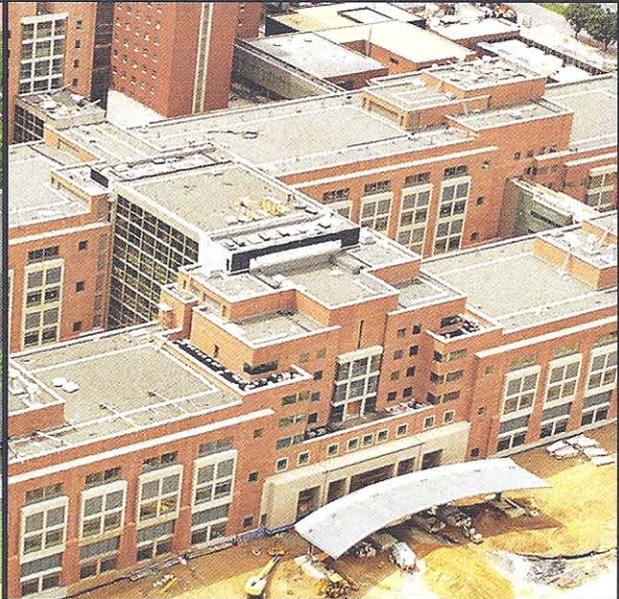
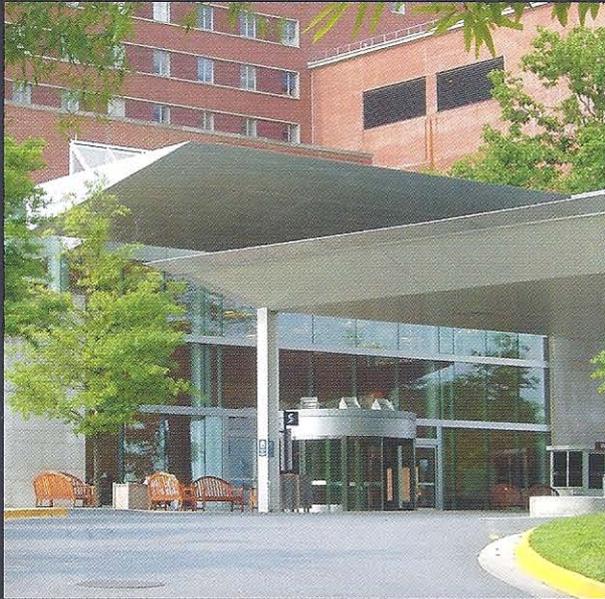
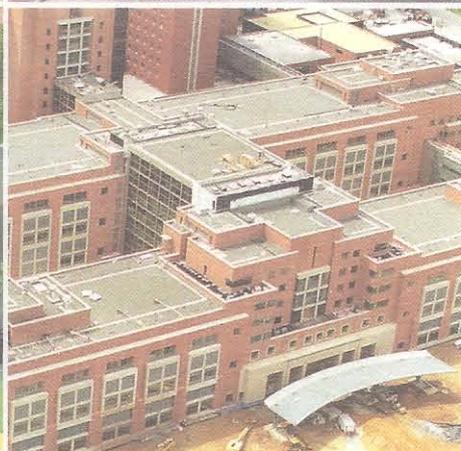


50 YEARS OF CLINICAL RESEARCH AT THE  
NIH CLINICAL CENTER



BUILDING TEN AT FIFTY

Cover art, clockwise, starting top left:  
The original north entrance to the  
Clinical Center; the Ambulatory  
Care Research Center (ACRF),  
added to the north side of  
Building 10 in 1981; the new  
Mark O. Hatfield Clinical Research  
Center (CRC); the south entrance  
to the Clinical Center; added in  
1999, after construction had  
begun on the CRC.





50 YEARS OF CLINICAL RESEARCH AT THE  
NIH CLINICAL CENTER

BUILDING TEN AT FIFTY

**Pat McNees**

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# TIMELINE

## OF EVENTS AND ACCOMPLISHMENTS IN BUILDING 10

This is a working timeline of significant events and accomplishments in Building 10, with an emphasis on clinical research. What happened in Building 10 involved both Clinical Center and institute investigators and staff. Clearly many important events and accomplishments are missing from the list. We ask that you help us complete this timeline by giving us information attached to a date (or a range of dates), with contact information in case we need more information. (Call Clinical Center Communications at 301-496-2563.)

After a period of doing descriptive biology in the 1950s and 1960s (studying individuals with health problems and characterizing their abnormalities), scientists in Building 10 were better able in the 1970s and 1980s to study cell biology and proteins and in the 1980s and 1990s to get down to root molecular causes. After gene-cloning technologies developed, scientists could clone and identify the genetic mutations associated with a disease. By identifying the causative gene and the causative protein, they began to learn where the disease started and could start building the sequence of events that led to abnormalities—thus providing a target for developing appropriate medical interventions.

**1798**

Congress establishes the U. S. Marine Hospital Service (predecessor of the U.S. Public Health Service) to provide health care to sick and injured merchant seamen.

**1870**

The Marine Hospital Service is reorganized as a national hospital system.

**1930**

The National Institute of Health (singular) is established through the Ransdell Act.

**1935**

On August 10, Mr. and Mrs. Luke I. Wilson make a gift of 45 acres of their estate "Tree Tops" for use of the National Institute of Health in Bethesda, Maryland. Additional gifts through 1942 bring the total gift from the Wilsons to 92 acres—the nucleus of the NIH's present 306.4-acre reservation. Additional land is later acquired through a series of purchases.



**1937**

Legislation signed by President Franklin D. Roosevelt on July 23 establishes the National Cancer Institute to support research relating to the causes, diagnosis, and treatment of cancer.

**1938**

The cornerstone is laid for Building 1, Congress approves construction of new, larger laboratory facilities, and NIH prepares to move to Bethesda.

**1940**

President Roosevelt comes to Bethesda on October 31 to dedicate NIH buildings and grounds. His speech portrays medical research as part of the national mobilization effort then much on his mind: "We cannot be a strong nation unless we are a healthy nation. And so we must recruit not only men and materials but also knowledge and science in the service of national strength."



**1944**

Public Law 78-410, the Public Health Service Act, is approved on July 1, consolidating and revising existing public health legislation and giving NIH the legislative basis for its postwar program, with general authority to conduct research and to establish the Clinical Center.

**1946**

The Hill-Burton Act (the Hospital Survey and Construction Act), introduced by Senators Lister Hill and Harold H. Burton and passed on August 13, authorizes grants to the states for construction of hospitals and public health centers, for planning construction of additional facilities, and for surveying existing hospitals and other facilities. (P.L. 79-725, 60 Stat. L. 1040)



1947

Under P.L. 80-165, research construction provisions of the Appropriations Act for FY 1948 provide funds "for the acquisition of a site, and the preparation of plans, specifications, and drawings, for additional research buildings and a 600-bed clinical research hospital and necessary accessory buildings related thereto to be used in general medical research...."

1948

The National Heart Act, signed June 16, authorizes the National Heart Institute and changes the name of the National *Institute* of Health to National *Institutes* of Health.



**Jack Masur is Clinical Center director, 1948-51.**

Construction begins in November on Building 10, the NIH Clinical Center.



1950

The outbreak of the Korean War in June creates a consensus for a "doctor draft," to provide the physicians and dentists needed by the military. Research at the NIH takes on a new appeal for young doctors eligible for the doctor draft.

1951

President Harry S Truman lays the Clinical Center cornerstone on June 22, praising the Public Health Service and claiming that "Medical care is for the people and not just for the doctors—and the rich."



**John A. Trautman is the Clinical Center's first operating director, 1951-54**

1953

The 14-story Clinical Center is dedicated by HEW Secretary Oveta Culp Hobby on July 2. Roy Hertz admits the first patient on July 6.



1953-80

The Blood Bank describes novel red cell antigens and the clinical consequences of red cell alloimmunization.

1954

**Donald W. Patrick is Clinical Center director, 1954-56.**



The Clinical Center is essential in the 1950s and 1960s for the epilepsy program and neuromuscular disease studies of Milton Shy and W. King Engel, followed by M. Dalakas. Mark Hallett does pioneering studies on patients for movement disorders and motor control. For decades, Tom Chase does clinical studies on parkinsonism and other movement disorders.

Researchers in the National Institute of Mental Health discover that chemicals alter the mind—and move, as Irwin Kopin puts it, "from psychoanalysis to urinalysis." Many institutes are studying basic aspects of how the body works—especially how it metabolizes whatever enters it. Scientists

looking at how catecholamines in the brain manifest as affective disorders develop the basis for a more biochemical approach to therapy for mood disorders. As a locus for intramural work, the Clinical Center is an ideal place to study pharmacological treatment of mood disorders.

The Clinical Center's diagnostic x-ray department has the only Schonander angiocardiographic unit in the U.S. It takes films in two planes at the rate of six films per second, permitting a graphic demonstration of contrast substances as they pass through the heart, making diagnosis faster and more accurate. NCI and the x-ray department develop a technique for taking serial films of ureters.

1955

Between 1955 and 1968, NIH Director James A. Shannon presides over the spectacular growth now fondly remembered as "the golden years" of NIH expansion.



Robert L. Bowman, P. A. Caulfield, and Sidney Udenfriend report in *Science* magazine on their development of the spectrophotofluorometer, which allows scientists to use fluorescence to identify and measure previously unmeasurable substances in the body. Bowman works in the D wing of Building 10.

## EVENTS AND ACCOMPLISHMENTS IN BUILDING 10, CONTINUED

1956



**Jack Masur is Clinical Center director a second time, 1956-69.**

The Health Amendments Act of 1956 authorizes the Surgeon General to help increase the number of adequately trained nurses and professional public health personnel. It also authorizes PHS grants to support the development of improved methods of care and treatment of the mentally ill. (P.L. 84-911, 70 Stat. L. 923.)

1957

Using large doses of methotrexate (a folic acid antagonist), Min Chiu Li, working under Roy Hertz, achieves total cure of choriocarcinoma (a rare cancer of the placenta, until then invariably fatal)—the first successful treatment for malignancy in a human solid tumor.

Having earned a Ph.D., Julius Axelrod—Steve Brodie's former lab technician in the Heart Institute—moves to NIMH to work on his own experiments. Using the new spectrophotofluoremeter, he studies neurotransmitters, present in the body in such minute amounts that no previously existing technology could detect them.



The Clinical Pathology Department starts an approved residency training program, admitting its first two residents, one of whom—Ruth Kirschstein—



will rise through the ranks and become acting director of the NIH. During this decade, working with an engineer, George Brecher

develops the first automated machine for counting red and white blood cells (previously counted manually), from which later comes the Coulter counter. Katherine Sanford of NCI takes cells from patients and works out methods for growing cell cultures for studying cancer. Harry Eagle's department of cell biology (NIAID) makes major advances in cell culture methods that will underpin all sorts of clinical research thereafter. Similar advances are made in every department and institute.

The Blood Bank publishes its first research paper, delineating the post-transfusion hepatitis problem, firing the first salvo in a long but largely successful campaign.

In four years, 250 normal volunteers have served for periods ranging from a few weeks to more than two years, contributing a total of 22,650 person-days.

1958

Andrew Glenn Morrow (in cardiac surgery, the Heart Institute) and Eugene Braunwald (in cardiology) discover idiopathic hypertrophic subaortic stenosis, or IHSS (later called hypertrophic cardiomyopathy) in two patients they initially thought had valvular disease. The genetically transmitted disease involves a thickening (hypertrophy) of the heart muscle that in 25 to 30 percent of patients resembles aortic stenosis (narrowing of the heart valve). Morrow develops a surgical procedure (myotomy myectomy) to relieve the malformation. When beta blockers became available (in 1965), Braunwald develops a medical treatment. HCM is later shown to be a common cause of sudden death from heart attacks—in athletes, for example. For many years patients with the problem are referred to the Clinical Center.

1959

Construction begins on a new, circular surgical wing (10A), adding 45,000 square feet.

1960

Nina Starr Braunwald (with Glenn Morrow at the table) performs



the first successful mitral valve replacement in a human, completely replacing the diseased mitral valve of a 44-

year-old woman—at a time in the history of open-heart surgery when complete replacement of the mitral valve has not been previously done. Working with another young investigator, Theodore Cooper (later Assistant Secretary of Health and CEO of Upjohn), Braunwald had begun

"laboratory investigations of a prosthesis that would completely replace the mitral valve at a time when patients with end-stage mitral regurgitation were dying regularly despite vigorous medical treatment."



1961

On the 8th floor of the Clinical Center's D wing, Marshall W. Nirenberg performs his first successful experiment leading to the deciphering of the genetic code, with the help of many NIH colleagues. In 1968 he will become the first NIH (and federal) employee to receive a Nobel Prize. His work on how the triplet code governs DNA's behavior advances understanding of the chemical mechanisms by which genetic language or information is translated into various proteins that determine the nature and characteristics of all living things.

Glass syringes are replaced with sterile plastic disposable syringes, the beginning of replacing glass with plastic (for safety).

1963

A new surgical wing for cardiac surgery (on 2) and neurosurgery (on 4) is dedicated by Surgeon General Luther L. Terry. The two cardiac operating rooms are unique in being dedicated to cardiac surgery, with special systems for monitoring, lighting, communications, and storage and retrieval of large amounts of research data. Open-heart surgery can be viewed through an observation room directly

above, on the third floor. Disposable surgical gloves are also introduced.

The Blood Bank moves to a new circular building (the "fish bowl"); blood collections begin on the NIH campus.



1964

Harvey Alter (Clinical Center) and Baruch Blumberg (Arthritis and Metabolic Diseases) codiscover the Australian antigen, which Blumberg later shows to be the surface coating of the hepatitis B virus, leading to the isolation of this medically important virus. Blumberg later wins Nobel Prize. Alter does pioneering work in the causes and prevention of blood-transmitted infections, which helps lead to the discovery of the virus that causes hepatitis C and the development of screening methods that will reduce the risk of transfusion-transmitted hepatitis.

The Vietnam War brings an upsurge in clinical associates, young doctors subject to the doctor draft. From 68 physicians reporting to the NIH in 1960, the total climbs to 153 in 1965, 206 in 1970, and 229 (a peak) in 1973.

A special virus-leukemia program is initiated under a special appropriation, included in the FY 1965 appropriation.

John L. Doppman and associates in diagnostic radiology report the first successful imaging of the arteries that supply the spinal cord. The technique of spinal angiography makes surgical intervention possible where spinal arterial malformations, lesions, or tumors cause paralysis.

Emil ("Tom") Frei and Emil ("Jay") Freireich (NCI) achieve the first cures with acute lymphocytic leukemia, one of the major malignancies of childhood, with intensive combination chemotherapy—introduced against strong resistance. The forerunner of all four-drug therapies is VAMP: vincristine, amethopterin (later named methotrexate), 6-mercaptopurine, and prednisone.



Roscoe Brady (NINDS) discovers and the next year describes the underlying enzyme defect in Gaucher disease, an enzyme deficiency disorder that disproportionately affects Ashkenazi Jews. See full story at <http://history.nih.gov/exhibits/gaucher/full-text.html>



## EVENTS AND ACCOMPLISHMENTS IN BUILDING 10, CONTINUED



While studying enzymes, Martin Rodbell develops a method for isolating single fat cells from fat

tissue. After learning that the fat cells react normally to the hormone insulin, Rodbell shifts from studying the metabolism of fat to examining the actions of hormones. The procedure for isolating fat cells is a boon to hormone research, because fat cells respond to many hormones. Many researchers begin using Rodbell's method, making his 1964 paper "The Metabolism of Isolated Fat Cells" (*J. Biol. Chem.* 239:375-80) one of the most widely cited in the field. See Office of NIH History exhibit <[http://history.nih.gov/exhibits/rodbell/text/2\\_1\\_rodbell.htm](http://history.nih.gov/exhibits/rodbell/text/2_1_rodbell.htm)> In 1994 Martin Rodbell will share the Nobel Prize in Physiology or Medicine for his discovery in 1970 of G proteins, signal transmission molecules that are activated by a cellular component termed GTP.

1965

Donald Frederickson coauthors an article about two patients with Tangier disease. His work in the Heart Institute is the first attempt at a biochemical and genetic classification of lipid abnormalities. With Levy and Lees he classifies lipid disease, the analysis of which serves as basis for the later classification of risk factors

for coronary artery disease and better public understanding of things like good cholesterol and bad cholesterol.



Jay Freireich introduces the first clinically usable germ-free environment: the "Life Island," a soft, clear plastic canopy that encloses a patient's hospital bed—the first of a series of experiments with different forms of isolation to prevent infections. From this experiment evolves the less restrictive laminar flow room in 1968.

Donald Tschudy (NCI) describes the enzymatic abnormality in acute intermittent porphyria.

NCI and IBM develop a continuous-flow blood cell separator.

Vincent DeVita and colleagues (NCI) report the first chemotherapeutic cure of Hodgkin's disease, even in its advanced form.

Clinical Pathology (CPD) acquires a Control Data 3200 computer, which fills a room the size of a small living room. Some instruments are placed online; other data are entered on key-punched cards. CPD begins using computers to manipulate lab data and report test results.

1965-67

Using exercise-treadmill tests and beta blockers (which block the sympathetic nervous system's action on the heart), researchers in the Heart Institute show that blocking the sympathetic nervous system significantly compromises an individual's ability to exercise.

1966

A Department of Nuclear Medicine is established in the Clinical Center, headed by Jack Davidson, to centralize imaging facilities for patients in any institute. Radiation Safety, Diagnostics and the Whole Body Counter Division become part of

Nuclear Medicine, and the old Radiation Safety Division is abolished. President Lyndon B. Johnson visits the new department.

Roscoe Brady describes the enzyme deficiencies in Niemann-Pick disease.

Wanda S. Chappell, chief nurse in the Blood Bank, comes up with a simple but ingenious method for separating blood platelets (the smallest blood cells) from blood plasma, so that the platelets can be used for transfusion to leukemia patients and the rest of the blood can be used by others, including patients undergoing open heart surgery.

Additions to the Clinical Center (a library, cafeteria) are begun.

1967

Roscoe Brady describes the enzyme deficiencies in Fabry disease.

1967-79

The Heart Institute's cardiology branch helps define the use of beta-blocking drugs and calcium antagonists to treat chronic stable angina pectoris and hypertrophic cardiomyopathy.

