three different doctors before somebody does the crucial blood test.

Nearly 250,000 American women suffer from the rare disease’s symptoms—absent or irregular periods, hot flashes, infertility, irritability, and poor concentration. Nelson, who has been studying POF at the National Institute of Child Health and Human

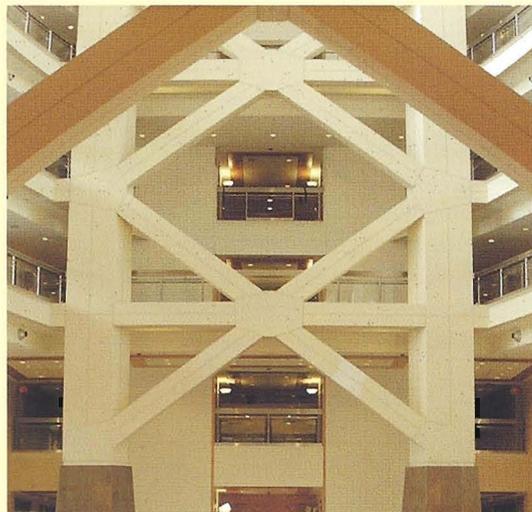
Development for 16 years, has been working to better understand the type of ovarian failure that occurs when the immune system of young women attacks their egg-producing machinery. He and his colleagues are studying a similar problem in mice and are trying to find the mechanism in humans. They know that the disorder causes the ovaries to prematurely stop producing eggs, cutting off the hormones needed for bone strength and to ward off heart disease. And they have learned that women with POF should be screened with a simple test for Addison’s disease because they are 300 times more likely than others to develop the potentially fatal adrenal insufficiency.

Early diagnosis and treatment are vital, says Nelson. “When dealing with osteoporosis, an ounce of prevention is worth a pound of cure.”

Coming to NIH, having the best doctors, having tests done, finding out what happens with the syndrome, not having to battle anybody, was a great

relief, says Carmen. “Somebody was actually listening, believed me, and had a name for the problem and a way to treat it that really made me feel better.” Since her diagnosis, Carmen and her husband have adopted three children, Carmen bore one child conceived through in

vitro fertilization with a donor egg, and they foster-parent children for the state of Ohio. Hormone replacement therapy has alleviated her symptoms. And by participating in research she knows she is helping other young women with POF get earlier, better treatment.



View from the science court. Above right: Carmen Simpson and her daughter Katie

“SOMEBODY WAS ACTUALLY LISTENING, BELIEVED ME, AND HAD A NAME FOR THE PROBLEM AND A WAY TO TREAT IT THAT REALLY MADE ME FEEL BETTER.”

## DIANE DICKINSON

# BEATING THE ODDS



**Only one in a million** Americans has the genetic disorder called homozygous familial hypercholesterolemia (FH) type IIa, which causes too much LDL (the “bad” cholesterol) to accumulate in their bodies. By all counts, Diane Dickinson, who is one of them, should never have made it this far. In patients like her, LDL levels are characteristically between 600 and 800 instead of the recommended level, 130. “Thanks to the attention I’ve received at NIH, I’ve had the chance to raise a family and have grandchildren,” she says.

Diagnosed when she was 2, she is one of the lucky pioneers who blazed a trail from research to reality—a trail that’s led her through 27 years of varying treatments, including drugs and blood-cleansing techniques. At 66, she’s the longest living patient with FH. Since 1977, she has come to the Clinical Center every 2 weeks.

“She’s unique,” said Robert Shamburek, a physician researcher with the National Heart, Lung, and Blood

Institute, who spent a decade following her—the most recent of a series of researchers to do so. “When she came to us in 1976, she had perhaps 6 months to live. She was picked up under one of our protocols, and as so often happens an investigational process leads to a number of proven treatments. You could say that Mrs. Dickinson is a milestone in modern cholesterol treatment.”

The focus on her rare condition has led to knowledge and treatments that benefit large numbers of Americans at risk from high cholesterol. One achievement is drugs called statins, which increase the liver’s ability to metabolize LDL. Others include plasma exchange or plasma clearance, and more recently, LDL apheresis, which physically removes LDL from the circulating blood.

“I am so very grateful to everyone at the NIH,” says Diane (shown above, with her husband Neil). “Without them I wouldn’t survive.”

## BILL HUTCHINSON

# HIS BLOOD ADVANCED HEPATITIS RESEARCH

**Losing consciousness** on a mountain climb in the mid-1970s led William E. Hutchinson indirectly to the NIH Clinical Center, where in the course of open-heart surgery he was transfused with 17 units of blood. As he recuperated at home, an alert nurse visiting from the NIH detected the first signs of acute hepatitis.

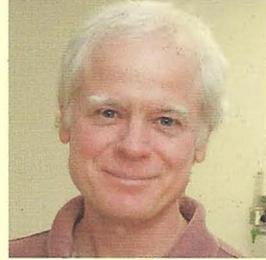
Harvey Alter, a physician-scientist in transfusion medicine, immediately collected 500 ml (about a pint) of Bill’s plasma and then, 14 days later, another 500 ml, for his enormous serum repository—a gold mine for researchers. Bill’s sample, greatly diluted, was shipped to researchers all over the world, becoming perhaps the most widely shared and deeply studied sample in hepatitis research. With Alter’s help, Bob Purcell of the National Institute of Allergy and Infectious Diseases showed that 1 ml of a 1-to-a-million dilution of Bill’s blood was enough to infect a chimpanzee—proving that Bill had a virus, a transmissible agent.

Meanwhile, Alter and his many collaborators studied Bill’s pattern of infection and recovery. After an attack of acute hepatitis C (“I’ve never been sicker in my life,” he says), Bill developed a mild, mild form of chronic hepatitis, persistent but asymptomatic.

Bill is no longer climbing mountains, but in April 2004—at a lecture in the Clinical Center—he received an award for his 27 years as an invaluable patient volunteer. The citation read, “For his dedication to clinical research, his contributions to science and his important role in the understanding and discovery of the hepatitis C virus.”

Alter received a Lasker Award for his work and was elected to the National Academy of Sciences. He has been widely recognized for reducing risk of blood transfusion-associated hepatitis from 30 percent in 1970 to virtually zero in 2000.

GOING THE DISTANCE



**A cross country skier** for 30 years, 46-year-old Richard “Sam” Breidenbach had always wanted to enter the American Birkebeiner, an arduous 51-kilometer cross country ski race that drew 6,000 skiers this year. Cancer inspired him.

In September 1999, a Madison, Wisconsin, doctor removed a mole on his back that had developed into melanoma, a skin cancer of the worst kind. Two and a half years later it had spread to his left hip and he was treated with interferon, but in March 2003 melanoma cells were found in the lymph nodes in his groin. His skiing buddy, Pete Daly, who was also fighting melanoma, encouraged him to go to the NIH, where Pete was taking part in a cancer vaccine trial. Sam became a research patient of Steven A. Rosenberg, a surgeon-immunologist with the National Cancer Institute who has pioneered in biological approaches to fighting melanoma and renal cell cancer. Studying melanomas he had removed in surgery, in the mid-1980s Rosenberg had found

what looked like immune cells. He wondered if they were there for a reason—and if the body’s immune system could be better harnessed to fight the many cancers that surgery, radiation, and chemotherapy fail to eliminate. Working first on cultures in the laboratory and then on mouse models, he and his research team developed and improved an approach to immune therapy, at each stage establishing the “proof of principle” needed before they could undertake research on humans. This often took years. They showed first on a mouse model and then on human patients the effects of interleukin 2, or IL-2, a natural immune booster. The response rate increased to 15 percent—a notable improvement, but not good enough. Next Rosenberg’s lab took tumor-infiltrating lymphocytes (or TIL cells, a form of immune cell) from a tumor and spent 5 years cloning the genes that encode cancer antigens and learning how to generate immune cells called T cells that could recognize them. In other words, they would take the TIL

cells out of the patients, expand them, rev them up, and give them back to the patient along with IL-2. They tested this model successfully on patients with far-advanced cases of metastatic melanoma, on whom all standard treatment options had failed.

By the time Sam Breidenbach came along, Rosenberg’s team had added a third crucial step to the therapy: By wiping out the immune system before administering the IL-2 and jazzed-up TIL cells, Rosenberg had increased the response rate for metastatic melanoma patients treated with TIL cells to 50 percent. Many patients still died, but the treatment produced some amazing turnarounds.

Rosenberg tried two or three other approaches to fighting Sam’s melanoma in an effort to buy Sam some time, but his melanoma grew so fast over a 28-day period that by November it had replaced half of his liver and invaded both lungs. Rosenberg’s lab was trying to grow Sam’s immune cells

in culture, but Sam’s future looked short and bleak.

Sam, who was trying to sustain a business restoring and renovating houses, was still weighing his options when the cells finally began to respond—aggressively. On Thanksgiving, Sam and his family were preparing to leave for dinner with relatives when the phone rang. “Your cells are jumping out of the petri dish,” Rosenberg told Sam, with barely concealed excitement. “You have to come in. We want you here Monday.”

In early December Sam went through 7 days of chemo to wipe out his immune system, so it wouldn’t compete with the new jazzed-up lab-grown immune cells. “On the seventh day, they injected me with my new cells—half of them through a catheter into the main artery into my liver and the other half through the port they’d used to administer chemo.” The treatment felt rough to Sam—especially three days of IL-2, which induced nausea and gave him bizarre dreams.

REBECCA MCDONALD

## SURVIVING A DEEP-VEIN BLOOD CLOT



Pete, visiting to cheer him up, proposed that they sign up for the Birkebeiner, a tough race even for skiers in good condition. Life itself was tenuous and Sam felt so weak that just getting out of bed was an accomplishment.

A week and a half after Sam got home from Bethesda, his strength returned almost full force. He began skiing a little. Scans done at the Clinical Center a month later showed that 80 percent of his tumors were gone. A month or two later the cancer was gone completely.

And so, 71 days after beginning treatment for a melanoma that had replaced nearly half his liver, Sam and his buddy Pete took on the Birkebeiner. February 21 was a beautiful day for skiing. At about 30 kilometers they both considered getting on a bus and cutting their race short, but they decided to finish “just to have fun and be with one another.” It took them 7 hours, 13 minutes, and 57 seconds to ski 31.7 miles, but they went the distance.

**Three weeks after** giving birth to her third child, Jordan, 35-year-old Rebecca McDonald felt a pain in her calf, which quickly moved up into her hip. A doctor in the local clinic diagnosed a blood clot, and put her on a strong blood thinner. After 5 days in a Boise, Idaho, hospital, she was sent home and told to stay on the blood thinner, keep her foot elevated, and wear compression hose.

The treatment didn't work. One leg was twice the size of the other, she couldn't go up and down the stairs, and pain pills were like TicTacs. On the Internet she found Clinical Center doctors Richard Chang and McDonald Horne, who were recruiting patients for a clinical trial for treatment of acute deep vein thrombosis, or DVT, a blood clot in the lower part of the body.

Anticoagulation drugs are effective in most of the nearly 200,000 people a year who suffer from DVT, says Chang, a radiologist who does special procedures in imaging sciences.

“Anticoagulation is extremely effective in preventing pulmonary embolisms and fairly good at preventing DVT in the first place. Where it fails is in clearing the clot in the leg and preserving the function of the veins in the legs.”

Anticoagulation didn't work for Rebecca, whose DVT developed during pregnancy, as her heavy uterus pressed against veins in her pelvis, narrowing the channel and allowing blood to clot. DVT can also be brought on by cancer, surgery, birth control pills, hormone replacement, and long airplane flights when passengers don't get up and move around. If the clot moves to the lungs, it can kill a person. According to Horne, a senior clinical investigator in hematology in the Clinical Center's Department of Laboratory Medicine, if a patient takes anticoagulants his clot will dissolve within weeks or months but it is likely to leave behind damage to the vein, especially to the delicate valves within veins that allow blood to flow up the leg.

In Rebecca's protocol, Chang and Horne were testing rtPA, a “recombinant” enzyme synthesized in the lab but identical to a natural protein that dissolves clots. The drug, often used to treat heart attacks, sticks directly to clots, allowing prolonged enzymatic action that restores a channel for blood to flow again, within days, if not hours. Using a catheter, Dr. Chang sprayed the enzyme directly into Rebecca's clot, which extended from her calf into her pelvic veins. He sprayed the clot, advanced the catheter, sprayed the clot, advanced the catheter, and so on. Rebecca's clot was so severe that the treatment took 16 hours over two days. But it worked. Within 3 days, Rebecca—shown here with three-month-old Jordan and his father, Robert—was walking. Within a week, she was back home taking care of her growing family. Within six weeks she was running regularly.