1968

As clinical associates (1968-70), Michael Brown (in Arthritis and Digestive Diseases, working in Earl Stadtman's lab) and Joseph Goldstein (in the Heart Institute, working in Marshall Nirenberg's lab) become intrigued by a six-year-old girl, a patient of Donald Frederickson's who has had a heart attack. Her cholesterol level is 1,000; her condition, homozygous familial hypercholesterolemia. In 1972 Brown and Goldstein both go to the University of Texas Southwestern and pursue research on the

mechanisms underlying such conditions. In 1985 they will win the Lasker Award and the Nobel Prize for their discoveries about mechanisms regulating cholesterol metabolism.

Diagnostic radiologist John L. Doppman develops a method for locating the parathyroid, a group of glands (each about the size of a BB pellet) that regulates calcium metabolism.

**1969**

Jack Masur dies suddenly. Masur Auditorium is named for him.

The first cancer patient enters the laminar flow room on 13-East.

Roscoe Brady and colleagues describe the specific defect in Tay-Sachs disease.

Fred Goodwin, Dennis Murphy, and William ("Biff") Bunney conduct the first controlled trials of lithium's effects on depression.

**1970s**

Originally intent on reducing funding for biomedical research, President Nixon is under pressure to launch a war on cancer. The growth of NIH slows, but the war against cancer and heart disease intensifies, largely through the efforts of two women philanthropists and healthcare activists: Mary Lasker and Florence Mahoney.



**1970**



**Thomas C. Chalmers is Clinical Center director, 1970-73**

The first national guidelines for the prevention and treatment of heart disease are based on metabolic research studies conducted by Clinical Center dietitians partnered with NHLBI researchers, who study how diet affects lipid levels.

Julius Axelrod (NIMH) receives a Nobel Prize for his many contributions to the development of concepts of neurotransmitter function.

Efforts begun in the 1960s by Sheldon Wolff and Tony Fauci result in a "cure" of patients with Wegener's granulomatosis, a formerly lethal non-neoplastic disease. They use low-dose cyclophosphamide (which does not suppress bone marrow—thereby avoiding the complications of opportunistic infections) with alternate-day glucocorticoids (which produce far fewer side effects than daily glucocorticoids).



The Blood Bank switches to an all-volunteer donor system, adding a test for hepatitis B surface antigen. Those two measures alone reduce the hepatitis rate from 30 percent before 1970 to about 11 percent after. Later, when more sensitive tests for hepatitis B are added, hepatitis B virtually disappears as a problem in the Blood Bank.

**1971**

Julius Axelrod discovers mechanisms that regulate noradrenaline, an important neurotransmitter in the brain, which leads to the development of better drugs for treating mental disorders.

**1972**

Authority for regulating biologics is transferred from the NIH and the Division of Biologic Standards to the Food and Drug Administration. The NIH is out of the business of regulation. Later that year FDA mandates that donated blood be labeled paid or volunteer.

Most of the 17 Lasker Awards presented in 1972 for research on the chemotherapeutic treatment of cancer go to researchers who have worked in the Clinical Center: Paul P. Carbone, Vincent T. DeVita, Jr., Emil Frei III, Emil J. Freireich, Roy Hertz, James F. Holland, Min Chiu Li, Eugene J. Van Scott, and John L. Ziegler, with a special award to C. Gordon Zubrod, NCI's first clinical director. These investigators also provide invaluable training to many others.

Studies in cardiology show that administering atropine to treat slow heart rates in patients presenting with acute myocardial infarction—standard treatment at the time—is harmful, increasing the likelihood of sudden death and the amount of damaged myocardium. Henceforth atropine is no longer routinely administered.

EVENTS AND ACCOMPLISHMENTS IN BUILDING 10, CONTINUED

Clinical Pathology's Richard B. Friedman develops a computer program to teach students to diagnose illnesses by having the computer report symptoms and inform on test availability and cost, test results, and reactions to treatment.

Blood Bank scientists develop a test for antigen associated with hepatitis. The test will be used nationally.

1973

Negotiation of a peace settlement in Vietnam brings an end to the "doctor draft," which has provided a rich supply of clinical associates.

The development of recombinant DNA techniques for cloning genes begins to change the focus of much intramural work.

Studies in cardiology demonstrate (first with dogs, later with humans) that treatment with nitroglycerin in patients undergoing acute myocardial infarction reduces the amount of damage to the heart and lowers the risk of arrhythmic death. Standard teaching before was that treatment with nitroglycerin was useful for angina patients, but should never be used in patients undergoing AMI.

Section 504 of the Rehabilitation Act of 1973, designed to eliminate discrimination on the basis of handicap, affects research in the Rehabilitation Department.

1974



**Robert S. Gordon Jr. is Clinical Center director, 1974-75**

During the next decade, the Blood Bank develops a nationally recognized program in automated blood collection (apheresis) and tissue typing (HLA) and an international reputation for research studies of red cell serology and hepatitis.

Tom Lewis leads team that will design a large-scale computer-based medical information system (MIS) to support Clinical Center's clinical research and patient care.

1974-90

Cardiology identifies indices predicting long-term survival and sudden death in patients with aortic regurgitation or aortic stenosis, providing a basis for deciding when to delay or proceed with surgery.

The pharmacy department introduces the use of unit dose medications. Nurses no longer fill patients' prescriptions from bulk orders sent up on dumbwaiters.

1975

**Roger Black is acting Clinical Center director, 1975-76.**

Donald S. Fredrickson, NIH director, 1975-81, leads development of 1976 guidelines for scientists using new recombinant DNA techniques, to ensure the safety of genetic research.

Hybridoma technology is developed for production of monoclonal antibodies.

PET shows seizure focus in patients with epilepsy.

1976

**Mortimer B. Lipsett is Clinical Center director, 1976-82**



The new medical information system (MIS) goes live, one nursing unit at a time. Anxiety is nearly universal; nurses help quell resistance by doctors.

1977

*Medicine for the Layman*, a series of health seminars, is launched.

A critical care medicine department is established.

Kenny Kent first uses real-time radionuclide cineangiography for the noninvasive evaluation of global and regional left ventricular function at rest and during exercise.

The Blood Bank establishes therapeutic apheresis/exchange programs that for decades will improve the lifespan and welfare of patients with such illnesses as sickle cell disease, hyperlipidemia, and autoimmune disorders. It also establishes the first automated platelet-pheresis center, collecting platelets for transfusion from volunteer donors using automated instrumentation.

1980

The Clinical Center is renamed the Warren Grant Magnuson Clinical Center of NIH, in honor of the former chairman of the Senate Committee on Appropriations, who has actively supported biomedical research at NIH since 1937. (P.L. 96-518.)

Cardiology helps determine the mechanisms of sudden death in athletes.

Richard Krause, director of NIAID, predicts in his book *The Restless Tide* (completed in 1980), that we have not seen the last of infectious diseases. Many scientists feel it is time to move on to more pressing health problems.



1981

On June 16, the first patient with the new disease that will later be named AIDS/HIV is seen at the NIH, admitted under Dr. Thomas Waldmann's NCI Omnibus Metabolism Branch protocol. The patient is transferred to the care of Stephen E. Straus in NIAID's Laboratory of Clinical Investigation for management of severe herpes virus infections, under a protocol studying intravenous acyclovir, a new antiviral drug. A full timeline of Clinical Center and intramural NIH involvement in what would become a major crisis is posted at <http://aidshistory.nih.gov> along with oral history interviews with major participants.

Tom Waldmann's lab discovers anti-Tac, a protein that prevents the activation of T cells of potential importance in preventing graft rejection, in treating autoimmune diseases, and in controlling those cancers in which T cells proliferate out of control. The next year Bill Paul's lab discovers another protein that activates B cells.

Immunology flourishes in the Clinical Center.



The 13-story Ambulatory Care Research Facility (ACRF) opens, responding to the growth in outpatient care.

Clinical research dietitians participate in the Clinical Center's first nutrition support team, develop standards of care for clinical nutrition service, and develop diets with controlled intake of certain nutrients (iodine, tryptophan, sodium, saturated fats, nitrates) to support clinical research.

1982

On January 15, during a snowstorm that shuts down the government, the second AIDS patient seen at NIH is admitted to the National Institute of Allergy and Infectious Diseases service (NIAID) and is seen by Anthony S. Fauci. Fauci and his colleagues will do important work on the pathogenesis and treatment of this new infectious disease that involves opportunistic infections arising from an immune disorder. The number of cases reported escalates. NIAID scientists conduct a study of adenovirus in patients with the new disease, and NCI establishes an epidemiology working group on Kaposi's sarcoma. At a July 27 meeting in Washington, DC, federal officials, university researchers, community activists, and others select a name for the new disease: "acquired immune deficiency syndrome," or AIDS.

A Clinical Center protocol is approved to study the etiology of immunoregulatory defects in the disease as a collaborative effort among Clinical Center departments, NIAID, NCI, the National Institute of Neurological Diseases and Communicative Disorders and Stroke (NINCDS—later NINDS), the National Institute of Dental Research (NIDR, which later adds "& Craniofacial," becoming NIDCR), the National Eye Institute (NEI), and the Food and Drug Administration (FDA). An NIH working group is set up to study the new disease, with representatives from each institute and liaisons from the CDC and FDA.

Under Henry Masur, Critical Care plays a key role in managing treatment for the opportunistic infections that are the main threat to immune-suppressed AIDS patients. The department becomes world-recognized in its field, first for treating *Pneumocystis pneumonia* and then for experimental treatments with patients in shock. As the number of HIV and AIDS patients and protocols increases, nurses increasingly take on a new role as case managers for a group of patients, working with a study investigator.

Steve Straus admits first patient into a placebo-controlled, double-blind NIAID trial of acyclovir pills for suppression of frequently recurring genital herpes in otherwise healthy people. Two years later the study results show safe and efficient suppression of herpetic outbreaks—the first antiviral drug to manage a viral disease successfully for a sustained period, foreshadowing later triumphs with HIV/AIDS and viral hepatitis.

## EVENTS AND ACCOMPLISHMENTS IN BUILDING 10, CONTINUED

In 1985, FDA approves oral acyclovir, revolutionizing care for a painful sexually transmitted disease.

As part of the design for the new ACRF, Clinical Pathology services (previously scattered) are brought under one roof—working together in one vast open room, except for specialized functions sequestered for safety purposes (such as the containment of radionuclides).



A new surgical facility opens on the second floor of the ACRF, with more space for equipment, larger operating suites, two viewing galleries, and better delivery systems. Surgical Services performs more than 2,000 cancer, eye, and general surgical procedures a year. A surgical intensive care unit (2J) opens in conjunction with the new surgical suites. Nurses in the new nursing unit face new challenges in caring for patients in septic shock and providing such therapies as continuous veno-venous hemofiltration (CVVH), hemodynamic monitoring, and ventilator support.

Cardiology makes early use of angioplasty to treat coronary artery disease and demonstrates that myocardial function improves during exercise after successful percutaneous transluminal coronary angioplasty.

Bill Gahl, in studying a rare genetic disease called cystinosis (which destroys the kidneys, eyes, and other organs), finds that the disease is caused by the defective transport of cystine out of the lysosome, a cellular compartment responsible for breaking down large molecules into smaller molecules. His study shows that cells salvage small molecules by transporting them from lysosomes to the rest of the cell by means of integral membrane proteins. Gahl spearheads a national collaborative effort that later results in effective drug therapy for cystinosis, approved in 1994.

1983



**John L. Decker is Clinical Center director, 1983-90**

NIDR opens the first multidisciplinary pain clinic in the U.S. devoted exclusively to research. It also establishes a Dry Mouth Clinic. Studies by Bruce Baum and Phil Fox lead to a new drug treatment that increases saliva production in patients with salivary gland disorders. NIDR also operates a dental clinic, providing dental care to inpatients on various NIH protocols and supporting research by NIDR clinical investigators.

Orphan Drug act passes January 4—good news for patients with rare diseases, many of whom will find their way to the Clinical Center.

Roscoe Brady (NINDS) receives a Lasker Award along with Elizabeth Neufeld (NIDDK, recognized for identifying the enzyme defect that causes mucopolysaccharide—carbohydrate—storage disorders) and Robert Gallo (NCI, for his work leading to isolation of the retrovirus HTLV-I).

Clinical Pathology creates an immunology service, reflecting growing demand for sophisticated antibody and cellular-level diagnostic services.

1984

The Cancer Institute's pediatric branch hires the Clinical Center's first nurse practitioners.

The Blood Bank is renamed "Department of Transfusion Medicine" (DTM) because its activities extend well beyond traditional blood banking. DTM achieves the first transmission of HIV (HTLV III) to a primate through transfusion and describes the HIV seronegative window.



Research groups led by Robert C. Gallo Jr., (NCI) Luc Montagnier at the Pasteur Institute in Paris, and Jay Levy at

the University of California, San Francisco, all simultaneously identify a retrovirus (a variant of a human cancer retrovirus) as the cause of AIDS—calling it different names (HTLV-III, LAV, and ARV, respectively). Identification of the virus, renamed human immunodeficiency virus, or HIV, provides a target for blood-screening tests and for scientists conducting research. The next year Gallo

1985

develops a diagnostic blood test, which helps scientists calculate the scope of the crisis and allows healthcare workers to screen and protect the blood supply.

Michael Potter (NCI Laboratory of Genetics) shares a Lasker Award (with César Milstein and Georges J. F. Köhler, who have used his murine myeloma cells) for his fundamental research into the genetics of immunoglobulin molecules, paving the way for the development of hybridomas and monoclonal antibodies.

Two cyclotrons are delivered to the underground facility operated by the Nuclear Medicine Department.

At an Easton, Maryland, retreat, institutes complain about high costs and a new "fee-for-service" cost-allocation system goes into effect. This leads to a reduced flow of patients to the Center, as institutes realize they can save money by bringing in fewer patients.

On March 7, the first AIDS antibody test, an ELISA-type test, is released.

In December, Steven A. Rosenberg of the NCI announces the results of his work injecting patients in advanced stages of cancer with interleukin-2 (IL-2) or mixtures of IL-2 and LAK (lymphokine-activated killer) cells—white blood cells transformed into tumor-killing cells by exposure to IL-2. After 66 patients in a row die (patients for whom all standard treatments had also failed), some patients finally begin to



respond. In the *New England Journal of Medicine*, Rosenberg announces a 44% response rate in 25 patients treated. Linda Taylor, a 29-year-old naval officer with metastatic melanoma, is evidence that immunotherapy can work. Her tumors vanish.

Over the years Rosenberg, who initiates a training program in surgical oncology in 1974 (the year he becomes NCI's chief of surgery) trains 200 surgical oncologists, 40 of whom will head units of surgical oncology in major universities.

1986

President Ronald Reagan signs the Technology Transfer Act, October 20. Henceforth the development of a new and useful medical product at the NIH will probably occur under a *cooperative research and development agreement* (CRADA).

In May, the name of the AIDS virus is changed to human immunodeficiency virus (HIV) at the suggestion of a multinational committee of scientists.

As a charter member of the National Marrow Donor Program (NMDP), on December 2 the Clinical Center signs an agreement to become one of the first donor centers participating in the NMDP.

1987

In March the FDA approves AZT as the first antiretroviral drug to be used as a treatment for AIDS. Sam Broder, Hiroaki Mitsuya, Robert Yarchoan, and others have pulled AZT off the shelf—it has been rejected as an anti-cancer therapy—and to everyone's surprise, the symptoms of some AIDS patients improve greatly in clinical trials with the drug. Interested in the results, Burroughs Wellcome begins developing the drug.

The first NIH/DTM donor undergoes bone marrow collection for an unrelated recipient—one of the first five donors, nationally, to do so.

1988

Steve Rosenberg demonstrates that adoptively transferred cells can mediate cancer regression in humans, opening the field of adoptive immunotherapy for cancer.

On May 22, W. French Anderson (NHLBI) and Michael Blaese (NCI) work with Steve Rosenberg to test the safety and effectiveness of gene therapy in human cancer patients. The team grows tumor-infiltrating lymphocytes (TIL cells) from people with malignant melanoma. They engineer a virus to put a DNA marker into the TIL cells. The patient is infused with TIL cells altered by insertion of a gene. The marked TIL cells help them track the special cancer-fighting cells in the body, to increase their understanding of TIL therapy. They learn which TIL cells work best for cancer treatment. They also learn that the engineered virus is safe for use in humans.

## EVENTS AND ACCOMPLISHMENTS IN BUILDING 10, CONTINUED

A firm named Chiron, which since 1983 had secretly been working to clone the non-A, non-B agent that causes hepatitis, develops a test for what will be named hepatitis C. Many others have tried and failed against Harvey Alter's coded repository of highly pedigreed patient specimens.

**1989** NIAID's Laboratory of Host Defenses delineates the genetic basis for one form of chronic granulomatous disease (CGD).

**1990s** The metabolic kitchen provides a research diet low in vitamin C for a study that leads to revision of the recommended dietary allowance for vitamin C.

**1990** **Saul Rosen is acting director of the Clinical Center, 1990-94.**



Transfusion Medicine opens a state-of-the-art blood bank and transfusion medicine facility.

The Children's Inn opens its doors to pediatric patients and their families, thanks to the vision and hard work of Phil Pizzo (NCI).

The Recombinant DNA Advisory Committee approves the first experiments involving the transfer of human genes for therapeutic purposes. Transfusion Medicine collects and prepares gene-modified cells for the world's first clinical trial.

The first gene therapy treatment is initiated on September 14 in Ashanti ("Ashi") DeSilva, a 4-year-old girl with adenosine deaminase (ADA, or ADA-SCID) deficiency, a congenital immune deficiency syndrome that leaves

her defenseless against infections. W. French Anderson (NHLBI), R. Michael Blaese (NCI), and Kenneth Culver head the Clinical Center team working on the case. White blood cells are taken from the patient, the normal genes for making adenosine deaminase are inserted into the white cells, and the corrected cells are reinjected into the girl.

In January 1991 they treat a second patient with ADA deficiency, nine-year-old Cynthia Cutshall. Over two years, each girl is given repeated treatments—infusions of their own corrected cells—while continuing to receive infusions of the enzyme adenosine deaminase. The two girls attend school and lead normal lives.

Arshed Quyyumi, Julio Panza, and Richard Cannon (NHLBI) demonstrate that endothelial dysfunction leading to impaired vasodilator mechanisms is caused in part by the decreased availability of nitric oxide—a condition that can be improved by administering antioxidants—or, in postmenopausal women, estrogen.

NHLBI closes its cardiac surgery unit.

**1990** The World Wide Web is "born." Launched worldwide in 1991, it changes the way patients and their families learn about medical conditions, diseases, and research—and how they find their way to the Clinical Center.