## CLENTON WINFORD II

# ANOTHER TURN AT BAT

**Patients travel** many different paths—rarely direct—to arrive at the Clinical Center. Clenton Winford, a good-looking Texan who travels with a gentle black seeing-eye dog named Herman Winford I, first walked through Building 10's entrance in 1988, when he was 25. The Clinical Center had just begun to study families with a rare and complex hereditary condition called von Hippel-Lindau syndrome. Clenton, whose father was diagnosed with VHL the year Clenton was born, had volunteered for the observational study. His father also participated in the study.

VHL is a multi-system disorder in which, among other things, small blood vessels called capillaries knot together to form benign growths (“angiomas”) all over the body—typically starting in adolescence or early adulthood. A genetic condition, VHL increases the odds that a person will have one or more tumors (of various types) of the eye, ear, brain, spinal cord, kidneys, pancreas, and adrenal glands.

The disorder he inherited from his father brought tumors all over his body, and retinal tumors that made him blind—one eye at a time, at 11 and 22. A neurosurgeon in Dallas who operated on him in 1983, after following him for 5 years, said there was nothing more he could do. In 1988, Clenton came to the NIH to participate in an observational study he heard about from a cousin. He had no guarantee of being offered treatment, but he was so sick when he arrived that the research team decided it had to do more than observe him.

Since then he has come to Bethesda many times for the surgical removal of tumors and cysts from his brain, spinal cord, pancreas, adrenal gland, and endolymphatic sac—plus countless sessions of CT scans and other tests to chart the progression of his disease. (His father, incidentally, although he underwent surgery for four brain tumors, was never blind, and died of a heart attack at 68.)

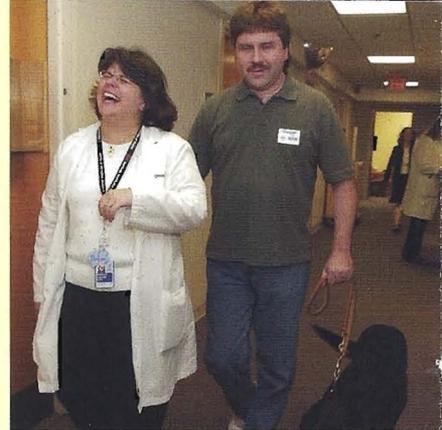
Because VHL is so complex a syndrome, Clenton has participated in protocols in more than one institute. Marston Linehan (NCI) and his colleagues spent nearly 10 years studying VHL families to identify the VHL gene, the sixth human cancer gene identified—the gene for the common kind of clear cell kidney cancer. The NIH Kidney Cancer working group—over 80 people from 20 labs and branches from 7 different NIH institutes and centers—has identified 3 different human cancer genes and discovered 2 new diseases. What has been learned from patients like Clenton benefits thousands of patients worldwide.

“Here at the Clinical Center we’re all kind of learning things together,” says Clenton. “There is this sense of community and solidarity. It’s a team environment, you might say, and we are part of the team.”

“If I remember the story of Pandora’s box correctly,” says Clenton, “the only thing left in the box was hope. Hope’s a

wonderful thing for patients like me, who consider the Clinical Center to be a place of last resort. When I came here, my doctor had dismissed me; I didn’t have anywhere else to turn. I was dreadfully ill and had no idea what I should do. I came here purely for research, and I was diagnosed, but then I was offered treatment. Those of us who have been dismissed elsewhere, and have been told there is nothing else to be done, by coming here, we have one more chance to look at our problems, maybe another roll of the dice—another turn at bat, if you will.”

Clenton—shown here with Angela Kokkinis, a clinic nurse for Surgical Neurology—is doing very well. In 2003, he was awarded a Ph.D. in political economy from the University of Texas at Dallas, and he and his wife, Betty Ann Shory, are organizing a new birthing center in Texas.



WANDA WHITE

## TOLERATING A TRANSPLANT

**Wanda White's struggle** to survive began 3 years ago, when complications from treatments for rheumatoid arthritis led to a condition that attacked her kidneys. Wanda had enrolled in a clinical study done by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The protocol helped stabilize the arthritis, but the kidney damage was so severe that she still had to undergo 9 hours of dialysis nightly just to stay alive. She needed a kidney transplant.

No good donor matches were found among her friends and family members. A stranger, Tammie Bell, volunteered to be tested and was found to be a match. Tammie's daughter, Jessie, had died the year before, when she was only 21. She felt the best way to honor Jessie was to "honor, celebrate, and make life possible for others."

Leading the surgical team were three physicians from National Institute of Diabetes and Digestive and Kidney Diseases: Allan D. Kirk, chief of the trans-

plant branch, transplant surgeon Douglas A. Hale, and nephrologist Roslyn B. Mannon, medical director of transplantation.

Also on the team was surgeon John Swanson, chief of the organ transplant service and chief of the Renal-Pancreas Transplantation Program at Walter Reed Army Medical Center's surgery department.

Transplant patients trade a disease for a condition, says Kirk. The immunosuppressive medications the patients take to prevent their body's rejection of the transplanted organ exact a significant toll in infectious, malignant, and physiological side effects. Conventional wisdom holds that since the immune system causes rejection, it must be suppressed to prevent loss of the grafted organ. Kirk and his study team contend that the immune system is an elegant and tightly regulated defensive network that provides measured responses; it can down-regulate as well as augment responses to specific threats to stability in the body's system. Kirk and his colleagues are studying ways to

SHE FELT THE BEST WAY TO HONOR JESSIE WAS TO "HONOR, CELEBRATE, AND MAKE LIFE POSSIBLE FOR OTHERS.

encourage transplant tolerance—when the immune response favors acceptance rather than rejection of an organ.

By customizing Wanda's immune therapy to suit the therapy required for her arthritis, researchers were greatly able to reduce her immunosuppression. She is on about 80 percent less immunosuppression than she would have been on if she had gone elsewhere. Most transplant patients in this country are given steroids; she was given none. Most have to take three drugs every day and Wanda has to take only one. She is completely off dialysis now and Kirk expects her to live a long healthy life with Tammie's kidney.