**1991** On January 29, NIH scientists treat the first cancer patients with human gene therapy. Two patients receive transfusions of special cancer-killing cells removed from their own tumors and armed in the laboratory with a gene capable of producing a potent antitumor toxin: tumor necrosis factor.

Thanks to Roscoe Brady, 12 patients with Gaucher disease receive and respond dramatically to the purified enzyme glucocerebrosidase. It has taken 17 years to perfect this therapy, which replaces an impaired enzyme. On April 5, 1991, FDA approves Brady's enzyme replacement therapy. Genzyme will produce the enzyme, glucocerebrosidase. In 1995, an equally effective recombinant version of the enzyme is developed.

In 1991 a thrombosis unit is established in Clinical Pathology's hematology service to help manage patients with coagulopathies. A virology section is redeveloped within Clinical Pathology's microbiology service. The original viral diagnostic unit had long since lapsed, for lack of clinical utility, but with the development of new diagnostic methodologies and new therapies, the need for such a service has become increasingly apparent.

NIAID's Laboratory of Host Defenses delineates the genetic basis for a second form of chronic granulomatous disease and successfully treats CGD with interferon gamma to reduce bacterial infections.

1992

An A-wing addition to the Clinical Center is completed in June, adding NCI and NIAID labs focused on AIDS research.

NCI's medicine branch integrates nurse practitioners into its clinical fellowship program, hiring more nurse practitioners as the fellowship program is downsized. Each nurse practitioner medically manages a population of patients, provides continuity of patient care, helps educate clinical fellows, and performs such procedures as lumbar punctures and bone marrow biopsies. Over the next few years, nurse practitioners are established in gynecology, rheumatology, endocrinology, pulmonology, cardiology, psychiatry, nuclear medicine, and infectious disease.

DTM begins a series of research innovations in granulocyte collection and transfusion and in peripheral blood stem cell collection, research activities that continue to this day.

1993

The Clinical Center's hematology/bone marrow unit opens on 2-West to investigate improved transplant procedures and to develop gene therapy techniques—in support of NHLBI protocols.

Researchers use gene therapy to treat newborn babies with ADA deficiency. The normal ADA genes are delivered to immature blood cells isolated from the babies' umbilical cords in the hope that these special stem cells will provide longer-lasting benefits. The newborn patients show steady increases in ADA in their immune cells following a single gene therapy treatment. Many scientific obstacles remain

1994



**John I. Gallin is Clinical Center director, 1994 to present time**

The Clinical Center opens the first multi-institute inpatient unit especially designed and staffed for children, on 11-East.

Between 1994 and 1998, Steve Rosenberg's team is among the first to clone the genes that encode cancer antigens recognized by the human immune system.



1995

In early 1995, Health and Human Services (HHS) Secretary Donna Shalala mandates a review of the efficiency of the Clinical Center led by Helen Smits, who is to consider, among other options, privatization of the Clinical Center (contracting out all or some services to nongovernment firms) to save money and improve efficiency.

Steve Straus and Michael Lenardo (NIAID) and Jennifer Puck (NHGR) describe in the journal *Cell* the molecular and cellular basis for a new disease they call autoimmune lymphoproliferative syndrome (ALPS), the first autoimmune disease whose genetic cause is known: a defect in the regulation of

before gene therapy becomes a practical form of therapy.

NHLBI's cardiology branch initiates studies demonstrating infection's role in atherosclerosis.

lymphocyte survival. This trio and their colleagues then characterize and manage over 150 more ALPs patients, making Building 10 the world center for research on the disorder.

Diagnostic Radiology installs a 20,000-pound magnetic resonance scanner in the courtyard outside Transfusion Medicine.

1996

The Smits report (*Opportunity: Revitalizing the NIH Clinical Center for Tomorrow's Challenges*), recommends that the NIH actively seek funding for a new Center facility; explore contracting out more Clinical Center services; find new ways to recruit patients to protocols; establish a Board of Governors; and have a stable budget of its own. Out of concern about a declining patient census, and advised by the new Board of Governors, the NIH replaces the *fee-for-service* model of funding with a *school-tax* model, under which the institutes pay because the Clinical Center is there, whether they use it or not.

Details on clinical research studies conducted at the Clinical Center are made available on the World Wide Web (<http://clinical-studies.info.nih.gov>), to increase awareness of NIH clinical investigations.

John B. Robbins and Rachel Schneerson (NICHD) receive a Lasker Award for their work developing an effective vaccine against *Hemophilus influenzae* type b (Hib), a deadly and disabling infectious bacterium—a leading cause of bacterial meningitis throughout the world, almost always fatal.

## EVENTS AND ACCOMPLISHMENTS IN BUILDING 10, CONTINUED

1997

Transfusion Medicine launches a 3,000-square foot model core [cGMP] cell processing facility, created to meet increasing investigative needs for cell products used in research into new cellular therapies, such as immunotherapy, gene therapy, stem cell transplantation, and pancreatic islet cell transplantation.

Edward H. Oldfield and coworkers (NINDS) use retroviral vectors to deliver the Herpes simplex gene for thymidilate kinase, rendering human brain tumors susceptible to the antiviral drug ganciclovir. Methods for delivering the gene need improvement.

Groundbreaking ceremonies are held for the Mark O. Hatfield Clinical Research Center, a modern research facility that will include a 240-bed hospital, outpatient care capability, and research laboratories—named for the Oregon senator because of his support for medical research in Congress, in the Senate (30 years), and on the Appropriations Committee (8 years).



1998

NHLBI phases out its clinical associate program, replacing clinical associates with nurse practitioners, who are felt to provide skilled services and greater continuity of care. In some institutes the nurse practitioners serve as consultants. The Internal Medicine Consult Service, an innovative program launched in November 1998, pairs physician Fred Gill with nurse practitioners Laura Shay and Tracy MacGregor. The team is consulted by other institutes for problems in protocol patients such as hypertension, hyperthyroidism, and hyperglycemia. The service also often helps manage patients with extremely complex medical problems, coordinating all testing and referrals for comprehensive work-up and management of the problem—allowing the attending research team to focus on protocol issues.

Telemedicine begins to develop for radiology and surgery and to expand clinical trials.

1999

Clinical Pathology is renamed Laboratory Medicine. A new laboratory information system is put in place for Laboratory Medicine, Transfusion Medicine, and the Pathology Lab.

NIAID's Laboratory of Host Defenses delineates the genetic basis for neutrophil-specific granule deficiency.

2000

The NIDDK and the Clinical Center (in collaboration with Walter Reed Army Medical Center, the Naval Medical Research Center, and the Diabetes Research Institute of the University of Miami) launch a new kidney, pancreas, and islet transplant program. The idea is to test novel therapies that may eliminate the need for the immunosuppressive drugs patients take to keep their bodies from rejecting new transplanted organs. Soon after the program starts, Allan Kirk performs the NIH's first successful kidney transplant procedure, and David Harlan performs one of the first successful islet allotransplants in the United States.

The Clinical Center launches a new Pain and Palliative Care Consult Service.

A cybercafe opens near the coffee bar in the lobby, a social focal point for graduate students (dedicated to former NIH director Harold Varmus). It overlooks the space in front of the original building where the Pools of Bethesda once lay.

Nursing pilots wireless systems for nursing documentation.

Harvey Alter receives the Lasker Award "for pioneering work leading to the discovery of the virus that causes hepatitis C and the development of screening methods that reduced risk associated with transfusion-associated hepatitis in the United States from 30 percent in 1970 to virtually zero in 2000." Alter, who is also elected to the National Academy of Sciences, shares the award with Chiron's Michael Houghton.

# 50

1953-2003

Nucleic acid testing is put in place for HIV. It can detect viral elements at a much earlier time.

Ed Oldfield and colleagues demonstrate benefit from simple decompressive surgery of syringomyelia and suggest that a commonly associated anomaly of the cerebellum (Chiari malformation) is acquired, not congenital.

The Imaging Sciences Program takes first steps toward filmless radiology, unveiling the pilot phase of its new Picture Archiving and Communication System (PACS) and Radiology Information System (RIS). RIS is a sophisticated patient tracking system, which will track patient arrival and departure times, the start and end of exams, and when reports are dictated, read, and signed. It is expected to reduce patient waiting times, improve image availability, and minimize loss and misidentification of images and reports. Images stored in PACS/RIS originate from procedures and exams conducted in the Diagnostic Radiology, Nuclear Medicine, and PET Departments. They include CT scans, MR scans, PET scans, nuclear medicine scans, ultrasound examinations, and digital radiography examinations.

**2001** A second bone marrow transplant unit opens to support NCI protocols.

**2002** DTM establishes a model program for collecting blood from subjects with hereditary hemochromatosis. This program supplies 10% of the hospital's red cell needs.

Taking advantage of information technology, Nursing develops e-learning programs for staff education.

The Human Genome Project (HGP), launched in the 1980s and overseen by the NIH and the Department of Energy, is completed in April 2003. The Office of Rare Diseases partners with the National Human Genome Resources Institute (NHGRI) to promote the diagnosis and therapy of rare disorders.

The Guinness World Records proclaims Howard P. Drew Jr., a regular at the Blood Bank, the world's most prolific blood donor. Between 1950 and 2000, Drew donated a documented 213 units of blood (about 28 gallons) at the NIH Blood Bank and the American Red Cross in Washington, D.C.

The Clinical Center accepts bids for development of a clinical research information system (CRIS) to replace MIS, the computerized medical information system installed in 1976. The new system will let the agency amass data for studies conducted over time, allowing it to use data for both clinical and research purposes.

**2003** NIAID's Laboratory of Host Defenses delineates the genetic basis for IRAK 4 deficiency and shows that itraconazole can be used to prevent fungal infections in CGD.

**2004** The Mark O. Hatfield Clinical Research Center (CRC) is expected to open in 2004, as part of Building 10.



The Edmund J. Safra Family Lodge will open at about the same time.



# PREFACE

Twenty years ago I had an amazing encounter with a hospital I didn't even know existed, although it stood 14 stories high not far from my own backyard in Washington, D.C. My nephew, Will, had Addison's disease, a rare hormonal disorder also known as chronic adrenal insufficiency—the disease John F. Kennedy had and concealed from the public. Will had also been suffering repeated headaches so excruciating that he couldn't hold a job. At 25 he had no health insurance himself and was too old to qualify for coverage under his parents' policies.

Having heard that the National Institutes of Health sometimes treated patients with special conditions but having no idea where the treatment actually took place, I called NIH's public information office and asked if they knew of someone who would consider for treatment a patient with Addison's disease and terrible headaches. As it happened, Will's symptoms fit a protocol (a specific research plan) in one of the institutes. I passed information about it along to Will and his mother in Florida, and in a remarkably short time his doctor had referred him and the NIH had invited him to come for a screening visit.

Soon I became acquainted with the huge hospital I knew only as Building 10 and now know as the NIH Clinical Center. It turned out that a ventricle in Will's brain had collapsed, making it difficult for the fluids in his brain to drain. The excellent surgeons in Building 10 installed a shunt through which his cerebral fluids could drain into his abdomen. They told him he was not a particularly interesting case—totally routine. Still, they studied him, cared for him, provided outpatient care for a period afterwards, and—a year later at the institute's expense—flew him back for a follow-up visit.

Building 10 fascinated me and I wanted to know more about it. On the floor where I visited Will, for example, were a number of short and oddly proportioned patients. Will explained that they were part of another protocol investigating endocrine disorders. What was going to happen to those patients? Why had I never heard of this hospital? Why was I unaware of the national treasure in my own backyard?

Two decades passed. I moved to Bethesda, Maryland, north of the NIH campus (as they call the land on which the National Institutes and the Clinical Center sit). When I learned that the Clinical Center wanted someone to write a brief history for its upcoming fiftieth anniversary, I leapt at the opportunity. Now, a year after undertaking the assignment, I am even more amazed by the place than I was the day I first brought Will to Building 10.

The National Institutes of Health is a collection of government-operated biomedical research institutes. The National Cancer Institute, created in 1937, has in many ways served as the model for the many institutes that have followed, created by Congress, often at the urging of others, especially advocacy groups. There is no consistency to the categories they represent. Some institutes are organized around a disease (such as cancer or allergy and infectious disease), some around an organ system (such as eyes, or heart, lung, and blood), some by life stage (child and human development, and aging), some by field of science (general medical sciences, environmental sciences, human genome, mental health), some by profession or technology (nursing, biomedical imaging and biomedical engineering).

Ninety percent of NIH-funded research is “extramural,” carried out by other (mostly academic medical) organizations all over the country. Only 10 percent of the research funding is spent on “intramural” research, done on NIH's Bethesda campus. Some of the research involves basic science (performed in laboratories or in experiments with animals). Some of it is clinical research—meaning it's conducted on human patients. When intramural NIH investigators conduct clinical research, they do so in the Clinical Center.

The NIH campus lies between Rockville Pike and Old Georgetown Road, south of Cedar Lane, in Bethesda, an increasingly urban suburb north of our nation's capital. Thousands of commuters pass the campus daily, fully aware of the tall and beautiful art deco National Naval Medical Center across the road on Rockville Pike, but generally unaware of the Clinical Center, which, tucked behind trees and other buildings, is less visible.

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# THE REMARKABLE HOSPITAL

On my first walk around the building a year ago, I chatted briefly with a nurse on the pediatric cancer ward. “We see miracles happen here all the time,” she said. I have learned that these miracles are often the product of dedicated and compassionate work by many very smart people who want to make a difference and do. Taking the best science has to offer, they are constantly thinking about new ways to deal with unsolved medical problems, coming up with solutions, and passing them on to the rest of the medical community, while they find new problems to tackle. The staff offers a level of patient care most of us thought had been managed out of existence. And the Clinical Center and the institutes have provided training and formative experiences for a sizeable proportion of the nation’s—and increasingly the world’s—biomedical establishment.

The Clinical Center is not the kind of place you come to for an appendicitis attack or to have a baby. If you broke your leg walking down its corridors, you would probably be taken across Old Georgetown Road to Suburban Hospital to have it set. The Clinical Center exists to provide patient care in the context of clinical research, and if you have the bad luck to have a medical problem that standard medical practice can’t deal with—but the good luck to qualify for one of the institutes’ protocols—there is probably no better place to be.

There are problems with the Clinical Center. Its infrastructure is aging (but a new hospital—still part of Building 10—will open in 2004). Nobody has enough space in which to meet or work. The food in the cafeteria is nothing to write home about. And parking, which is limited, is definitely a privilege, not a right. But certain themes emerged in interviews with several dozen people who work, or worked, in the Clinical Center: “Here I could practice medicine the way I learned that it should be practiced,” which I heard especially from the nurses. Also: “Every day I look forward to coming to work” and “I could make more money elsewhere, but I can’t imagine more rewarding or important work.”

Victoria Harden, the historian who runs the Office of NIH History, briefed me as I started this project, giving me a list of books to read for background, offering me full access to her office’s resources, and any

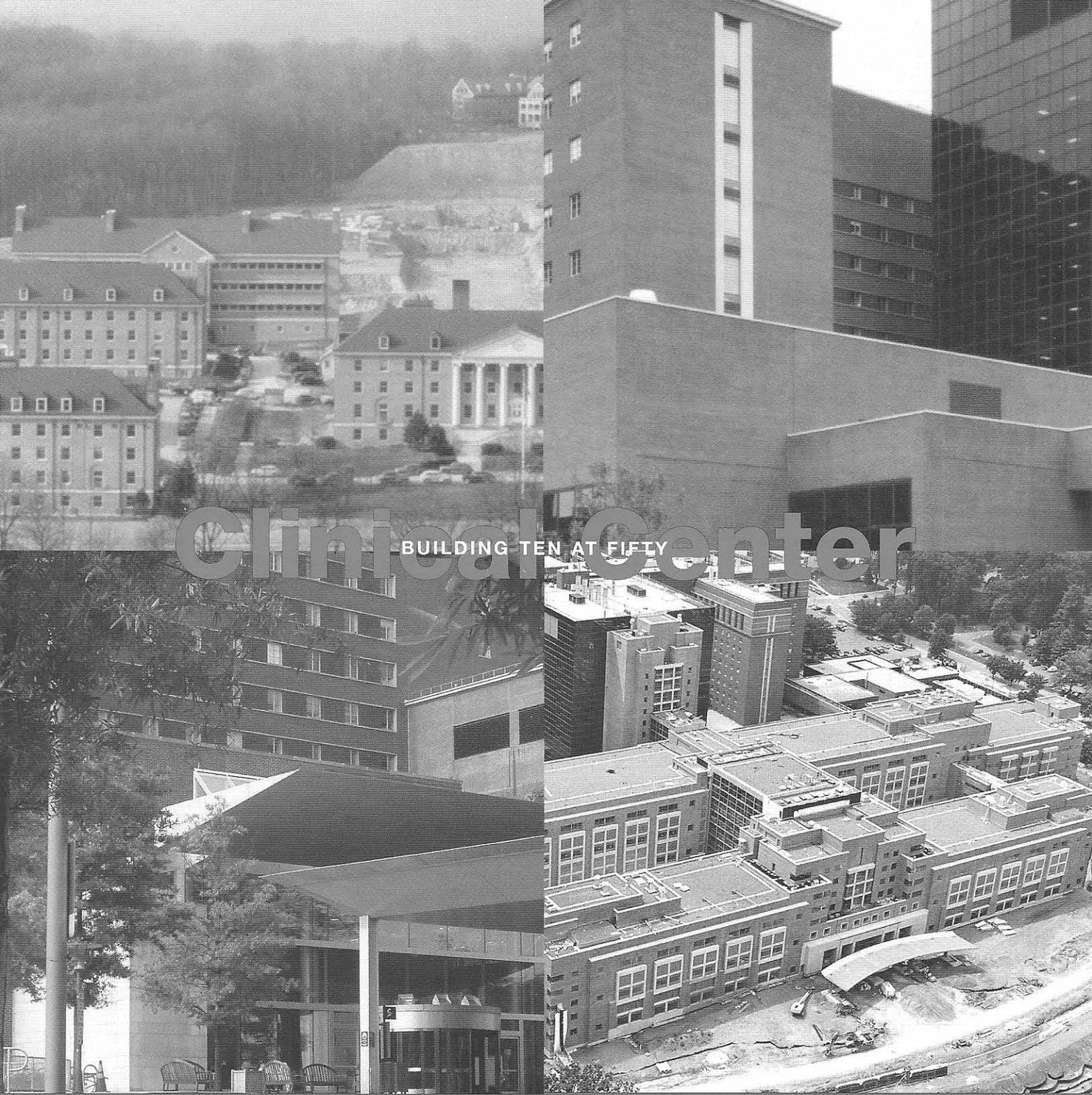
other help her office could provide. But she also told me that writing even a brief history of the Clinical Center in the scant year before its fiftieth anniversary would pose a mighty challenge. What an understatement. It was months before I stopped getting lost in Building 10 (it is labyrinthine as well as huge) and with a thousand protocols a year—some lasting decades but many turning over in three years—how could one find a focus?

My interest, and my assignment, was to write about the people and the clinical research in the Clinical Center. Who are the researchers and how and why do they do their remarkable work? Who are the patients who participate in the research and how do they find their way to Building 10? In the end, this book is less a history than a sampler. It describes some of the work that has gone on in the building in the past and some of the work that is still going on. Its organization is entirely arbitrary, based on neither importance nor chronology. Here you will find stories about experiments with chemotherapy and cooking tumors with needles, about early work in the Heart Institute that we now take for granted, about basic and clinical research in immunology, about the first days of the AIDS crisis, about some rare and inherited diseases, about childhood schizophrenia, and about transplantation, all mingled with tales of people who benefited directly from this research—the patients and their families.

The Clinical Center deserves a fuller history, and the investigators and institutes whose work has not been covered here may feel justifiably slighted. Many wonderful stories remain to be told, and I hope to help tell them. But here’s a start. For now, let us just say, Hats off to the Clinical Center, the people who work there, and the patients, who, everyone agrees, are the most important partners in the research that goes on in Building 10.

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# NOBODY KNOWS ABOUT



# Clinical Center

BUILDING TEN AT FIFTY

“What a wonderful institution for the people who are taken care of there—for the families of the people who are taken care of there and for the patients themselves. But also what a wonderful institution for the people who work there. It is a place that trains and respects and listens to the people who are in there every day trying to literally save the world.”

—**Cokie Roberts**, congressional analyst for ABC News

# THERE IS NO OTHER HOSPITAL LIKE IT

**O**n Monday mornings, vans carry patients from three airports in Maryland and Virginia to the NIH campus in Bethesda, Maryland. At the heart of that campus sits Building 10: the NIH Clinical Center, a research hospital and clinic where patients from all over the nation—and in some cases the world—receive cutting-edge medical care. Other hospitals do research, but one-half the research beds in the United States are in Building 10. It serves as an international model of collaborative excellence and innovation in clinical research. It provides an ideal environment for uncovering the knowledge that will help prevent, detect, diagnose, and treat disease and disability—from the common cold to the rarest genetic disorder.

It's the institutes that do the science, conduct most of the research that goes on in the Clinical Center, and produce so many Lasker Award and Nobel Prize winners. Much basic science work goes on before someone comes up with an intervention such as a vaccine, treatment, or approach to diagnosis for a medical condition. The Clinical Center is the final common pathway for translating scientists' work in labs and with animal models into natural history studies, medical interventions, or clinical trials with human patients. In the Clinical Center, scientists and clinicians working together with a broad-based team of other experts establish proof of principle. In recent years the number of protocols, or research plans, involving multiple institutes has increased dramatically. The nature of science in the twenty-first century is inherently collaborative, and collaboration is the Clinical Center's strong suit.

Research protocols may be interventional (experimental studies in humans to investigate the safety and/or efficacy of a drug, gene therapy, vaccine, behavior, device, or procedure) or observational (to record specific events occurring in a defined population). Observational protocols include natural history, screening, and psychosocial studies.

Clinical trials of new drugs account for roughly half the protocols in the Clinical Center. Most of the clinical trials conducted here have been phase 1 or 2 trials, testing for safety and efficacy. These trials mark the first time these agents have been tested in humans. After these early studies, the drugs move into phase 3 trials, which are usually conducted off-campus in large populations by extramural researchers. Back at the Clinical Center, intramural researchers then turn their attention to other challenges requiring innovative or untested research that couldn't easily be done elsewhere.

The other half of the protocols involving Building 10 are natural histories of diseases—often rare diseases—to elucidate their pathogenesis and to develop new medical interventions or approaches to diagnosis, prevention, and treatment. The natural history studies are typically long-term studies, usually involving patients from all over the nation and sometimes the world. Some studies go on for decades, with investigators studying patients from infancy through adulthood. Many of these studies probably would not have been done if they had not been done in the Clinical Center.

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Facing page, clockwise, starting top left: The original north entrance to the Clinical Center; the Ambulatory Care Research Center (ACRF), added to the north side of Building 10 in 1981; the new Mark O. Hatfield Clinical Research Center (CRC); the south entrance to the Clinical Center, added in 1999, after construction had begun on the CRC.

The Clinical Center supports about 1,000 active clinical research protocols. Its projected hospital admissions in 2003, with a 267-bed capacity, are 6,723, plus an expected 98,172 outpatient visits. Investigators will see 9,175 new patients in 2003, bringing the total number of active patients to 80,245, including the largest population of patients with rare diseases anywhere. The Clinical Center itself employs a staff of about 2,000, in addition to which staff and fellows of the various institutes work in Building 10. The Clinical Center's job is to provide the resources the institutes need to carry out their research and patient care missions.

There is no other hospital like it.

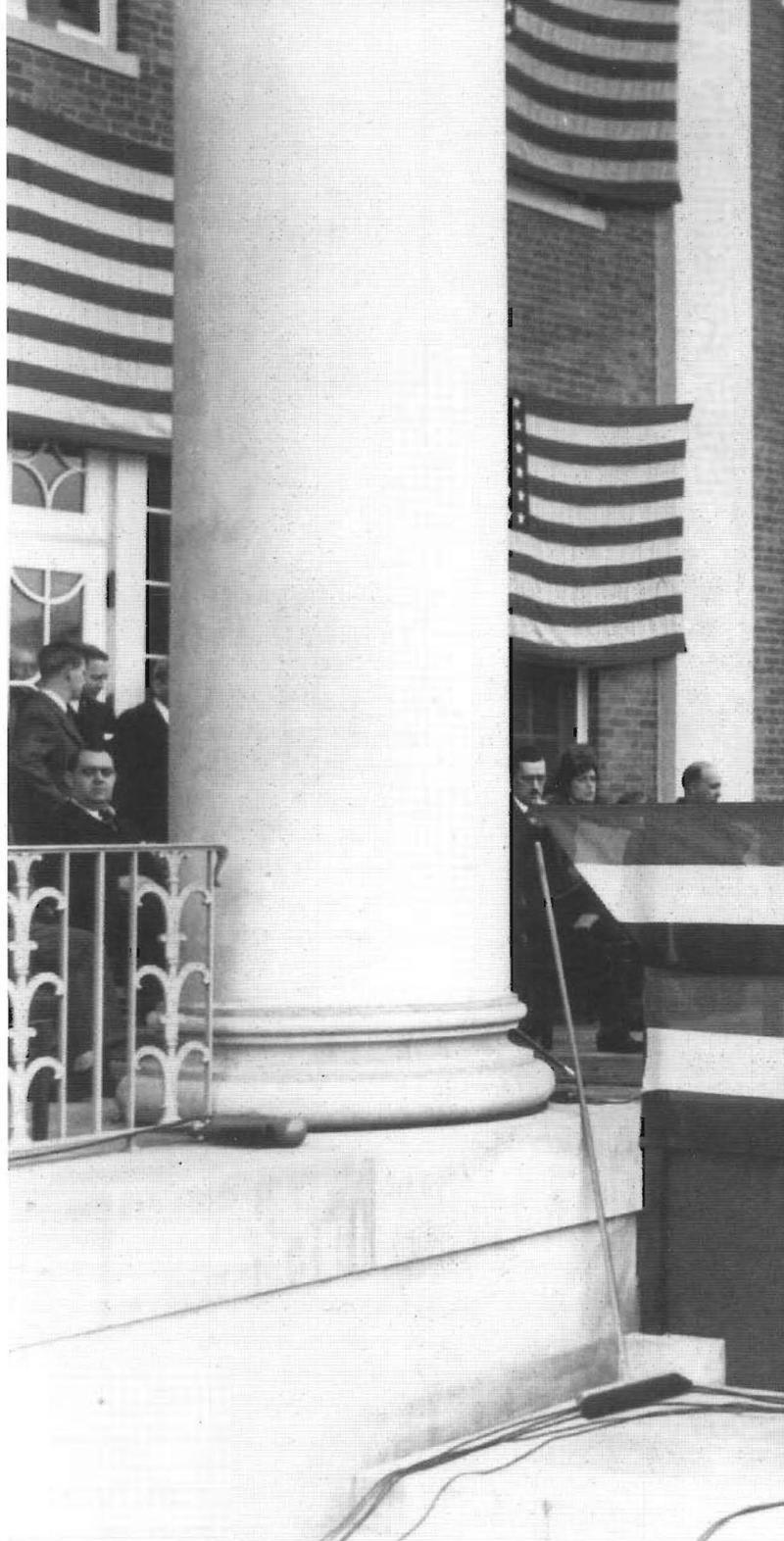
### A biomedical giant starts small

The NIH campus covers more than 300 acres that lie between Rockville Pike and Old Georgetown Road. But its origins lay in a one-room laboratory on Staten Island, in New York. There, in 1887, the Marine Hospital Service (which originally provided health care to sick and injured merchant seamen) invested \$300 in a microscope and other lab equipment and hired Joseph J. Kinyoun, a young physician who had taken a course in the new science of bacteriology. Kinyoun began researching cholera and other communicable diseases that waves of European immigrants carried into the country.

To regulate the quality of new vaccines, serums, antitoxins, and other "biologicals" being developed, in 1891 Congress moved Kinyoun's Hygienic Laboratory to a hilltop near the future Kennedy Center.



Construction on Building 10 began in November 1949. The research hospital would feature laboratories wrapped around patient care units.



THERE IS NO OTHER HOSPITAL LIKE IT



Dedicating the NIH buildings and grounds in 1940, President Franklin Delano Roosevelt portrayed medical research as part of the national mobilization effort then much on his mind. "The defense this nation seeks involves a great deal more than building airplanes, ships, guns, and bombs. We cannot be a strong national unless we are a healthy nation."

Victims of World War I were cared for with arsenicals and carbolic acid. After the war, chemists sought support for an institution that could apply chemical knowledge to medical problems. No philanthropic support materialized so with the support of Senator Joseph E. Ransdell of Louisiana the chemists persuaded Congress that curing diseases would require more government support for science. The Ransdell Act of 1930 named the Hygienic Laboratory the National Institute of Health.

As the institute grew, it needed more space—especially for an animal building in which to raise pure strains of the mice, rats, rabbits, and guinea pigs needed for research and for the control of vaccines, serums, and other biologics. Negotiations had begun for 45 acres of Department of Agriculture land in Beltsville when Mr. and Mrs. Luke Wilson offered half of their 94-acre "Tree Tops" estate to the government, to be used to benefit the people of the United States. Luke Wilson's wealth came from a Chicago sporting goods store. His wife, Helen Clifton Woodward, was the daughter of a founder of the Woodward & Lothrop department stores.

Bethesda was a lightly populated village and Rockville Pike was lined with prestigious estates. Construction of an animal farm aroused strong local objections. But in 1935 the Wilsons conveyed 45 acres (worth about \$750,000) to the government for the sum of 10 dollars. That same year, President Franklin Delano Roosevelt made public health research an integral part of his program of national social security. In the midst of the Great Depression, Congress authorized \$100,000 to build NIH's animal farm. The entire NIH operation moved to Bethesda, and continued to expand.

Concerned about deaths from cancer, Congress in 1937 authorized the National Cancer Institute and provided money for research. Luke Wilson died of cancer three days before the bill passed. Helen Wilson gave more of her estate to the NIH. By 1938, NIH had constructed Building 1 (Administration), Building 2 (the Industrial Hygiene Laboratory), and Building 3 (the animal farm). Buildings 4 and 5 were under construction.

NIH scientists in the early years studied infectious and parasitic diseases, biologics control, and nutrition. They attacked such diseases as cholera, yellow fever, measles, small pox, and tuberculosis. They proved the need for pasteurization and proper sanitation. They developed serum and vaccine therapies. They proved that psittacosis, a viral disease of parrots, could be transmitted to humans—indeed, several people working in the building where the disease was being studied contracted the disease.

The development of penicillin during World War II and the search for malaria treatments launched a revolution in clinical medicine, tying laboratory medicine to the clinician. Between 1945 and 1955, the percentage of U.S. deaths from influenza, pneumonia, syphilis, and childhood diphtheria plummeted. There were fewer deaths from bacterial infections. Congress and the public began to believe that medical science could do anything, given the right resources.

As the war drew to a close, three visionary Public Health Service officers—Thomas Parran (surgeon general, 1935-46), Lewis R. Thompson (NIH director, 1937-42), and Rolla E. Dyer (NIH director 1942-50)—guided through Congress the 1944 Public Health Service Act, which would shape medical research in the postwar world. The idea of the government conducting clinical research (research on patients) was new and far from universally accepted. Despite resistance to the idea, the vision of these clear-sighted Public Health Service officials—to strike a careful balance between basic and clinical research—prevailed, allowing the intramural NIH program, centered on the patient base in the Clinical Center, to flourish. The NIH mandate would be to produce not new knowledge for the sake of new knowledge but new knowledge that led to prevention, treatments, and, where possible, cures. From the beginning tension existed between scientists who wanted to do basic science, in the laboratory or in animal studies, and clinician-scientists who wanted to do clinical research, involving human patients.

In 1948, the National Institute of Health (singular) became the National Institutes of Health (plural) as new institutes were created to work on heart problems, dental research, microbiological studies, and experimental biology and medicine. Part of what drove research at the NIH in the postwar

years was discoveries made during the war. Why, for example, had so many men been declared unfit for service because of bad teeth or poor mental health? NIH shifted its emphasis to basic medical research on major chronic diseases, such as cancer, heart trouble, stroke, arthritis, and mental illness.

As the NIH grew, it needed more space. Luckily, developers had not gobbled up the land south and west of the campus. In 1949, the NIH purchased 200 more acres, from three owners: George Freeland Peter, the Sisters of the Visitation, and the Town and Country Golf Club. With a 306-acre reservation, the NIH had plenty of room to expand.

As the institutes launched investigations of the big killers of the day, it became clear that the NIH needed a place to conduct research on patients. And the same act that gave the NIH the basis for its postwar research program also established the authority to conduct clinical research and to establish the Clinical Center.

### **The NIH adds Building 10**

In November 1948, construction began on Building 10—the NIH Clinical Center, which would be a hospital embedded in a research facility. Laboratories were literally to be wrapped around patient care units, creating a physical environment in which interactions between basic scientists and clinicians would flourish. The building would be fully air-conditioned and wired for bedside television, which was expected to become available within five years.

On June 22, 1951, President Harry S. Truman laid the Clinical Center cornerstone, praising the Public Health Service (of which the NIH was a part) and claiming that “medical care is for the people and not just for the doctors—and the rich.” Warning that the 75 million Americans then without health insurance would soon become a “medically indigent class,” Truman challenged the scientific community to “translate the new knowledge gained by research into better care for more people.” About Building 10 he said, “This clinical research center will advance the work that is being done by all of us to achieve better health...chronic diseases



The NIH campus in 1949

Behind the formal Building 1, the foundations for the Clinical Center—Building 10—are being laid.

“They called NIH a reservation, not a campus,” says a nurse from the early days, “and that’s what it was: gorgeous walking grounds and not that many buildings.”

take a tremendous toll...Modern medicine must find ways of detecting these diseases in their early stages and of stopping their destructive force. That will be the major work of this clinical research center.”

As construction advanced, the heads of the institutes began recruiting clinical staff, so the institutes could begin seeing patients.

In the planning stages for clinical research, while waiting for the Clinical Center to open, the National Institute of Mental Health decided it would set up its first clinical facility—a community health center—in Phoenix, Arizona. NIMH sent John Clausen, Lyman Wynne, and Bob Hewitt\* to Phoenix to set it up. “There was some fanfare in the newspapers about this new facility that the federal government was going to set up in Phoenix,” recalls Wynne, “and at that point there was a big uproar because Barry Goldwater, who was a haberdasher in Phoenix, chose this moment to make a big splash, attacking the federal government for implying that people in Arizona needed mental health resources, saying that ‘in Arizona we are all rugged individualists and we don’t need mental health facilities and you should get the hell out of here.’” Although they had set up an office in Phoenix and had begun seeing a few patients, full operations weren’t really under way, and the publicity was so negative that Clausen consulted with Bob Felix and decided the wiser course might be to retreat to Bethesda. “So in late February, after we’d only been there six weeks, we came back to Bethesda with our tails between our legs and proceeded to set up the first NIMH mental health center in College Park, in an athletic building at the University of Maryland.” Their first offices on the NIH campus, before the Clinical Center was built, were in TC 6 (T standing for “temporary”), a structure only marginally sturdier than a lean-to, near the intersection of Cedar Lane and Rockville Pike.

President Dwight D. Eisenhower, who took office in 1953, was determined to scale back federal health spending. The Clinical Center’s staff was frozen, and the Clinical Center’s planned April opening was delayed for budgetary reasons. The incoming Secretary for Health, Education, and Welfare, Oveta Culp

Hobby, tried to mothball the center before it even opened. As a conservative, and the first secretary of a new department, Hobby did not want major increases in cost. And the costs for creating the Clinical Center were higher than expected, says Leonard D. Fenninger, one of the first doctors to admit patients there—“not only the construction costs, but particularly the operating costs, because the moment they had a patient there, they had to have all the patient services in order. They had to have the kitchen staff, the laundry staff, x-ray, and everything else, so the cost per day when the census was 10 patients was absolutely fantastic.” People were horrified because costs were 20 times the costs of other U.S. hospitals.

But they opened because they had to: Patients had been scheduled to come. Luther Terry had a unit at the Public Health Service Hospital in Baltimore, where he had started clinical research for the Heart Institute, and those patients had to be transferred over. Roy Hertz, in the Cancer Institute, had rented space in George Washington University Hospital, so he had patients scheduled for transfer to the Clinical Center. Pressure to open came from the NIH, from people on various advisory councils, and from the clinicians who had been gathered to do clinical research. Some opposed the opening, especially in universities that had received funding; they feared that this obviously expensive affair might interfere with their continuing contracts. It didn’t. The real extramural program got under way after that; its great burgeoning came in the 1950s.

Finally, on July 2, 1953, Secretary Hobby officially dedicated the 14-story Clinical Center.