This is good news for transplant candidates everywhere. "This is the best place in the world to

do science," says Kirk. "The Clinical Center is a resource that is incomparable in this country or anywhere in the world."

Wanda White, left, kept alive by Tammie Bell's kidney.



## PERFECT TIMING

**Brian Berman received** a death sentence at the age of 4.

He had had symptoms—bruising, nosebleeds, a low platelet count, bone pain, and an enlarged liver and spleen—since early childhood, and now his belly looked like a pregnant woman's. He could no longer climb the stairs of the family's Maryland home when doctors told his parents he had Gaucher disease, a crippling killer for which there was no known treatment or cure. Enjoy him while you can, they said.

This was a prospect Brian's parents simply could not accept. They scoured the globe for a scientist who was doing cutting-edge research on Gaucher disease and found him in their own backyard—and at just the right moment.

Physician-scientist Roscoe Brady had been stalking a treatment for Gaucher disease in his lab at the National Institute of Neurological Disorders and Stroke since 1954. Brady's pioneering efforts had identified

the metabolic defect underlying the inherited disorder—a missing enzyme called glucocerebrosidase, which is essential for clearing a fatty lipid substance from the body's cells. But the goal of creating a purified enzyme suitable for human use had eluded him time and time again—until 1984.

That year, Brady had finally discovered the magic formula. In the best tradition of the Clinical Center—science that moves from laboratory bench to bedside and back again—he was ready to test it in patients. He invited the Bermans to let Brian participate in the study.

Brian was the first patient in the world to be successfully treated with enzyme replacement therapy for Gaucher disease. The results were astonishing. His bleeding episodes stopped, his hemoglobin rebounded, and over time his enormous liver and spleen shrank to near-normal size. Despite occasional glitches in the experimental treatment and countless needles, punctures, scans, and radioactive



One of two courtyards that provide respite space.

tests, by and large he has led a normal life, marking many milestones he might have missed had he gone untreated: a bar mitzvah, a college education, a marriage, a job, and fatherhood. Still taking his enzyme infusions, he has no sign of bone, spleen, or liver damage or involvement. Brady, who still follows his case, was one of the most delighted guests at his wedding. In 1983 Brady shared a Lasker

Award for his work on Gaucher and three other metabolic diseases: Fabry disease, Tay-Sachs disease, and Niemann-Pick disease. In 1991, after a quarter century of continuous development at NIH, Brady's enzyme replacement therapy received FDA approval. It is now the standard treatment for patients with Gaucher disease.

LAURA KRUMMENACKER

## SEARCHING FOR ANSWERS

**Many researchers have** followed Brady's lead. Approaches to treatment being developed for storage disorders include enzyme therapy, protein therapy, and gene therapy. Bill Gahl (formerly with Child Development and now with the National Human Genome Research Institute) has saved many children from early death with his work on a rare disorder called cystinosis, a lysosomal storage disorder for which he has helped develop effective small-molecule therapy.

In 1988, when Laura Krummenacker was 2 years old, she landed in the intensive care unit of a New York hospital, severely dehydrated from a bout of flu. For a week the doctors tested and poked, but even when she seemed better, her lab results remained frighteningly out of kilter. Finally the puzzled doctors called in a pediatric kidney specialist who had recently attended one of Gahl's lectures—a lecture that described Laura's problem to a T.

Gahl's subject was an inherited disease called cystinosis. It is

extremely rare—just 400 people in the United States have it—but Gahl, a geneticist, biochemist, and pediatrician, had made it his life's work. In fact, he had discovered its cause: a faulty transporter in the lysosome. Lysosomes, tiny compartments within the cells, are responsible for breaking large molecules down into smaller ones so they can be transported out of the lysosome and recycled. But in cystinosis, the transporter for one of the molecules, cystine, doesn't function, so cystine gets trapped inside the cell, where it turns into crystals, slowing growth, damaging the eyes and kidneys, and eventually affecting organs all over the body.

The Krummenackers were invited to bring Laura to the Clinical Center for testing, and Laura was accepted into a protocol. On their next visit to the Clinical Center—Laura had to be monitored every 4 months—Marybeth, Laura's mom, discovered the cystinosis family conference, an annual event at which they learned about the latest research and met other

families struggling with the disease. Both Laura and Marybeth made fast friends, and the parents eventually founded a formal support group, the Cystinosis Research Network.

Laura, who returns to the Clinical Center every 2 years, belongs to the first generation of cystinosis patients to receive,

from a young age, the drug therapy offered through the Clinical Center. Nobody knows what quality of life they will face, but research at the Clinical Center continues to address their problems, and Gahl dreams of a newborn screening test that will enable patients to start drug therapy early enough to avoid kidney damage entirely.



Scientists study patient data in lab offices.

## A PROTOCOL OF HER OWN

**When Ashley Appell** was born, the pediatrician told her mother, Donna, that Ashley was a “tow-head,” which Donna heard as “toe-head.” She cried, thinking it was a major birth defect, until a nurse calmly explained that “tow-head” meant blonde. On the 2-week well-baby visit, however, Donna learned that Ashley had albinism. In addition to having an abnormally pale complexion, Ashley had vision so poor she was legally blind. When Ashley began to walk, Donna also noticed significant bruising on her little shins.

Donna took the toddler to several doctors, who disregarded her worries or could not come to any conclusions. Then, in a pamphlet on albinism, Donna eyed a paragraph about a rare type of albinism. Desperate to find help for Ashley, Donna called the pamphlet’s authors, who suggested she send a test-tube of Ashley’s blood so they could test it for Hermansky-Pudlak syndrome (HPS), a type of albinism that comes with a platelet bleeding disorder, blind-

ness, and other symptoms, the most severe of which could bring early death. They confirmed the diagnosis.

At 2, Ashley was one of only 23 people in the United States known to have the disease, which often led to death in young adulthood. Donna was desperate for information: “I wanted to find those 23 people. I wanted to know what research was going on.”

She could find none. She knew she was the only one who could help her daughter and set about doing so. She founded the Hermansky-Pudlak Syndrome Network, collected the names of everyone she could find who had the disease, got her organization listed in directories, and started a website. She kept her ears open and at meetings of families with sick children she kept hearing about the NIH. One night at a local support group of parents of children with chronic diseases she heard Marybeth Krummenacker talk about her daughter’s cystinosis.