At the end of World War II, writes scientist Alan Schechter of the National Institute of Diabetes and Digestive and Kidney Diseases (in an article about the state of clinical research), “the NIH was an agency largely devoted to biology and chemistry, and mice were the major experimental subjects.” The opening of the NIH Clinical Center “was the culmination of the NIH’s transformation from a small federal agency into the powerhouse that has since propelled a large part of all biomedical research in this country.”

\* Typically clinical investigators are M.D.s, although some also hold Ph.D.s. To avoid abbreviation clutter, I’ve dropped most honorifics.



President Harry S. Truman laying cornerstone, 1951

“Modern medicine must find ways of detecting these diseases in their early stages and of stopping their destructive force,” said Truman.

“That will be the major work of this clinical research center.”

## The Clinical Center opens

On a hot day in July 1953, flags waved and a military band played to celebrate the official opening of the massive new structure. Local papers likened the opening of Building 10 to “the launching of a great ship—the biggest ever built. She was filled with the latest equipment; she had a select crew and a select list of passengers. Great things were expected of her.”

Built at a cost of \$64 million, and occupying 1.3 million square feet, the 14-story hospital held a thousand research laboratories, wrapped around 540 patient beds. The original building was designed in the shape of a Lorraine cross. Patient rooms were placed along the south corridor. Along the north corridor and in wings adjacent to the patient areas, scientists worked in laboratories at waist-high benches—hence the term “bench to bedside,” referring to the relative ease with which, in such a setting, findings from basic science could immediately be translated into practical medical applications, and clinical observations about patients would often affect the science being done.

The hospital had no emergency room. A patient who went into labor or broke a leg would be taken to a community hospital for treatment. What it had instead was a bench-to-bedside design. The idea in building a 14-story research hospital with 500 research beds surrounded by twice that number of scientific laboratories was to create a self-contained community of clinicians, scientists, patients, and support staff, with the common goal of conquering both chronic and acute disease.

“They called the NIH a reservation,” not a campus, says nurse Connie Pavlides, “and that’s what it was: gorgeous walking grounds and not that many buildings.” The Bethesda pool, in front of the hospital on the north side, echoed the symbolism of the location. Bethesda was the Hebrew name for a pool in Jerusalem blessed by an angel, where the blind, lame, halt, and withered went for healing.

## JAMES SHANNON, A GENIUS AT RECRUITING SCIENTIFIC TALENT

In *Apprentice to Genius*, a fascinating account of mentoring relationships and lineages in the Clinical Center, Robert Kanigel attributes the strong start of the National Institutes of Health to James A. Shannon, who served as NIH director from 1955 through 1968, during what many regard as the “golden years” of clinical research. Shannon was a tall, bespectacled Irishman who tended to mumble but who had a legendary eye for scientific talent and a genius for recruiting. At a time when “science was still largely the province of gentleman investigators” and the world still looked to the great research centers of Europe for leadership, Shannon turned around scientific research in this country. Before Shannon made the NIH into the NIH, he had first led a program in the basement of New York’s Goldwater Memorial Hospital that sought an alternative antimalarial agent in the early days of World War II. Shannon was widely acknowledged to have developed the “creative research environment” that characterized first Goldwater and then—partly because he’d brought some of the Goldwater scientists down to

Bethesda with him—the National Institutes of Health.

James A. Shannon, master recruiter of scientific talent



Oveta Culp Hobby, Secretary of Health, Education and Welfare, dedicating the Clinical Center, 1953

In the early years, NIH had far fewer institutes than exist today. The bed activation schedule for 1953-54 shows the Cancer Institute with the most beds, at 35; Mental Health, Heart, Arthritis, and Microbiology had 25 beds each, and Neurology, 15. Today the following institutes and centers see patients:

- National Cancer Institute
- National Eye Institute
- National Heart, Lung, and Blood Institute
- National Human Genome Research Institute
- National Institute on Aging
- National Institute on Alcohol Abuse and Alcoholism
- National Institute of Allergy and Infectious Diseases
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Child Health and Human Development
- National Institute on Deafness and Other Communication Disorders
- National Institute of Dental and Craniofacial Research
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute of Environmental Health Sciences
- National Institute of Mental Health
- National Institute of Neurological Disorders and Stroke
- Warren Grant Magnuson Clinical Center

With 6,000 scientists on campus, the Bethesda campus contains the most powerful concentration of biomedical scientists in the world.

Rockville Pike was a two-lane road with few buildings along it—Serio's, the PJ Nees furniture store, and the Colonial Motel, where patients for outpatient treatment stayed, carried to and fro on a shuttle bus. The motel is still there, across and down from White Flint (where, until Korvette's came and went, there was a golf range). Though it was paved, Old Georgetown Road was dark and windy; Rockville Pike was used more because it was somewhat better lit. You could easily park in front of the Clinical Center.

A certain amount of chaos surrounded the hospital's opening. Some of the labs were ready, but many were not. Someone from the nutrition department made a run to the local grocery store to get meat to feed the first patients. And there was an enormous amount of unused space—it was perhaps the one time in the history of the Clinical Center when staff felt they had enough space.

Critical to the success of the research enterprise was the proximity of research labs to patients. Before, research tended to be divided into two cultures: clinicians doing case studies or drug studies and basic scientists working in the laboratory. The Clinical Center's innovative physical—and philosophical—structure permitted a single scientist to work in both the lab and the clinic. More important, it encouraged informal interactions in the corridors between clinicians and basic scientists. That as much as anything permitted physician-scientists first to get an education and then to stay scientifically alive. The physical set-up of the Clinical Center encouraged a cross-fertilization of ideas, enhanced by the presence in one building of trained, intelligent, and devoted caregivers; a critical mass of intellectually curious scientific and medical experts; and the world's best supply of patients with rare and research-worthy medical conditions. Finding solutions to those patients' medical problems through cutting-edge research would be the Center's sole mission, guiding all its activities. The physical presence of the patients would remind the researchers of the urgency of that mission.

Building 10, after construction of the Ambulatory Care Research Facility in 1981



## Building 10

Building 10, which began life as the NIH Clinical Center in 1953, was the tenth structure built on the Bethesda campus. It was unusual even in its naming: It was called a "clinical center," not a hospital. Along the north corridor and in the wings of the huge red brick building were laboratories; along the parallel south corridor were the patient rooms of the hospital. The hospital occupied less than half the space of the Clinical Center. The idea was to bring both basic and clinical science to the patient's bedside. That con-

cept has been followed in most of the construction that's taken place within and around the Clinical Center.

"We do three things here: medical research, patient care, and construction," visitors are often told. Designed for flexibility (to accommodate changing protocols), the Clinical Center began and remained in a constant state of growth and renovation. Renamed the Warren G. Magnuson Clinical Center in 1980, in honor of a loyal senatorial supporter, the

Clinical Center expanded significantly with the addition in 1982 of the Ambulatory Care Research Facility (ACRF), to accommodate the growing demand for outpatient care. As the length of the hospital stay decreased and outpatient medicine grew (recently with the addition of day hospital stations), the need for patient beds in the hospital declined to the current steady-state level of 250 beds.

## A magnet for young doctors of draft age

“Sometimes in medicine, there’s a moment in time when everything appears new, all things seem possible, and breathtaking advances occur—a moment usually triggered by the confluence of place, of technological breakthrough, and of the gathering together of a group of gifted people,” said cardiologist Steve Epstein at a 1997 symposium on intramural research at the NIH. “Such a time characterized those early years of the NIH.”

Neither a conventional hospital nor a medical school, the Clinical Center had no interns or residents—and it needed young doctors to provide patient care. The system for providing such care from the very first was to bring in “clinical associates,” young physicians and dentists who during their internship or residency arranged two years in advance to come to the Clinical Center for two years of training in clinical and laboratory research. During their first year, they provided patient care; during their second year they worked in a laboratory with the senior investigator who had selected them. This was at a time when graduates of medical schools had little or no training in research or in scientific method; they certainly didn’t get it in medical school, where the emphasis was on clinical practice.

The NIH is not a university, although there has been some discussion of developing a graduate school on the campus, but the senior investigators work closely with and depend on their trainees. Long-term technical staff provide a lab’s long-term memory, but much of the work is done by the trainees in the clinical program and by MDs and Ph.D.s who come through for basic laboratory training. The Clinical Center offers less formal teaching than a medical school, but the clinical associates have benefited from training in the form of day-to-day interactions and critiques of their work.

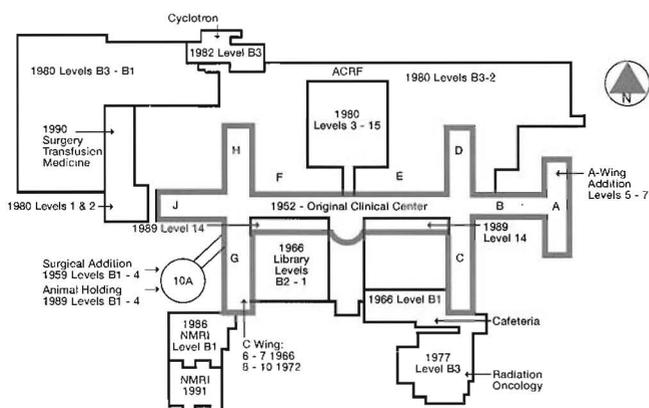
The Center owes its strong start partly to a brilliant recruiting device. The outbreak of the Korean War in June of 1950 had created a consensus for a “doctor draft” to provide the physicians and dentists needed by the military. An amendment to the Selective Service Act passed in 1948, in the

early days of the Cold War, revived the government’s authority to draft young men into the military. The prospect of two years’ obligatory service in the military influenced many to try a stint in medical research. For the two decades that the doctor draft continued (it ended in 1973), the Clinical Center had its pick of candidates from the top medical schools. People who would never have considered leaving the elite medical schools for the NIH did so for two years in lieu of military service.

Tony Fauci remembers a recruiter from the Armed Forces coming to Cornell in 1966, when he was about to start his internship and residency. Early in the fourth year of medical school, they gathered in Cornell’s auditorium—79 men and two women—and the recruiter said, “Believe it or not, when you graduate from medical school at the end of the year, except for the two women, everyone in this room is going to be either in the Army, the Air Force, the Navy, or the Public Health Service. So you are going to have to take your choice. Sign up and give your preferences.” At the time the NIH was just blossoming, says Fauci, and everyone who had any role in academic medicine spent some time there, so he put the Public Health Service as his first choice, followed by the Navy.

During the 1960s especially, the doctor draft brought many bright young physicians to Bethesda for an official two-year stint, an alternative to military service. In 1960, 68 physicians reported for the associate program. After the Gulf of Tonkin Resolution in 1964, which gave the President the authority to take military action in Vietnam without congressional approval, 153 physicians reported for the associate program. There were 178 associates in 1966, 206 in 1970, and 229 (the peak) in 1973, the year Henry Kissinger negotiated a peace settlement in Paris. The selection process became extremely competitive. At first, the young doctors were chosen through the old boys’ network, but very soon the Public Health Service developed formal application and testing procedures. “The best, the absolute cream, the ‘Tiffanys,’ all applied,” said Donald Frederickson, one of the first clinical associates and later director of the NIH. For a time, Frederickson helped decide who would be admitted in the

### Clinical Center’s Changing Footprint



### Building Elements - Gross Square Feet x 1000

1952	Original Clinical Center	1,302
1959/89	Surgical Addition (Building 10A/Animal Holding)	45
1966	Library, Cafeteria, G-Wing (2 Flrs.)	102
1972	G-Wing (3 Flrs.) Elevator Tower	28
1977	Radiation Oncology	38
1980	ACRF - Structure	740
	- Parking Garage	568
1982	Cyclotron	10
1986	NMRI Research Center - Phase 1	11
1989	Solarium	6
1990	Surgery/Transfusion Medicine	37
		<hr/>
		2,887

### Recent Additions

1992	A-Wing Addition	56
1991	NMRI Research Center - Phase II	10
		<hr/>
		2,953

Heart Institute.\* “Each Institute would do their damndest to get what they considered the very best....The art of picking, out of a whole group of qualified people, those who might become successful scientists was extremely difficult and still is today....The main objective was getting people who would use this environment to become scientists.”

There was a period during the doctors’ draft when two-thirds of the Harvard medical students applied to the NIH. They came not only to avoid the draft but also because it had become the place to be. The excitement of the new venture drew young investigators from all over the world, who came to learn, make their mark, and (usually) return to their home institutions. Some came intending to go into a special medical practice, says Tom Waldmann of the Cancer Institute, who also started as a clinical associate. But “some you could capture, some you could induce to stay.” Many of the great names in medical science got hooked on research and stayed. And given full support, they made discoveries at an amazingly rapid rate.

Their two-year period at the NIH gave many of these doctors their first taste of research, which they continued when they returned to academia. The NIH became an important training ground for the nation’s biomedical researchers, who, during their training period, provided care for the Clinical Center patients. It was, for many, a transforming experience. The Clinical Center provided superior facilities for research training and excellent mentors, including several Nobel laureates. Clinical associates had a chance to work with world-class scientists and their peers were top graduates from the country’s elite medical schools. The NIH’s seminars and courses were as good as those at any university, and one had only to walk down the hall or to the next building to find someone to answer a question, such was the critical mass of experts on campus. The program trained them to be clinical investigators rather than just skilled practitioners. “To their solid medical education were added scientific knowledge and experimental techniques,” observes Melissa Klein, “and in their career-oriented minds was implanted a vision of the physician-scientist

who would discover fundamental biological mechanisms and apply those insights to the cure of disease.”\* The associates became some of the nation’s most skilled researchers, part of an international network of scientists. They went on to train new generations of researchers—and to increase the number of centers at which such training was offered.

When the doctor draft ended, well over half the leadership in biomedical research had spent a couple of years at the NIH—which meant they spent time at the Clinical Center. The spectacular launching of clinical research that began in 1953 spawned a generation of research scientists in the 1950s and 1960s who established new centers of scientific creativity throughout the United States. Building 10 became a center for studying and training in clinical research as much as it was a place to conduct clinical research.

“The broad reach of the Clinical Center is evident in the stories of the people who pass through the Clinical Center,” says Harry Malech. “Not necessarily the ones like me who have been here a long time but people who have been here five, six, or seven years—but an amazingly formative five, six, seven years of their lives—and then they go someplace else and have extraordinarily distinguished careers as leaders in their clinical field. Some pretty remarkable people—including that first generation of superclinicians in the 1960s—have passed through these buildings, either for their whole careers or for some portion of their careers.”

### A haven for scientific couples

For two decades, the clinical associate program was a boys’ club. No women were accepted in the program during the doctor draft because doing so would put a promising young male scientist “in harm’s way.” The short-term effect of the unofficial all-male policy, concludes Melissa Klein, “was that few women had access to a highly regarded program that provided its participants with excellent mentors and an ongoing system of career support. The long-term effect was to penalize women by preventing their access to influential positions in

\* This section draws heavily on an excellent working paper by Melissa K. Klein, “The Legacy of the Yellow Berets.” No one is certain when the phrase originated, says Klein (whose father, Harvey Klein, heads the Department of Transfusion Medicine), and for some the term “yellow beret” must have conveyed a derogatory meaning, contrasted with the “green berets” (Special Forces Operatives trained for fierce combat in Southeast Asia). But by the war’s end most associates “used it as a badge of pride.”

## Decades of leadership

For more than four decades, reported *Science* magazine in 2001, Alan Rabson and Ruth Kirschstein had worked and lived on the NIH campus—in one of the few houses available to Public Health Service officers. (Their son, molecular geneticist Arnold Rabson, grew up on campus.) As first clinical resident in the Clinical Center’s clinical pathology department (now laboratory medicine), Kirschstein’s initial job was to help identify the organisms that gave exotic infections to the many patients immunosuppressed from chemotherapy for serious cancers. “It was a very, very exciting time,” she says. Rabson became deputy director of the Cancer Institute, and Kirschstein rose twice to acting directorship of the NIH.



academic medicine.” In short, the golden years of science at the NIH were golden mainly for men.

On the other hand, as Buhm Soon Park observes in a recent article about the intramural program at the NIH, the NIH was remarkably free of anti-nepotism rules, which made it a safe harbor for professional couples if both of them wanted to work in biomedical research. Most universities did not permit both husband and wife to work for them, so the NIH became an attractive alternative destination for many two-scientist marriages. Among scientific couples Park lists as adding to NIH’s luster were Earl and Theresa Stadtman (he turned down a position at the University of Chicago because it had such a rule), Jerald G. Wooley and Bernice E. Eddy, Julius and Florence White, John and Elizabeth Weisburger, Herbert and Celia Tabor, Marjorie and Evan Horning, Martha Vaughan and Jack Orloff, Barbara Wright and Herman Kalckar, and Alan Rabson and Ruth Kirschstein.

One couple that enjoyed the pleasure of working together at the NIH was the Braunwalds, both on the staff of the Heart Institute—she as a cardiac surgeon, he as head of the cardiology branch. “It was a special moment in time,” recalls Gene Braunwald, who with his wife of three years, surgeon Nina Starr Braunwald, drove down from New York in July 1955 to serve as cardiologist for the Heart Institute. “The first year, even though it was just across the street, we had to do night call in the hospital. I remember my first night in the Clinical Center’s on-call room. Later they relented. They realized they weren’t getting that many emergencies and decided we could do night calls at home.”

Home was an apartment building across the street from the Clinical Center, built to house doctors, nurses, and other staff who might otherwise find the Clinical Center too far out in the country to get to at night. “We lived in that apartment building for two years,” says Braunwald, “and not because we had to. We loved living there.” Construction on the apartment building was completed in June 1955, and in July the Braunwalds and 24 other families moved in. “We had a wonderful two-and-a-half-room apartment. We didn’t need any more until much later.”

There was a wonderful sense of community in the apartment building. “I had never experienced anything like that before or after,” says Braunwald, “with everyone the same age, mostly in their twenties, and most newly married. We were already three years married, so we were sort of an old couple, but we were young in age. Nina was finishing her residency at Georgetown, working most nights at the hospital, and John Ross [who also worked in cardiology] would cook for me. He would cook and I would eat. We cooked up some wonderful ideas. It was a very special time.”

After Nina Braunwald finished her residency, she accepted a position as surgeon in the cardiac surgery clinic, working with Glenn Morrow. Both of them were at the top of their field, achieving important breakthroughs both independently and in collaboration. “There were important things happening on a week-to-week basis,” says Gene Braunwald. “Very, very few times in anybody’s life do you get into a phase where things are happening constantly, and you realize that these are important events. At the same time, of course, we had our first house, we had our children, we had our first pets, so we were also establishing ourselves as a young family. These were wonderful years.”