“Don’t leave,” Donna told Marybeth. “I have to talk to you.” She grilled Marybeth about the NIH. It occurred to her that she, too, might be able to get his help. She soon had primary investigator Bill Gahl on the phone. She was not only Ashley’s mother, she explained, but also the founder of an organization of patients “who could definitely use research.”

In September 1993, he invited Ashley to visit the Clinical Center for a preliminary investigation. She was the index case—the first patient with HPS—and for the next 2 years she and Donna came several times for a week’s stay, as Gahl and his colleagues were figuring

out whether or not to research the disease. Donna was on the edge of her seat, hopeful, and jealous of the families who already had NIH research. The great day came in 1995. “Dr. Gahl met me in the children’s ward and said, ‘Mrs. Appell, I have the last signature on our protocol.’” Donna burst into tears—then called a local Italian restaurant to cater lunch for the entire floor. “I felt like Cinderella, and I just got the glass slipper. We weren’t famous and we had no money and we were just one stupid little rare disease that not a lot of people had in the world, and we just got research at the National Institutes of Health. It could only happen in America.”

Playful colors mark the pediatric nurses’ stations.



## TEARRA CHANTAE TYLER DANIELS

### FINDING FRIENDS AT NIH



**Tearra Daniels was diagnosed** with HIV when she was three and a half months old. Two years later, she became listless and developed a fever, rash, and diarrhea. The CD4 T cell counts that indicate a healthy immune system began falling, and her parents, Maryann and Doyle, applied for treatment under a National Cancer Institute protocol. NCI's Phil Pizzo had launched protocols for pediatric HIV and AIDS patients in the late 1980s, believing interdisciplinary approaches to be essential for advancing treatment.

In 1996, when Maryann brought Tearra to the Clinical Center, she was so sick and her counts had fallen so low that she was officially classified as having AIDS. A new class of drugs, protease inhibitors, had become available and the only place young HIV patients could get them was NIH, under a protocol run first by Pizzo and then by Lauren Wood. "Within two to three weeks after she was able to start on the drugs," says Maryann, "she was back to her old self. Dr. Wood has been

awesome." Tearra would also enroll in a study of interleukin-2's effects on the immune system.

Maryann had left her job as a nurse in March, before Tearra was born in June. "The nurses there knew I was a foster mom," she recalls, "and knew I loved babies. They said, 'Would you like to have this baby for five days?'" That's how Tearra came to live with them. Maryann had actually counseled Tearra's mother after her diagnosis with AIDS.

Twenty years ago, after having 4 children of their own, Maryann and Doyle had decided to make room in their baby-loving home for foster children and then, at the suggestion of the local Department of Mental Health, became an official group home for children with severe medical disabilities—children who are medically fragile or profoundly retarded. Tearra learned to walk pulling herself up on the wheelchairs of some of those children, who are like siblings to her. While Doyle cared for the

children at home in the Missouri Ozarks, Maryann brought Tearra (whom they eventually adopted) to Bethesda. At home, almost no one knew Tearra was HIV positive. "Probably my greatest blessing here was having other moms to talk to, in the clinic and at the Children's Inn. She was so sick when we came here that I had to carry her, and I was scared and sad. I remember going into the refrigerator in the Children's Inn that first night, where the medicines were kept, just hoping that I would find one other family with HIV, and there was AZT, so I knew there was one. Then I went into the main dining area and there were two tables of families talking out loud about their children and AZT and HIV and I sat down and started talking with them. It was just wonderful.

"And I think it's good for Tearra. I have pictures of her and all the girls waiting for their CT scans, or in the hospital together getting IL-2. At least here everybody's going through the same thing. The NIH and

the Children's Inn became a second home to us."

"It's a lot of fun," says Tearra, who tries to arrange her visits so she's here at the same time as her friends. When children back home ask her why she goes to Washington so often, she tells them, "To see my friends."

Tearra was on the same protocol and in good health for 6 years, until January 2002, when her T-cell count dropped a little and her viral load went up. It was time to change drugs. The NCI changed her medications and over the next month she gained 2 inches and 10 to 20 pounds. "Never was her viral load undetectable until 2 years ago, and now it's stayed undetectable," says Maryann. "I came here hoping but, my goodness, my hopes were way more than realized."

## MATT HARPER

# AN UNUSUAL EAGLE SCOUT



**Mike and Diana Harper** loved Matt, but they knew something wasn't quite right with their son. Enrolled in "noncategorical" special education classes, Matt was tested frequently; his parents were told he had an IQ between 45 and 55 and would never function above the level of a 10-year-old. They searched for a diagnosis, but Matt didn't fit neatly into categories. By the time he was 11 his anxiety levels were so high that it was hard to tell who Matt was or might become.

Mike and Diana were considering one hospital's offer to provide a 30-day evaluation (at \$1000 a day) when Diana, looking for a special summer program, met a woman whose son had similar problems and was enrolled in a National Institute of Mental Health study of developmental problems in children. NIMH investigator Judith Rapoport was testing clozapine on children with schizophrenia. The family was interviewed and Matt was accepted—none too soon. For 30 days and nights his anxiety had kept him awake. All

three of them were exhausted. "The NIH was really our last hope," says Mike. "Matt, God bless him, didn't want to be this way. But we thought that if the NIH experience didn't help us, we might have to institutionalize him."

Matt lived in the Clinical Center from Labor Day 1990 until the end of April 1991. After he was weaned from the medications he had been taking, to establish a baseline, and when he'd turned 12, they started him on clozapine. The medication reduced Matt's anxiety, so it was easier for him to focus and to develop a relationship with the people around him, because he wasn't mentally off in space. His hallucinations and sensitivity to noise went away. He became more thoughtful and perceptive, and began learning to plan and think ahead.

"He has made remarkable progress just as a result of the care he got in that 8-month period," says Mike. Among other things, at 22 he finished his school's vocational training

program. He took on supervised jobs—and loved working.

One night at the dinner table, years before, Matt had said, "Dad, I would really like to have friends." Matt had trouble socializing, so his parents tried involving him in activities like tae kwon do, T-ball, and church. But it was the Scouts Matt finally took to. After he left the Clinical Center, he threw himself into earning a series of merit badges, which helped him learn two important things: how to interact with others and how to provide for himself. Troop 1970 was especially good at helping boys with medical problems, and Matt flourished. Matt spent 8 weeks away from home at a Scout camp, where the other boys cut him no slack, and his social skills improved. His third summer he was hired as quartermaster in charge of camp supplies. There was no need to log in shovels and other equipment because Matt, whose camp nickname was "Numbers," kept everything in his head. A savant like the Dustin Hoffman character in

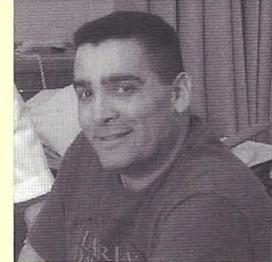
the movie *Rainman*, he'll tell you the day of the week if you tell him your birth date.

He also developed empathy. When he learned that a boy who rode his school bus lived in a homeless shelter in Reston, Virginia, he organized the troop, which collected nearly 2,000 pounds of such essentials as diapers, socks, towels, and toothpaste. When the Fairfax County Board of Supervisors presented Matt with an award for his project to help the needy, Mike Harper told the Council, "If you wondered if the money you're spending on special education is doing any good, here's your answer."

Matt became an Eagle Scout.

DAN MAGRINO

## SEARCHING FOR A DIAGNOSIS



**Dan Magrino's layoff** in 2002 was a godsend. After three years laying undersea fiber-optic cable, the 37-year-old scuba diver and merchant marine officer from New Jersey wasn't feeling well, and he was worried about his recently acquired "pregnancy" belly—straight out, like a basketball. For years he had maintained a 34-inch waist and a weight of 175 pounds on his 5-foot-10-inch frame. Lately, no matter how much he dieted or exercised, he kept adding pounds.

Both his primary physician in New Jersey and an endocrinologist ascribed the extra weight to creeping middle age. His wife Sharon made the diagnosis. "I think you might have Cushing's disease," she said. Rolling his eyes, Dan asked where she'd earned her medical degree. When she produced a printout from a medical website, he admitted that many of the symptoms fit. A nephrologist echoed Sharon's words and sent him back to the skeptical endocrinologist, who reluctantly sent

him for a test. The results surprised her.

In Cushing's disease and syndrome, a rare and complicated glandular disorder, the complex regulating mechanism for cortisol goes awry, and the body produces too much of the "fight or flight" hormone, which the adrenal glands secrete to enable us to respond to threat. The cause of Cushing's is usually a tumor in the pituitary gland (in the brain) or an abnormality in the adrenal gland (near the kidney); in the remaining cases there is an ectopic ("out of place") tumor with the odd capacity to stimulate cortisol production. Ectopic tumors can grow anywhere, so finding one can involve a search of the entire body.

A CT scan of his abdominal region revealed a mass near his adrenal gland. He awoke from surgery to find that it was harmless and unrelated to his symptoms—but the surgeon had removed his right adrenal gland anyway, and his cortisol was as high as ever. The doctor

sent Dan's records to the National Institutes of Health, "the definitive experts on Cushing's," but didn't follow up, so Dan took matters into his own hands. Dialing an 800 number he found on the Internet, he was soon talking with Lynnette Nieman, a physician-scientist with the National Institute of Child Health and Human Development who had seen as many Cushing's patients as anyone in the world.

She started her investigation a few days later, and ultimately the findings were clear: Dan had Cushing's, originating in a pituitary tumor. Within weeks, Ed Oldfield, a skilled neurosurgeon with the National Institute of Neurological Disorders and Stroke, had operated and removed it.

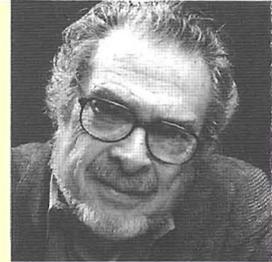
Nieman can't guarantee that he's cured (about 12 percent of patients have a recurrence), and it will take up to 18 months for his adrenal and pituitary glands to work again. But he has lost 35 pounds and is feeling more like himself. His determination to get to the root of his problem paid off. "I'm proud that, knowing my own body, I pursued an answer and called the NIH myself," he says. "There is no place like it. This is the best of America. I'm proud to see my tax dollars at work in this way."

Space for informal gatherings supports both morale and research.



## LEON FLEISHER

# HITTING THE IVORIES WITH BOTH HANDS



**“One of the most** gifted of the younger generation of keyboard artists,” wrote the *New York Times* critic in 1944, when Maestro Leon Fleisher made his professional debut as a pianist in Carnegie Hall, playing a Brahms concerto with the New York Philharmonic. He was only 16. At 35, he was performing with the Cleveland Orchestra when he noticed the fourth and fifth fingers on his right hand curling inward. Ten months later, he couldn’t play the piano with his right hand and also had trouble performing such everyday tasks as writing and brushing his teeth. He was in a state of despair. “In effect, I felt my life was over,” he says.

Specialists worldwide were vaguely familiar with the symptoms but had no name for the problem, no understanding of its causes, and no treatments to offer. Every day he tested his right hand on the piano, and for decades he looked for medical answers. After nearly 30 years, he learned that others with his condition were being offered experimental treatment at the NIH.

Before providing treatment, the NIH team identified the disorder—a major step for people who have gone undiagnosed for years. What Leon Fleisher has, explains neurologist Mark Hallett of the National Institute of Neurological Disorders and Stroke, is a form of dystonia, a debilitating neurological disorder that produces muscle contractions that can interfere with basic body movements in any part of the body. About 300,000 people in North America are afflicted with these involuntary muscle contractions. Dystonia is the third most common movement disorder after Parkinson’s disease and Essential Tremor. Leon Fleisher has focal hand dystonia, or “occupational cramps,” which afflicts roughly 10,000 musicians worldwide but can strike anyone who uses his or her hands to perform repetitive tasks—including dentists, surgeons, writers, golfers, and typists.

In 1991, after their diagnosis was made, Leon Fleisher was injected with botulinum toxin—better known these days

for smoothing out facial wrinkles. In their experience with 165 patients over 15 years, Hallett and his colleagues have found that 70 percent of patients get some relief from occupational cramping after at least one injection. The toxin acts at the neuromuscular junction to reduce the effectiveness of communication between nerve and muscle, which is useful if the communication is overactive, as it is with dystonia patients. It treats the symptoms but is not a cure. The real problem is generally thought to lie in the brain, the neuromuscular junction being simply a convenient site at which to interrupt communication between the brain and muscles.