Nina Braunwald became deputy director of the surgery clinic and recalled later of her decade at the Clinical Center, “At the end of the 10-year period, I was as happy and I felt as accepted as at the beginning. We lived only four minutes from the NIH, so I could run home for supper, see the children to bed, and then get back in time to deal with the postoperative bleeder, stay up all night, be back home in time for breakfast, see them off to school, and then be able to get back for the day’s case. I elected to wait to start a family until I had my surgical boards and to time my pregnancies so that I never would appear at an oral pregnant. I felt that in those days that was pushing the system a little too much, since ‘publish or perish’ was a very important dictum at the NIH. When I wasn’t in the operating room, I was working on manuscripts. I only took two weeks off each time each child was born. Between delivering the children, I wrote papers right up to the end. I operated up until I was eight months pregnant, and I only took two weeks off. I had this sense that . . . if I left a void, it would be filled regardless of where I was.”

## The lure of mentoring, collegiality, and independence

Salaries were so low at first that in 1957 one of the hospital's most qualified technologists left to accept "a better paying position as a grade school teacher in Virginia." Over time, salaries became more competitive, but earning potential was never what drew the critical mass of scientists, clinicians, and technical staff needed to man an experimental hospital. The greatest magnet for the research staff was that the Clinical Center promised an atmosphere of scientific freedom. Research would be investigator-driven. Buhm Soon Park quotes a 1965 NIH Study Committee report to President Lyndon Johnson, applauding NIH scientists' independence:

The NIH scientist has at least as much, and probably more, "academic" freedom than his university counterpart. He chooses his own research project and determines his own direction of approach (within wide limits set by general agreement with his superior). He finds it relatively easy to secure modern equipment. . . . In general he is better shielded from "redtape" annoyances than are most university scientists. He has fewer distractions to keep him away from his laboratory—faculty meetings, department administrative assignments, committee activity, and the like. . . . Not being in an educational institution, he need not teach; he can devote all his time to research."

The Clinical Center served as a magnet for bright young people excited about the work they were doing, with the intellectual capacity to ask important questions and to find ways to answer them. After a brilliant dash from the starting gate, the Clinical Center developed a reputation as a site that combined cutting-edge patient care with intensity of research, ranging from molecular and cell biology to animal studies and clinical research. Patient care and research fed each other: Physicians made observations in patients that they couldn't explain, and they could go straight to the laboratories to find

the answers. In the 1950s through the 1970s, such capacity for sophisticated research in a clinical care facility was rare, and the intramural research done in the Clinical Center became a model for great research universities all over. What made the Clinical Center a wonderful place to work was the concentration of brilliant clinicians and scientists and the combined possibilities of research and patient care.

The place encouraged collaboration like few other places before or since. A report by Ed Rall, who during his time as deputy director for intramural research enriched collegiality among researchers, pointed out that intramural research really wasn't different from extramural research; what was important was the quality of the research, and one special feature of intramural research was the collaborative nature of interactions with scientists.

"The mentorship in this institution is extraordinary," says Tony Fauci, whose mentor was Sheldon ("Shelly") Wolff. "He took me under his wing and showed me some basic principles about research." The young associates were often more adept at new gadgets and new molecular techniques than the older staff, says Fauci, but the established staff had "the experience, the judgment, the way of analyzing data, of keeping a proper perspective—being enthusiastic but not so enthusiastic that it blinds your objective evaluation of the data. One generation passes that on to the other. They complement and feed on each other, and it makes for a very good relationship."

Whenever they weren't working, the scientists could be found talking about their work. In the beginning, they often brought their lunch and ate it in the library. They would meet in journal clubs, data clubs, lab meetings, and other gatherings. Discussions of what was presented helped strengthen their sense of what was "good science."

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THE NIH SCIENTIST HAS AT LEAST AS MUCH, AND PROBABLY MORE, "ACADEMIC" FREEDOM THAN HIS UNIVERSITY COUNTERPART.

## Crowded labs and slow elevators

Beyond formal training in research, constant presentations about up-to-the-minute research, and regular though informal gatherings, above all the Clinical Center has always been a place where people learned things in elevators and corridors, as Nobel laureate Martin Rodbell explained in a talk at a 1997 symposium on intramural research:

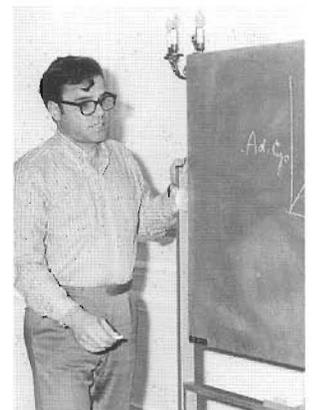
“By the time of the Golden Sixties, the threat of A- and H-bombs coupled with Russia’s shooting off the Sputnik in 1957 had changed the thrust of support for science in America. . . . the corridors suddenly became crowded with refrigerators, ultracentrifuges, beta counters, supplies, and equipment of all types. The labs were at least four deep with postdocs. Isolation of fat cells became my claim to fame, even to the extent of being called “Professor” by Europeans who call everyone by that title. Thinking that I was another Einstein, they searched in vain for a large pretentious office with my name in bronze on the door mantle. The laugh was on them—my colleagues love to recollect—as they bowed their way into my closet after removal of the typewriter.

[F]inally I had a sensitive, understanding community of scientists surrounding me in those crowded NIH labs and corridors. A community of effort seemed possible, but I realized that there was little room for me except in my sardine can of an office. Discussions were impossible. My only recourse was to descend to the Building 10 cafeteria, eight floors below. That descent was a godsend for me. Invariably it was slow enough to have spirited conversations about the latest results before the elevator door opened and we spewed forth to the cafeteria. There, long discussions with many others continued. . . .



Martin Rodbell,  
Nobel laureate

With laboratories four-deep in postdoctoral fellows, scientist Martin Rodbell retreated to the cafeteria eight floors below for conversations. “Crowded labs and slow elevators” elicited fruitful exchanges among the community of scientists, said Rodbell in a memorable talk about scientific breakthroughs.



THE LAUGH WAS ON THEM—MY COLLEAGUES LOVE TO RECOLLECT—AS THEY BOWED THEIR WAY INTO MY CLOSET AFTER REMOVAL OF THE TYPEWRITER.



The Clinical Center's  
first patient

On July 6, 1953, Roy  
Hertz (left) admitted  
Charles Meredith, a  
Maryland farmer with  
prostate cancer.

# THE BATTLE AGAINST CANCER

**R**oy Hertz admitted the Clinical Center's first patient—Charles Meredith, a Maryland farmer with prostate cancer—on July 6, 1953. Since then, NIH investigators have seen more than a quarter million patients. As protocols changed so did the diseases the nurses would see on the wards. In 1953 polio patients in respirators got special care from nurses on the eleventh floor. When an effective vaccine came along, polio was no longer an active protocol. But cancer was always there.

These were the early days of single-agent chemotherapy and the side effects of drugs were “pretty rough,” says Leonard Fenninger. The NIH had a special arrangement with the United Mine Workers (before they built their own hospitals), through which the union would refer children with untreated leukemia to the Clinical Center. “We had a number of children who came out of the hollows of West Virginia, who had never been away from home, whose mothers came with them, and *they* had never been away from home.” The mothers were used to death in the mines, but they were also used to tremendous community support, and in Bethesda they were completely removed from that—except for the doctors, nurses, and social workers at the Clinical Center. By the end of that first year, all but one of the 32 patients Fenninger saw were dead. He decided he couldn't divorce himself from the people he was caring for, whom he felt were doomed to die, so he left the NIH in 1954.

There was tremendous opposition to the Clinical Center's experiments in chemotherapy, especially with a population of beautiful young children. The children's deaths produced major emotional stress, not only for the parents but for everybody around them. “And there had always been a feeling that you really shouldn't interfere with God's will,” says Fenninger. Meanwhile, Jim Holland, Fenninger, and others got the Cancer Institute labs up and running so that everything was in place when a more successful intervention came along.

## Pioneering in combination chemotherapy

Histories of the NIH intramural program often refer to the 1950s and the 1960s as the golden years, and so they must have seemed when so many investigators were striking out in bold new directions and laying the foundation for biomedical research for decades to come. But the path to remarkable medical achievements was not always easy. Major breakthroughs in cancer research came fairly early in Building 10, for example, but the protocols that brought them were not wholeheartedly welcomed at the time.

A young Chinese postdoctoral medical fellow, Min Chiu Li, brought from Sloan-Kettering some women with gestational choriocarcinoma, a rapidly fatal and rare cancer of fetal tissue of the placenta. Ann Plunkett, one of the first nurses on the cancer service, recalls, “They would come in, these young women, and die within a matter of weeks to months.” Li proposed

Gordon Zubrod,  
NCI's first clinical  
director

Oncologists were known as “poison doctors,” when Zubrod came to the Clinical Center. He fought for chemotherapy when it was considered bad science and helped change thinking about clinical trials.



administering large doses of a new folic acid antagonist, known now as methotrexate, and Roy Hertz allowed him to decide for himself whether to proceed. At first the drug made the patients ill; then one patient responded, and a second, and a third. “It made you a real believer in medical research, to see these young women begin to live,” says Plunkett. In 1957, with single-agent chemotherapy, they had achieved not just remission, but a cure—the first successful chemotherapeutic cure for malignancy in a human solid tumor. Because it was an unusual tumor, with an immunological component (the placenta being considered tissue the mother’s body could reject), that first success was attributed to “spontaneous remission.” Nobody would accept it as proof that chemotherapy could cure cancer, and Li was asked to leave NIH.

After Roy Hertz admitted that first cancer patient, NCI’s scientific director, Bo Mider, recruited Gordon Zubrod, an oncologist with a solid scientific background and excellent administrative skills, to be clinical director for the NCI. As part of the team that had worked on the anti-malarial drug program at Goldwater Memorial in the early days of World War II, Zubrod had learned something about drug development. “When Gordon came in 1954, oncology was one of the lesser disciplines in clinical medicine,” says Alan Rabson. “Clinical medicine was dominated by people who studied the kidney, who measured clearances and had all sorts of data. At the bottom of the barrel of clinical medicine were oncologists, who were known as poison doctors. Gordon played more of a role in changing that image than any other single person.”

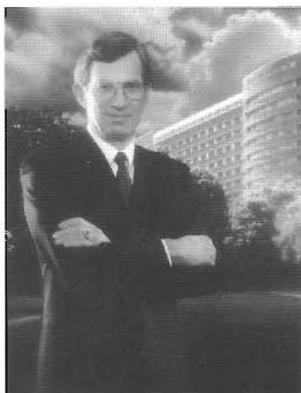
Zubrod began recruiting a cadre of promising oncologists, two of whom had remarkably similar names: Emil Frei III, whom everyone called Tom, and Emil Freireich, whom everyone called Jay. Frei and Freireich were aware of preclinical studies of combination chemotherapy by Howard Skipper and Abe Goldin, and, as luck would have it, Jay Freireich had rented a house in Bethesda next door to Lloyd Law, a giant in cancer biology and one of the NIH’s first “mouse” doctors. Law and Freireich had adjoining backyards, unseparated by a fence, so they got to know each other. Freireich learned that Law had had some success administering combinations of chemicals, or “combination chemo” as it would become known, to leukemic

mice. Lloyd told Freireich about his experiments, Freireich told Frei, they consulted with Zubrod, and against strong external resistance from a cancer community that felt the science wasn’t ready for it, Frei and Freireich introduced intensive combination chemotherapy for the treatment of acute lymphocytic leukemia of childhood. At the time, a diagnosis of leukemia amounted to a death sentence.

In the early 1960s, surgery and radiotherapy were considered the only appropriate treatments by mainstream cancer researchers. Denouncing Frei and Freireich’s approach as “toxin of the month,” they felt chemotherapy drugs should never be used in combination because they were poisonous and because tumors developed resistance to them. “The dogma was you must treat with single agents one at a time,” says Rabson, “and when the tumor became resistant to the first one, you still had the second one, and the third. The concept of mixing them together was thought to be absolute madness.” Rabson, NCI’s good-humored deputy director, remembers with amused regret that he said at the time, “If you take one ineffective drug and mix it with another ineffective drug, don’t expect an effective combination.”

It had been shown, however, that some combinations of drugs had a synergistic, not just an additive, some effect, so there was some reason to think combination chemotherapy would work, and Frei and Freireich had strong support from their boss, Gordon Zubrod, who proposed dividing clinical trials with new cancer drugs into three phases. Frei and Freireich administered four different drugs, with non-overlapping toxicity (so you could use them at full dose), which attacked cells at different phases of the cycle.

Frei and Freireich proved the naysayers wrong and produced the first cure by chemotherapy of a childhood cancer, which helped to establish the intramural Cancer Institute as willing to take high risks for high rewards—based on evidence of a good chance an experiment would work. At first, only a small percentage of the young leukemia patients treated were cured, but the research has continued, and today acute lymphocytic leukemia is curable in 80 percent of children. Now the NCI is testing the long-term effects of radiation therapy given long ago



Vince DeVita

In helping to prove that cancer could be cured with chemotherapy, DeVita also helped establish Building 10 as the center for “proof of principle.” You needed a place like the Clinical Center, he says, and you needed people willing to let the unaddressable questions be addressed.

“NO OTHER INSTITUTION IN THE WORLD WOULD EVEN DARE TO ASK THAT KIND OF A RADICAL QUESTION.”

for children with leukemia that had reached the brain (most drugs do not cross the blood-brain barrier).

A young clinical associate named Vincent DeVita would take the lead in similar work on Hodgkin's disease, the first adult cancer of a common organ system to be cured by chemotherapy. And in the multidrug therapy trials for Hodgkin's, huge proportions of the patients treated were cured.

Li, Frei, Freireich, and DeVita were asking the question, "Could you ever cure advanced cancer with chemotherapy?" at a time when cancer was believed to be an incurable disease, and chemotherapy was regarded by many as the cruel use of toxins in patients already facing certain death. "Tom Frei created the environment where you could ask the question," recalls DeVita, now at the Yale Cancer Center. "No other institution in the world would even dare to ask that kind of a radical question. Between the two diseases we proved the point, that cancer could be cured with chemotherapy—something that's been subsequently proven many times over. You had to have a place like the Clinical Center, and you had to have people who were willing to let the unaddressable questions be addressed." The Clinical Center became the center for "proof of principle."

"I don't think it could have been done elsewhere," says Tom Frei, now at the Dana Farber Cancer Institute. "We were definitely swimming upstream. And you had people who were totally devoted to that program. In practice we see patients with various diseases for the most part, and that's essential for good practice, but it doesn't allow for the kind of focus that we were able to achieve in one disease for a long period of time. Taking care of patients today is a major effort—all the reading and studying and talking to basic scientists, working in laboratories, developing protocols, working with lab technicians—that's a big effort. We were fortunate in that we were allowed to focus just on the one disease and the things we needed for that one disease."

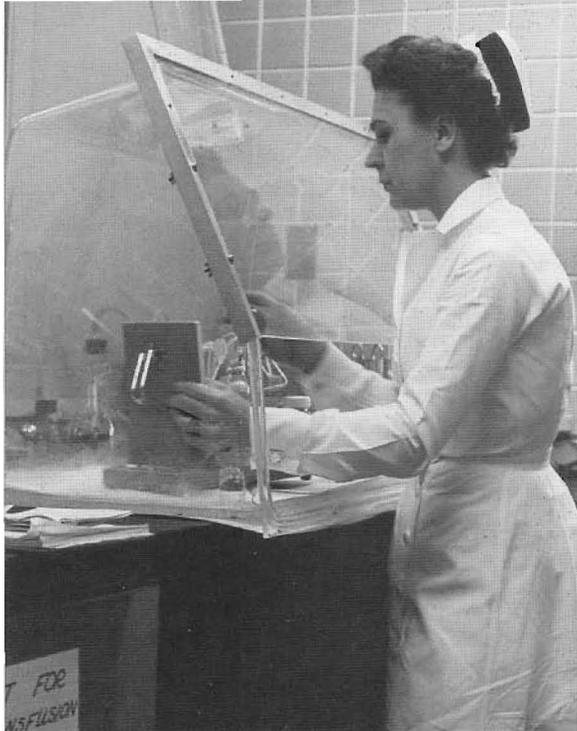
More conservative academic cancer researchers considered Frei and Freireich to be "just maniacs," says DeVita, who is writing a book about the war on cancer. "They were really taking a terrible beating in those days. Cancer was a fatal disease and the idea that chemotherapy could cure it was only in the thoughts

of people who were somewhat deranged. I'm only slightly exaggerating. Gordon Zubrod fought the battles at the higher levels, to allow people like Frei and Freireich and myself to do things that otherwise couldn't possibly be done. He provided a protective umbrella over us, and it paid off. But in those days I think we couldn't have done it anywhere but the Clinical Center.

"Medicine doesn't just move smoothly forward," says DeVita. "Strong feelings influence what goes on and what people can do, and in the environment of the Clinical Center, although those strong feelings existed, you still had the freedom to move, whereas strong feelings at a university would stop you cold because any tenured professor can object to something. You needed to do it in a place like the Clinical Center, and then it opened the door for the same things to be done at Yale, and Harvard, and so on." Thanks to work done in the Clinical Center, combined chemotherapy is now the predominant treatment for many types of cancer and has saved countless lives.

Using high-dose regimens to destroy tumors successfully treated the underlying diseases, leukemia and Hodgkin's, but often destroyed bone marrow. With too few platelets, the patients could bleed to death; with too few white blood cells, they would develop opportunistic infections. NCI and the Clinical Center staff together developed techniques to support intensive combination chemo, including transfusions of white cells and blood platelets. Freireich and his colleagues pushed for development of machines to remove platelets from normal volunteers' blood for infusion into cancer patients undergoing chemotherapy. NCI investigators, in collaboration with George Judson, an IBM engineer, developed what became the IBM 2990 blood cell separator, still considered the most effective means for collecting adequate numbers of leukocytes from normal donors. Freireich was also involved in infusing white blood cells into patients. To provide a germ-free environment, a laminar air flow room was installed on 13 East, which took its first cancer patient in 1969 and was later used to treat patients with severe combined immunodeficiency (SCID).

Later Bob Young, who went on to run the Fox Chase Cancer Center, together with others at NCI, developed some of the first regimens of curative chemotherapy for ovarian cancer.



## INGENIOUS BLOOD BANK NURSE DEVISES BLOOD-SAVING TECHNOLOGY

In 1966, Wanda S. Chappell, chief nurse in the Clinical Center blood bank, came up with a simple but ingenious method for separating blood platelets (the smallest blood cells, which play an important part in clotting) from blood plasma. By using this technique, the hospital could use platelets for transfusion to leukemia patients and keep the rest of the blood for other patients, including patients undergoing open heart surgery.