The day after the toxin was injected into the Maestro’s forearm, the treatment had relaxed the tension in his muscles, allowing his fingers to reassume their full, extended length. He sat down at the piano and played a Brahms concerto with both hands.

“It was pretty wonderful,” he says.

“Before I was just a two-handed piano player,” he told a *Newsday* reporter. “What happened to me has expanded my life, my awareness, and my humility.” Few doctors are trained to spot the disorder and, when they do, many musicians hide the disorder for fear they’ll lose their jobs. The Maestro speaks publicly about his problem, to give musicians who are suffering in silence the courage to seek treatment. He and the Dystonia Medical Research Foundation are launching a global awareness campaign (“Freedom to Play”) and a worldwide tour in celebration of his return to two-handed performance.

## DR. JOHN HAUGHTON

# IMPROVING THE SYSTEM



**They say cancer** changes your life. In John Haughton's case, treatment for cancer at the Clinical Center changed it.

John's journey to the NIH was a short one. He injured his leg when he was 18, a senior at Bethesda-Chevy Chase High School. As a pole-vaulter and runner, he was used to injuries, but this was different: His swollen calf hurt too much. The local hospital sent him to a local orthopedist who recognized the shadow on his X-ray as a telltale sign of a fairly rare tumor. The orthopedist picked up the phone, and within a week John was a pediatric oncology patient of the National Cancer Institute.

The diagnosis was Ewing's sarcoma, a rare cancer of the long bones that often required partial amputation. But John was lucky. Surgeons successfully removed the tumor and part of his fibula, and he kept his leg. During the radiation and chemotherapy that followed, the NIH staff adapted to his senior-year schedule. He rode his moped to the Clinical Center for lunch-hour radiation

treatments during high school and, when he started college, they wrote a letter requesting schedule accommodations for trips back to Bethesda.

During the following year of chemotherapy, Phil Pizzo, John's attending physician, and almost everyone he encountered at the NIH, went out of their way to make him feel like a person, not just a patient. The chemotherapy fellows helped him sift through the meaning of various research studies and opened his eyes to the complexity of medicine. John began rethinking his future. He had planned to study engineering in college—he was a systems person—and he could see that medicine had not only many systems but also many unanswered questions, large and small.

Not so long ago, he had thought there was just one kind of cancer. Now he knew there were many kinds and many cures. And he could see problems begging for solutions. He decided to combine engineering and medicine, bringing

the perspective of both patient and health care provider to creating systems that work for everyone. With dual degrees in medicine and engineering, John specialized in rehabilitation medicine. He is working on computer systems to improve health care delivery for people with chronic conditions.

Now 41 and cancer-free, he waterskis and windsurfs in his

spare time. He also serves on the Clinical Center's Patient Advisory Group, which helps shape smarter systems—and is listened to. When patients reported that the speed bumps in the patient parking garage made patients in chemotherapy sick, the bumps were immediately removed. It's a system that works.

THE DIAGNOSIS WAS EWING'S SARCOMA, A RARE CANCER OF THE LONG BONES THAT OFTEN REQUIRED PARTIAL AMPUTATION.

## ANNIE BROWN

# BREATHING EASIER NOW



**Since childhood,** Annie Brown has experienced the recurrent pain crises associated with sickle cell disease, a chronic and often fatal form of anemia in which the red blood cells, normally doughnut shaped, become crescent-shaped and function abnormally. Small blockages in blood vessels result, giving rise to such symptoms as jaundice, leg ulcers, and severe, recurrent body and bone pain. In the United States, this inherited disease mainly strikes African Americans.

What brought Annie to the Clinical Center was one of the disease's secondary effects, suffered by a third of sickle cell patients: pulmonary hypertension, or high blood pressure in the arteries that supply the lungs. "I used to not be able to walk down the steps without stopping," says Annie. "I couldn't do anything before. I mean, nothing."

Pulmonary hypertension greatly increases the risk of death. So Annie is participating in a collaborative study by the Clinical

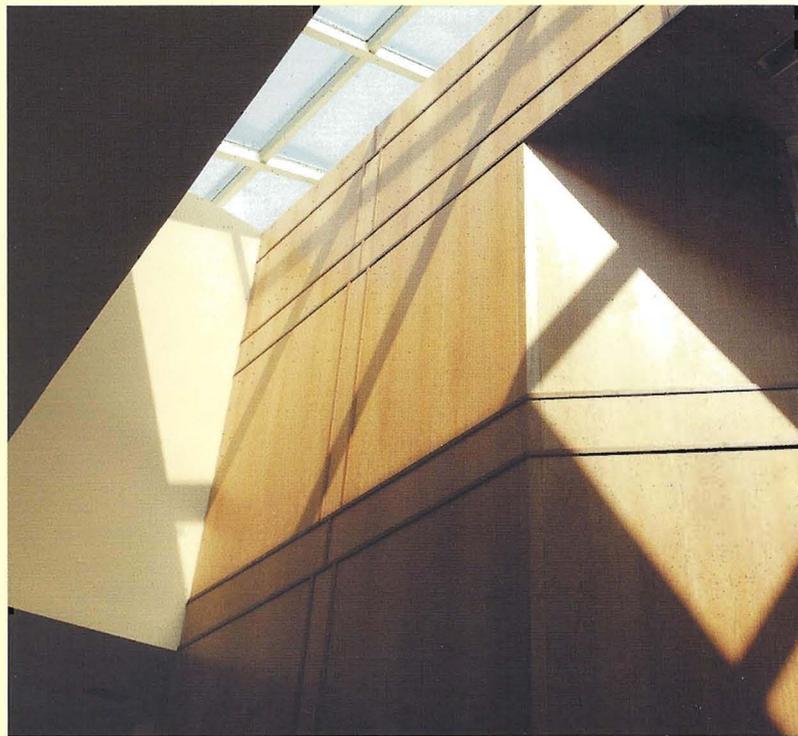
Center's critical care medicine department, the National Lung, Heart, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases and the Center for Sickle Cell Disease at the Howard University College of Medicine. Among interventional therapies the study team is trying are blood exchange transfusions, inhalants such as oxygen and nitric oxide, and the use of vasodilators that open the blood vessels of arteries.

She is doing far better than doctors in Rowland, North Carolina, predicted when she was a child. Doctors told her parents that Annie "wouldn't live past age 18 and that she would never have children." Now 53, Annie has exceeded the median life expectancy for people with the disease (42 for men and 48 for women) and has two grown children.

She's grateful to principal investigator Mark Gladwin and the other members of his NIH team. "No matter what question you have to ask, they take time

to answer," says Annie. "If they don't know what, they're going to find out. It's the best hospital I've been to—a real nice place. I am stronger. Have more energy. Once I passed out but now I don't feel as faint or out of breath. It's just better to feel good."

The chapel on the seventh floor offers services in many faiths.



ELLEN BERTY

## AN ISLET TRANSPLANT CHANGED HER LIFE



For 40 years, diabetes was part of Ellen Berty's life. Diagnosed at 13 with type 1 (or juvenile) diabetes, she counted her carbohydrates and gave herself daily insulin shots. She married, had a son, and went to work testing children for special education classes. She also found time to hike, ski, bike, and do aerobics.

But 5 years ago her blood sugar levels began dropping so quickly and drastically that she passed out—sometimes for 3 hours. Several times at night she was already in seizure when her husband Peter awoke and gave her a shot of sugar solution. Her colleagues got uncomfortably good at dialing 911.

Nothing her doctors suggested helped. Then Ellen read about the NIH and the Edmonton protocol for type 1 diabetes (named for the Canadian city where it was invented). She was accepted into the NIH protocol in 2001.

Type 1 diabetes is an autoimmune disease, in which the immune system sets about

eradicating the insulin-creating beta cells in the islet of the pancreas—and no one knows why. Even careful management cannot always prevent the disease's consequences: blindness, amputation, kidney failure, nerve damage, strokes, heart attacks, and a life cut short by as much as 15 years.

The dream of David Harlan and others in the National Institute of Diabetes and Digestive and Kidney Diseases is to cure type 1 diabetes by coming up with a therapy to replace or restore the insulin-producing beta cells, or a treatment to prevent their loss. Harlan's department is trying to make it easier for transplant patients to accept another person's cells, which the immune system regards as foreign and tries to reject.

The procedure they are using is less like surgery than like a blood transfusion, in which the physician infuses hundreds of thousands of donor islet cells into a tube in the portal vein that feeds the liver. The portal vein lies deep within the body,

so there is a danger of both bleeding and clotting. But the new islets that Harlan injected into Ellen's liver produced insulin almost immediately and she no longer has spells of low blood sugar. Asking why she alone has needed only a single transplant, she was told, "That's why we call this experimental. We don't know yet."

"Good research is painfully slow," says Harlan. But some interesting results are emerging. Harlan and his team have discovered—or "rediscovered" what several older, similar clinical studies have also found—that a significant proportion of patients with longstanding type 1 diabetes, thought to have absolutely no capacity to make insulin, actually do produce some. Increasingly, investigators are pursuing the hypothesis that the pancreas may have some heretofore incompletely tapped capacity to heal. The NIH team has data to support the idea that newly transplanted islet cells function better when they don't have to work overtime right away, and perhaps this is also

true of indigenous cells. Harlan and his colleagues are currently pursuing protocols to explore these issues. For this reason Ellen recently began taking a low "protective" dose of long-acting insulin to protect her islets from doing too much work.

Ample space for relaxing—and hope.



## CHARLIE HARLES

# SURFING THE 'NET WITH A PURPOSE

**Charlie Harles** was diagnosed with fibrous dysplasia at the age of 8. Not until he was 51 did he meet someone else who had the bone disease. Fibrous dysplasia is one of the cardinal features (along with café-au-lait skin spots and hormonal disorders) of a disease called McCune-Albright Syndrome, or MAS.

In 1998 Charlie was in a Maine hospital with yet another broken leg—easily broken bones are a hallmark of the rare disorder. Bored, he got on the computer. To his astonishment he found that his disease had a website and a brand-new support group, started by a man in Arizona whose daughter was afflicted with the disease. Charlie signed up. Through chats on the Internet with other patients, he learned that the NIH was studying his disease.

Back home in Washington, DC, he contacted Michael T. Collins, a physician-scientist at the National Institute of Dental and Craniofacial Research. Collins told him he was a perfect candidate for a natural history study

of McCune-Albright Syndrome. Charlie would be one of about 100 people the institute would follow for a number of years, so they could learn how the disease unfolds over time.

In 1999, he arrived at the Clinical Center for his screening visit. “Dr. Collins and the nurses were absolutely wonderful about telling us what was going on and what the implications were for their research,” he says. The research team, under principal investigator Pamela Robey, tests several patients at once, so Charlie finally got to meet many others in the same boat. Most of them came by the same route he did, learning about the research on the Internet or through support groups. Charlie has driven to Bethesda to welcome about 50 patients who joined the study.

Charlie participated in a drug study, and the rehabilitation department has helped him maintain strength in his leg muscles, which tend to atrophy after years on crutches. His involvement with NIH and the

support group have fed his own work, helping to shape national disability policy. Informally, he tries to provide for children and their families the kinds of connections and guidance he didn't have when he was 8. He is helping establish the Fibrous Dysplasia Foundation, running the group's e-mail system, which serves about 700 people worldwide. He hears constantly from parents in search of medical care for their children and information about the disease. “Whatever we are going to find out,” he says, “will help the children.”





The Mark O. Hatfield Clinical Research Center is the low-lying building in the front, with four wings. Rising 14 stories behind it is the original hospital, the Warren Grant Magnuson Clinical Center.

For more information, go online:  
[clinicalcenter.nih.gov](http://clinicalcenter.nih.gov)

Zimmer Gunsul Frasca Partnership served as architect for the Clinical Research Center, after winning an international design competition.

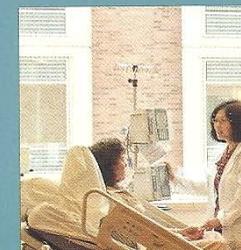
Pat McNees, author of "Building Ten at Fifty," a history of the NIH Clinical Center, researched and wrote the patient stories included here.

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