In 1967, Chappell received an "Economy Champion" citation from Civil Service Commissioner John Macy and a check for \$1,645. Her idea for concentrating

platelets was saving 3,700 pints of blood a year at the Clinical Center blood bank and many more at other hospitals throughout the country. At the time, the Clinical Center was administering 10,000 to 12,000 platelet transfusions a year.

A Public Health Service official who screened the award recommendation before it went to the Surgeon General said, "A number of researchers with advanced degrees and qualifications were working on the problem. Chappell thought of something practical that can be used by everybody. It was the application of common sense to a difficult problem."

Until 1966, platelets were transfused while still mixed with most of the blood's plasma. The red cells that remained could be used for ailments such as anemia, but if the platelets could be concentrated, the saved plasma could be remixed with the red cells—to provide whole blood. The trouble was, platelets separated from plasma would stick together and be useless.

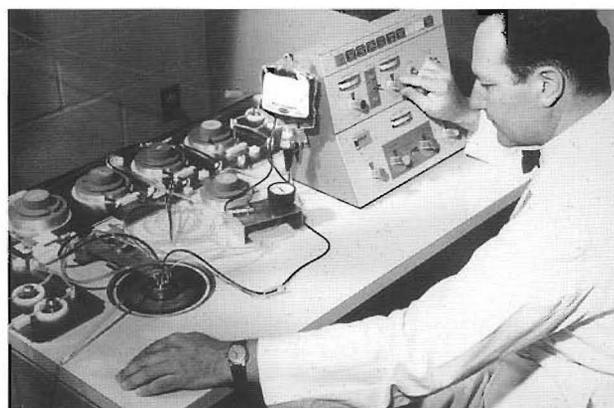
In 1965, Dr. Richard Aster, formerly at the blood bank, had explained that platelets could be kept from sticking together by adding extra acid used normally to keep stored blood from clotting, but this created other problems. Chappell remembered that plastic blood bags were manufactured with a little more acid than was needed to prevent clotting. She suggested some of this acid be pushed from the main blood bag through a connecting tube to a smaller bag that would hold the platelets.

After using Chappell's method on a trial basis for the first six months in 1966, the blood bank adopted it fully. "A large amount of money is being saved," said Paul J. Schmidt, chief of the blood bank. "However, it is more important that blood is an irreplaceable human resource from which multiple use must be obtained. Mrs. Chappell's idea advances us and the country as a whole toward that goal."

*Transfusion*, the official journal of the American Association of Blood Banks, reported on the method in the July-August 1966 issue, and the procedure was readily adopted by other blood banks. It required only standard equipment. An associate professor at the University of Michigan Medical Center wrote, "I am sure many people must have thought, 'Why didn't I think of that?'"

Chappell had earned her RN at Massachusetts General Hospital.

Wanda Chappell



Emil ("Jay") Freirich (photo on left) abounds with ideas, both possible and impossible. Emil ("Tom") Frei III specializes in the possible. Together they changed medical history.

Marc Lippman, who went on to head the Lombardi Cancer Center at Georgetown, developed the breast service at NCI and worked out some important aspects of the hormonal treatment of breast cancer and combinations of hormonal and chemotherapy treatment.

As NCI's director of drug development, Sam Broder, who played an important role in developing the drugs now used to treat AIDS, also contributed to the development of taxol, one of the major cancer drugs. Broder looked at the data on some human trials of the drug after it had been discarded as too toxic and bucked resistance to figure out ways to make it practical.

M.C. Li finally did get recognition for his early work in chemotherapy. In 1972, most of the Lasker Awards presented for research on cancer treatment went to researchers in the Clinical Center: Paul P. Carbone, Vincent T. DeVita, Jr., Emil Frei III, Emil J. Freireich, Roy Hertz, James F. Holland, Min Chiu Li, Eugene J. Van Scott, and John L. Ziegler, with a special award to C. Gordon Zubrod. More important, these investigators provided invaluable training to many others. Vince DeVita alone trained 93 people, a third of whom have gone on to head cancer centers around the country.

### Cooking tumors with needles

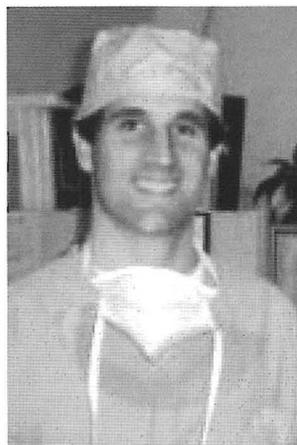
Cooking tumors with needles may become an alternative to surgery for patients with kidney and other cancers, according to Bradford Wood, a clinical investigator in Diagnostic Radiology. Radiofrequency ablation (RFA) uses radiofrequency energy—the same energy that carries radio signals—to “cook” and kill cancerous tumors, without cutting them out.

RFA is a minimally invasive image-guided surgery that harnesses the power of an electrical current and delivers it with an electrode-tipped needle, destroying tumors without affecting surrounding healthy tissue. This technique is being used on tumors throughout the body, including painful tumors and cancers of the kidney, adrenal, liver, prostate, and bone, and “preliminary results look promising,” says Wood.

Wood did a series of studies on kidney tumors, using RFA guided by CT and ultrasound. If after a month or two the tumor stops growing and doesn't take up x-ray contrast dye, it is considered dead. “What matters is whether or not any growth recurs, or if there is any irregularity at the periphery of the treated area that might suggest recurrence,” says Wood. In the NIH study, patients with small, recurrent, hereditary kidney tumors experienced little or no pain, no major complications, and no change in kidney function, and, after 2 to 24 months, 70 to 90 percent of kidney tumors were totally destroyed. For those patients, “RFA may provide an effective, minimally invasive option that spares normal kidney and prolongs function,” says Wood. A related Clinical Center study of tumors of the adrenal glands had similarly promising results, with no major complications.

“RFA is less expensive, safer, and generally easier for patients than surgery,” says Wood, “and early results are optimistic, but without randomized, prospective trials and long-term results, it is not yet an alternative to surgery, the proven treatment of choice for most solitary or small liver tumors.” Nor is RFA appropriate for every patient, but the fact that it is a low-risk procedure allows researchers to apply it in new situations where there is a possibility it may help, says Wood.

How is it done? A very small needle with an electrode on the tip is inserted into the tumor, typically guided by computerized tomography (CT) or ultrasound. RF energy is fed to the tumor



Brad Wood, advancing interventional radiology

Image-guided therapies change the role of the radiologist from diagnosis to therapy. The late John Doppman created a model for interventional radiology. Investigator Brad Wood, shown here, is advancing the tradition.

### A scientific “marriage of convenience”

In presenting the Charles F. Kettering Prize to Emil Frei III and Emil J. Freireich in 1983, Charles F. McKhann explained that the joint award was a rare exception, awarded only because it was impossible to determine which of the two men had greater responsibility for their joint achievements. In describing their traits, he suggested that the audience would recognize the qualities that “make for a good marriage”:

“One is politically conservative, the other

is very liberal; they probably cancel each other out in major elections. One could probably eat a little more, the other is a gourmet cook. One abounds with ideas, both possible and impossible; the other specializes in the possible. One is verbal and volatile, often right but never wrong. The other is quieter, contemplative, and reasoning. One is relaxed and casual in his lifestyle; the other is neat, precise, almost compulsive. Perhaps most important, both firmly attest that they have never, ever, agreed on anything. However different Frei

and Freireich may be, each brought to this scientific ‘marriage of convenience’ a willingness to reason and compromise that allowed them to do a monumental piece of work—to cure childhood leukemia.”

through the needle. The electrode generates heat up to 100 degrees Celsius. After 10 to 12 minutes of contact, the RF energy cooks a 1- to 2-inch sphere, killing the tumor cells or damaging them to the point where they will die. The dead cells become scar tissue and eventually shrink. A small margin of normal tissue may be destroyed, too. Complications can include infection and bleeding. Typically, the patient is lightly sedated for the procedure and may go home hours later, usually feeling no pain.

“RFA appears to be an effective option, especially for people with hereditary kidney tumors,” says Wood. “This is not a magic bullet or a panacea. But when we need to debulk or get rid of a certain focus of a tumor, it makes sense. Partial removal of the kidney may sacrifice too much of the organ. These patients are likely to have more tumors in the future, and we want to save as much of the kidney as possible.”

RFA may soon be improved by the use of microwaves, which distribute heat uniformly and may be less susceptible to the “heat-sink effect,” in which a large blood vessel nearby cools the area by removing warm blood. “Focused ultrasound can also destroy tissue mechanically, without using needles,” says Wood. “We can’t treat the same size tumors as with the needle techniques, but we may be able to five years from now.” There is also evidence that RFA combined with radiation, chemotherapy, or chemo-embolization—these therapies seem to work better in combination—may improve the outcome. Heat-activated drug delivery is an area of active study at the Clinical Center, where small particles called liposomes deliver drugs or therapy (in this case chemotherapy) locally to the tumor. This local delivery may enhance efficacy without the systemic side effects to normal tissues.

### Pediatric cancer today

Fifty years ago, NCI chose to work with the cancer that caused the most fatalities in children, acute lymphocytic leukemia. Now the pediatric branch tends to work more with cancers on which there has been less progress. To enter one of the protocols, patients have to have failed standard therapy—yet have to be ambulatory, have good organ function, good blood counts, and a fairly good chance of survival. Pediatric oncology tends to emphasize chemotherapy, with some surgery and radiation.

### KIMBERLY ROE, PEDIATRIC CANCER PATIENT

Kimberly Roe, undergoing chemotherapy through a Hickman monitor in her chest, is a delicate, beautiful 15-year-old who looks considerably younger than her age because her cancer has stunted her growth. A middle child, she is more articulate than most adults—calmly, knowledgeably answering questions she’s been asked before, when we interview her in December 2002. Her mother, Leslie Roe, describes their experience with the Clinical Center as Kimberly goes about the business of eliminating cancer cells from her body.

Kimberly was 13 when they suspected something was wrong. “Liver cancer is very silent until it is advanced,” says Leslie Roe. “Kimberly had stopped growing, and her pediatrician asked us to wait half a year and see what happened. At our follow-up check-up, she couldn’t get a good feel of Kimberly’s abdomen. She ordered a full spectrum of tests, including blood work and an ultrasound of her abdomen, which showed a grapefruit-sized mass in her liver. A CT scan later that day showed other masses in her abdomen and chest. Three days later, doctors at a local Virginia hospital did an open liver biopsy, which showed benign tissue—it was not a good sample.”

The Roes took Kimberly to Johns Hopkins, a teaching hospital in Baltimore, where surgeons removed tissue that showed Kimberly had a rare form of childhood cancer of the liver called fibrolamellar hepatocellular carcinoma. The oncologists told the family that they were rarely in a situation where they could do nothing, but that Kimberly had terminal cancer of a type that was very refractory to chemotherapy. Moreover, it was already impinging on the hepatic vein. All they could offer was to put Kimberly on a Hickman catheter for pain control.

Kimberly’s best friend, Rebecca, who lived in India, wanted to visit Kimberly before she died. The Make-A-Wish Foundation expedited arrangements so Kimberly could have a trip to Italy. The Roes signed her up with a pediatric hospice program, made a goodbye book, and picked out a cemetery. Then a fellow at John Hopkins connected them with the NIH, where oncologists offered to put Kimberly in a solid tumor trial. She had profound bone marrow suppression with that protocol, and there was no impact on her tumors. She was the first pediatric patient they had with that form of cancer so her presence in that first trial was important.

Kimberly was then shifted to a natural history protocol, to study the course of the disease. The surgeon at Hopkins had suggested that if a chemo regimen could shrink her tumor by 25 percent, it could possibly be resected (removed), buying Kimberly some time for life. The NIH oncologists noted a small abstract offering some hope, but the regimen had not even been published in a peer-reviewed journal. They got the details directly from the physician in charge of the protocol at M.D. Anderson Hospital in Houston and started Kimberly on the first of 14 cycles of this new regimen. Her functions improved significantly, but scans showed only minimal shrinkage in the plane that was being measured. Then Brigitte Widemann used her expertise to read them in an unconventional

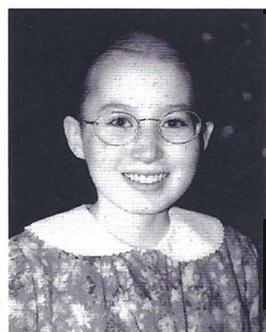
way. Volume analysis found that the tumor's actual shrinkage amounted to 31 percent over a period of months. She consulted with Richard Alexander, an internationally known endocrine surgeon at NIH, who was willing to take on the challenge of removing Kimberly's tumor. In July of 2002, he and associates performed an extended right hepatectomy, removed her gallbladder and a part of the diaphragm the tumor had invaded, as well as a mass in her pericardial sac. At the end of surgery he told the family, "She is clear of all known cancer."

On Christmas day, Kimberly completed six more post-surgery cycles of chemo, a combination of 5-fluorouracil and peg interferon. During the months of chemo in three-week cycles, she had two weeks of continuous-IV chemo, which she managed at home, and a pegalated form of alpha interferon, of which she got two deposits per cycle. She preferred to get her shots at the Clinical Center, where she was followed regularly by Kathy Carnighan Kuhn, her nurse practitioner, and became close to her clinic nurses, Holly and David. She tolerated the chemotherapy with few side effects and grew stronger.

Although mortality for this kind of cancer is still 100 percent, Kimberly was able to enjoy many more months of life than was thought possible. She saw Rebecca not once but several times, took part in debate competitions with other home schoolers, and celebrated her sixteenth birthday in the Clinic in December 2002 with cake, balloons, and hugs from many who had become dear to her.

"We know we are getting cutting-edge treatment," says Leslie Roe. "The generosity the government has shown in providing this treatment has been wonderful for us. It's a gift. And the medical team has already learned so much from treating Kimberly that they can use with the next patient who has this cancer." They have never been in a hospital with a better team approach—with all the disciplines working together. "It takes a big heart to provide this kind of care. The compassion they demonstrate is remarkable, from the attendants in the parking lot to the nurses and physicians." They have given Kimberly more years of life than she might have had otherwise. Even if we hadn't had that, just to experience this outpouring of love and service is significant. We feel very much a part of the family here."

*Kimberly died quietly at home on May 20, 2003.*



*We are so grateful for the extraordinary care you have given Kimberly! We deeply appreciate your excellent medical skills, your compassion, and the friendship you have extended to us.*

*Brian, Leslie, Daniel  
Kimberly, & Emily*

It's hard to back off from successful therapy, "but you also have to look at its long-term effects, and the Clinical Center is in a position to do that," says Lee Helman, current head of the NCI's pediatric oncology branch. The pediatric branch is looking at patients who were first treated 20 years ago at the age of five. It is studying the long-term effects of those earlier treatments and is finding, for example, that high-dose radiation increases the risk of secondary tumors by 5 to 10 percent and that radiation to the head can affect IQ in the long run. (David Poplack—who came to the NIH in the 1970s and left in the early 1990s—was one of the first to study the devastating effects of cranial radiation.) They are looking for equally effective treatments that won't produce the same long-term damage.

### NIH works with Camp Fantastic

Camp Fantastic was started in 1983 by Tom and Sheila Baker, whose daughter, a patient at the Clinical Center, had succumbed to lymphoma. Every August, up to 100 children with cancer, aged 7 to 17, get a chance to sing, swim, canoe, do crafts, and sit around nightly campfires—to enjoy the often forgotten happiness of childhood. The week-long, live-in camp for children only (no parents) is held at the 4-H Center in Front Royal, Virginia.

"Camp Fantastic helps children with cancer develop a positive self-image by using old-fashioned camp activities to help them overcome feeling 'different,'" says Special Love's executive director, David Smith. "For a whole week these kids get to do something that cancer often keeps them from doing—just being normal kids." They can choose classes three days a week in golf, fishing, canoeing, swimming, horseback riding, cooking, creative expressions, and various kinds of arts and crafts—and there are junior and senior challenge courses. They write, print, and distribute a daily newspaper.



Dinner is prepared and served by a different local civic organization each evening and then there is an evening campfire and special event, such as a talent show, banquet and dance, or a luau around the pool.

The camp accepts children with end-stage cancer, children on chemotherapy or up to three years off, and children with special needs—including children who are respirator-dependent at night. The NIH volunteers—who come mostly from the Cancer Institute's pediatric branch—are authorized to administer chemotherapy, antibiotics, or other medications—and occasionally to administer transfusions—under a Cancer Institute protocol.

When NCI's pediatric branch began accepting children with the AIDS virus for treatment, some of the kids wanted to go to camp, too. In 1994, Phil Pizzo, former chief of NCI's pediatric branch, helped organize a special camp for children with human immunodeficiency virus (HIV). Camp Funshine holds weekend camps twice a year.

Camp Funshine has its own special requirements—for example, bottled water, because the youngsters' immune systems could be harmed by the bacteria in tap water. The camp tries to provide a respite for families from the isolation and social stigma they may feel at home—an “environment free from judgment, where everyone is in the same boat,” so they can draw strength from each other and the staff. The diagnosis isn't even mentioned at the camp, although social workers are available for parents who want someone to talk to.

### Biological approaches to cancer treatment

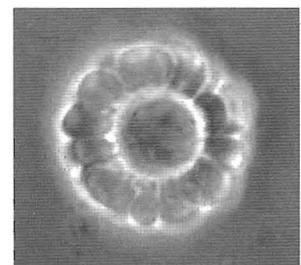
Three kinds of treatment—surgery, radiation therapy, and chemotherapy—will cure half the people who develop cancer this year. But the half who cannot be cured will account for half a million deaths in America alone, says Steven A. Rosenberg, chief of cancer surgery. In working on a fourth therapeutic approach—biological approaches using the body's immune system—Rosenberg's team in the NCI is converting research on interleukin and other cytokines into tools for adaptive immunotherapy. Cutting across melanomas removed from

human patients and finding that some of the cells looked like immune cells, Rosenberg reasoned they were there for a reason—and that perhaps the body's immune system could be better harnessed to fight the cancer that surgery, radiation, and chemotherapy fail to eliminate.

With tumor-infiltrating lymphocytes (or TIL cells) taken from the tumor, Rosenberg's lab spent five years cloning the genes that encode cancer antigens, learning how to generate T cells that could recognize them. Then they developed a mouse model of melanoma, showing the effects of giving the mice IL-2. Having done the preclinical science, they tested the model on patients with far-advanced cases of melanoma on whom all standard treatment options had failed. Rosenberg took the TIL cells out of the patients, expanded them, revved them up, and gave them back to the patient along with interleukin 2 (IL-2). Many patients died, but the treatment also produced some amazing turnarounds. A young boy with large tumors on the chest and abdomen—expected to die in six weeks—showed no signs of cancer after four months of treatment.

When people talk about research at the Clinical Center being “bench to bedside and back again”—this is what they are talking about. This pioneering use of IL-2 and TIL cells to treat melanoma and renal-cell cancer started at the laboratory bench, translating human tumor cells into a mouse model, expanded to treatment of patients in the Clinical Center, and has returned to the bench many, many times, for refining of the model.

When the Clinical Center opened in 1953, T cells were not yet part of the research vocabulary.



“This hospital is a jewel in the medical universe. For someone like myself who wants to do serious science and seriously apply it—in my case, finding new treatments for patients with cancer—there’s no place in the world like the Clinical Center of the National Institutes of Health.

“We have spectacular research resources. We have 250 state-of-the-art hospital beds married to world-class research facilities and world-class scientists—over 2,000 PhDs who are doing basic scientific research, eager to collaborate with clinicians. Half of all the clinical research beds in the United States are in this building, paid for by the U.S. government for the sole purpose of developing improved management for patients.

“This gives us an opportunity to do things that would be very, very difficult to do elsewhere. We can bring patients into the hospital and perform studies in a scholarly way that would be impossible if patients were paying for their care. The beds are available to do research and to look at experimental

means for managing and treating patients in our care. We don’t have to worry about the \$2,000 a day that patients are paying in most hospitals. We have no emergency ward or trauma center. No local population depends on us for care. We can control patient flow so that the only patients we bring into this hospital are patients who can help us answer questions. We might accept only one out of every ten patients referred to us. Our community is the world of patients who have intractable medical problems. The patients are the explorers—in a sense, the adventurers—experiencing new treatments for their own benefit and for the benefit of patients who follow.

“We have our own research laboratories literally a few steps away from our patient wards, and often we literally carry the materials we develop from the laboratory to the patient wards for treatment. This intermingling of scientists with clinicians and clinician-scientists creates an environment that is unsurpassed for enabling innovative, groundbreaking research.”

—STEVEN ROSENBERG, NCI, pioneer in cancer immunotherapy

Pioneering in immunotherapy to treat melanoma and renal-cell cancer, surgeon Steve Rosenberg and his team in the Cancer Institute shift constantly between laboratory science, mouse models, and the treatment of patients in the Clinical Center.





Cardiac surgeons  
Nina Starr Braunwald  
and Glenn Morrow.  
Braunwald, the first  
woman to perform  
open-heart surgery,  
performed the first  
successful mitral valve  
replacement in 1960.  
Morrow, who trained  
generations of cardiac  
surgeons, developed a  
surgical procedure for  
relieving a malformation  
associated with IHSS,  
a common cause of  
sudden death from  
heart attacks.

No better example exists of the productive collaborative relationships that flourished in the Clinical Center than the one that developed between Andrew “Glenn” Morrow, who established the Heart Institute’s surgery clinic in 1953, and Eugene Braunwald, who came to the Clinical Center in 1955. Braunwald ran Morrow’s catheterization lab for a while until Robert Berliner, the Heart Institute’s scientific director, made him head of a new cardiology section, which in 1960 became the cardiology branch. (Being given a branch is the emblem of respect for a clinician, the equivalent to a basic scientist being given his own lab.) John Ross Jr. took over the cath lab and became part of the team.

Morrow would become the grand old man of cardiac surgery, an extraordinary mentor who trained many surgeons who went on to distinguished careers elsewhere. At the time he was only 34 to Braunwald’s 28—at that age a sizeable difference, making Morrow senior collaborator. “Glenn was a thinking surgeon instead of just a cutting surgeon,” says Braunwald. “He had a way of conceptualizing the heart in three-dimensional fashion and figuring out the effect of pressure on heart muscle. He brought something to the table that frankly I needed, which gave me a tremendous heads up on other cardiologists. And we played off each other.”

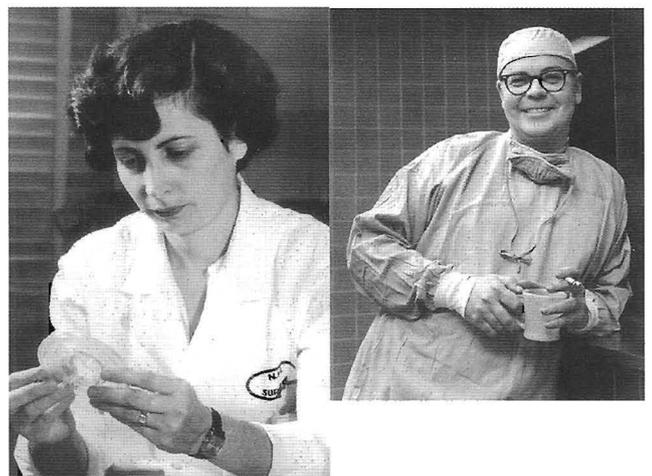
There was not much high-powered cardiology research going on at the time anywhere, and Braunwald helped make the field into a science. He made a science of understanding the heart’s

energy flow and of knowing when and why to do (or not do) surgery to correct problems. He realized that a lot of what was observed clinically could be modeled in animals and tested scientifically. He understood the heart’s physiology and the function of cardiac cells; he began measuring things instead of merely observing them.

“As the heads of cardiology and cardiac surgery, Glenn and I worked as a single unit,” says Braunwald. “Now that is much more commonplace—is the rule—but at that time it was the exception.” Typically, in the 1950s, surgery existed separately from cardiology and to some extent in competition with it. At most teaching hospitals, one person was an expert on high blood pressure, another on rheumatic fever, “but you didn’t have this concerted team approach. In the Clinical Center, we were going to focus on this new way of treating heart disease through surgery—especially valvular heart disease and to some degree congenital heart disease. We were going to get our arms around it and conquer it—as a group effort. There were no walls between medical and surgical cardiology. In a sense the two specialties worked hand in glove. It was a time when a lot of things broke open and there was a wonderful collaboration. It was a period when cardiologists learned from surgeons and surgeons learned from cardiologists. I haven’t seen this kind of a period repeated.”

Braunwald was in the operating room three times a week. The surgeons sewed things into the heart that allowed the cardiology team to study the effect of drugs on the human heart, which had never before been imagined. “I believe the Clinical Center was

Cardiac surgeons  
Nina Starr Braunwald  
and Glenn Morrow



the first place in the world where there were comprehensive programs in cardiology and cardiac surgical research and patient care that went from the biochemistry of heart muscle all the way to valve replacement, with everything in between,” says Braunwald.

### Successful replacement of a mitral valve

In 1958, Gene Braunwald’s wife was invited to join Morrow’s cardiac surgery unit in the Clinical Center. Nina Starr Braunwald had decided to become a cardiac surgeon during her residency at the Georgetown University Medical Center, where another young investigator, Charles Hufnagle, was the new head of cardiac and thoracic surgery. Hufnagle had become interested in developing a heart valve to be placed in the descending aorta of patients with aortic insufficiency. One of her first lab assignments was “to make this thing work in the heart. “Twice a week we tried and twice a week we failed but, by the end of the year, we had learned something.”

The field of cardiac surgery was just emerging when she was given her own laboratory and offered one of three staff positions at the Heart Institute’s surgery clinic, along with Joe Gilbert. “The alphabet of cardiac surgery was being worked out, so it was just incredibly exciting,” says Nina Braunwald, in a video profile produced by the Association of Women Surgeons (she died in 1992). “I was happy as a clam during that ten-year period.” At the time, patients with end-stage mitral regurgitation were dying regularly despite vigorous medical treatment. Patients with aortic and mitral stenosis (or narrowing) and insufficiency were being lost from the outpatient department at six-month intervals. In the Heart Institute’s surgery clinic, Nina Braunwald, working with another young investigator, Theodore Cooper (later Assistant Secretary of Health and CEO of Upjohn), began laboratory investigations of a prosthesis to completely replace the mitral valve. Using hearts from animals and humans, they developed plaster casts to create an artificial valve. They replaced the mitral valves in 24 dogs with prostheses—with the aid of a recently introduced technique called cardiopulmonary bypass.

The surgical team pressed ahead with the experimental valve replacement despite the general skepticism most felt about it—which boiled down to “it will never work.”

If Morrow was a thinking surgeon, he had found a good collaborator in Nina Braunwald, a technician supreme. On March 11, 1960, Nina S. Braunwald (with Morrow and Cooper at the table) performed the first successful mitral valve replacement in a human, completely replacing the diseased mitral valve of a 44-year-old woman—at a time in the very brief history of open heart surgery when such a procedure had never been done. The patient had had a heart murmur of mitral regurgitation since the age of eight and was suffering severe congestive heart failure. When she was discharged from the Clinical Center on May 22, she was clinically improved, with no audible heart murmur. Four months later her referring cardiologist called to report that she had been admitted to a local hospital for arrhythmia and died a day later. But the surgery performed that day in March provided important proof of concept. Of the first 100 patients who underwent valve replacement between 1961 and 1965, 83 survived the operation and 64 percent were still alive eight years later.

“The surgeons were developing new valves, new operations, and new techniques for getting patients through what is now terribly routine—but these were very formidable obstacles,” says Gene Braunwald. “Those first valve replacements were like climbing Mount Everest for the first time. What went on then was all new—it was the first time—and we had to feel our way.”

### Putting hypertrophic cardiomyopathy (a.k.a. IHSS) on the map

Morrow and Gene Braunwald identified and pioneered in understanding a genetically transmitted disease now known as hypertrophic cardiomyopathy (HCM), which involves a thickening (or hypertrophy) of the heart muscle. One of Glenn Morrow’s greatest contributions to cardiac surgery was the myotomy myectomy, a surgical procedure to relieve a congenital malformation present in 25 to 30 percent of HCM patients. Functionally the malformation resembles aortic stenosis, in which the valve itself is so narrowed that pressures must build dangerously high in the left ventricle, the heart’s major pumping chamber, to force the blood out of the ventricle. But the valve hasn’t actually narrowed; instead, the heart muscle tissue just below the valve has thickened abnormally, making it hard for the left ventricle to eject blood.

“THE ALPHABET OF CARDIAC SURGERY WAS BEING WORKED OUT, SO IT WAS JUST INCREDIBLY EXCITING.”

They would later show HCM to be a common cause of sudden death from heart attacks—one of the most common causes of sudden death in athletes—but at the time the NIH got interested in the condition nobody knew it existed. Braunwald had diagnosed valvular stenosis (or narrowing) in a patient and when Morrow opened the patient's heart he found a perfectly normal valve. He asked Braunwald to show where the valve should be opened and Braunwald was chagrined to find no narrowed valve. After the patient had recovered from the chest incision (there had been no heart surgery), Braunwald recatheterized the patient and found that the obstruction was still there.

"We called the condition idiopathic hypertrophic subaortic stenosis, or IHSS," says Braunwald. "Now it's been redubbed hypertrophic cardiomyopathy, or HCM. I can't say that we discovered it, but we thought we discovered it." In 1958, they were slowly gathering data to write up the first two U.S. cases when another case was described in the British literature. Had they reported their two patients a year earlier, it might be known as Morrow-Braunwald disease, but they didn't know they were in a race. They thought the condition was a curiosity.

To find out what was going on, John Ross Jr. did some sophisticated studies in the catheterization lab, placing a catheter in the aorta and slowly pulling it back, in order to show that the pressure gradient occurred at the valve level. Morrow operated, found and removed a protuberance of heart muscle tissue, and when the patient was recatheterized weeks later, the pressure gradient was gone. As the group's understanding of hypertrophic cardiomyopathy grew, they came to realize the condition was not as rare as they initially believed—though uncommon enough that most heart centers had few candidates for the surgery each year. Because the procedure was complex, most cardiac surgeons felt uncomfortable doing it, so for many years patients with the problem were referred to the Clinical Center. It became something of a Clinical Center joke that half the people admitted were diagnosed with IHSS.

Braunwald devised a medical way to treat the disease (using drugs called "beta blockers," which came on the market in 1965) and Morrow improved the surgical technique for correcting the malformation that obstructed outflow from the

ventricle in many patients. If the medical approach didn't work, surgery often would—unless the most prominent muscle thickening was elsewhere in the heart, causing other symptoms, and not amenable to surgical correction. Forty years later, the same medicine is still used, and the surgery is still known as the Morrow procedure.

### Measuring how the heart works

Otto Frank, working in the frog heart in 1895, and Ernest Henry Starling, working in dog hearts in 1912, established what became known as Starling's law of the heart, or the Frank-Starling mechanism—that is, essentially, that the heart ejects whatever volume is put into it. Thus the main principle of intrinsic cardiac regulation had been known for years: that the more the ventricle fills, the more the heart muscle stretches, the more forcefully it contracts, the more energy is set free at each contraction, and the better the heart works as a pump—so cardiac output goes up. What was not known was whether the simple relationship described in Starling's law of the heart also pertained to the human heart, and in a series of innovative animal studies, Braunwald, Ross, and colleagues showed that it did. Their work showed that animal studies could provide insights into the physiology of the human heart as well as opportunities for developing new approaches to cardiac therapy.

Angina and myocardial infarction are the two main causes of death from heart disease, killing more people than any other condition, including cancer and AIDS put together. Both diseases result in the heart muscle being starved for blood and the oxygen it carries. Insufficient blood flow to the heart causes heart attacks; insufficient blood flow to the brain causes strokes. A heart attack comes from an imbalance: too much demand, not enough supply, or some combination of the two. The most common kind of heart disease is coronary disease, which causes something called ischemia, or not enough blood flow to the heart. Ischemia can be caused by gradually choking off the vessel (as in atherosclerosis, or clogged arteries) or by the sudden release of a blood clot (which could be the result of atherosclerosis). Angina is the pain caused by a temporary imbalance between the heart's demand for blood and the arteries' ability to deliver enough of it. With myocardial infarction

Eugene Braunwald, who helped make cardiology a science. "There were important things happening on a week-to-week basis."



(the medical term for “heart attack”) the inadequate supply of oxygen and other nutrients the blood normally carries to the heart causes the death of muscle cells in the heart.

Braunwald, Ross, and their colleagues spent 10 years doing research essential to figuring out how to treat patients with severe angina. Their main focus was learning how much energy the heart—a pump—requires to function. Braunwald developed the concept that if you could equalize the balance between supply and demand, you could save heart muscle, even though you had a coronary obstruction. He and his colleagues tested that hypothesis first in experiments with animals and then in clinical trials in patients with severe angina.

In the mid-1960s, most measurements of the heart were done with the patient at rest. In 1936, Dr. Arthur Master had developed the first standardized exercise stress test for measuring cardiac function, the Master’s two-step test, in which a patient would walk up and down a two-step device for 90 seconds—recording an electrocardiogram before and after the test, and measuring pulse rate and blood pressure. Braunwald saw the importance of stressing the heart, to see whether when the patient was under stress it was possible to distinguish a normal from an abnormal heart as well as to distinguish between different degrees of heart failure. Braunwald assigned Stephen Epstein, a clinical associate who came in 1963, the project of testing heart patients and normal volunteers for the presence or absence of heart disease while they were exercising on a treadmill.

By current standards the exercise-treadmill tests they conducted appear antiquated, but when they put a catheter into the heart of a patient who was going to exercise on a treadmill, it probably hadn’t been done before. They thought it would be safe but they couldn’t be absolutely certain. Starting the catheter in the arm vein, Epstein advanced it into the right atrium, then the right ventricle, and then into the pulmonary artery. Thus he was able to measure pressures and output in the right heart, the pulmonary artery, and the right ventricle—not just at rest but during exercise, and not just during short bits of exercise but during maximal intense exercise. Braunwald’s cardiology team did experiments with heart patients, demonstrating what happens to the pressures in the heart, how high they

could go and how low levels of circulating oxygen fell with exercise. These tests provided enormous insight into how, when the heart was compromised, it couldn’t perform as well, which led to symptoms.

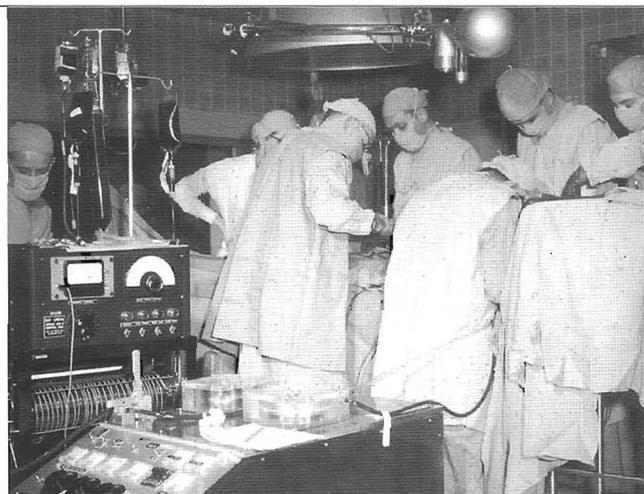
These advances in cardiology research are so basic that they are taken for granted today but often seemed stunning at the time. “Every day brought something new, and every day was an adventure,” says Braunwald. “It was very different from what goes on in heart research nowadays.”

By 1965, beta-adrenergic blocking agents (or beta blockers, which block the sympathetic nervous system’s action on the heart) had come on the market. Using beta blockers, the cardiology group measured and quantified how compromised the heart becomes when it doesn’t have access to the sympathetic nervous system. Studying both heart patients and normal volunteers, they found that blocking the sympathetic nervous system significantly compromised an individual’s ability to exercise. Their early work with beta blockers also showed that reducing the amount of oxygen the heart needed reduced the amount of damage from myocardial infarction.

With Glenn Morrow and other collaborators, Braunwald did important basic work in clinical physiology correlating myocardial damage with various clinical presentations—describing how to diagnose valvular heart disease and make a decision about whether a patient would benefit from surgery. Through many studies he and his colleagues improved understanding of how heart failure in the right and left heart differ and on how blood flow and pressure are controlled. They also developed important models of acute coronary artery obstruction .

### Exploring the left side of the heart

The cardiac group advanced the art of diagnosis by developing and describing important new techniques for left heart catheterization so they could identify and characterize abnormal valves—how leaky they were, or how stenotic (narrowed)—and from that conclude who might need surgery. “It’s hard to imagine now, when some of the things we’re talking about are so routine, how charged the atmosphere was when almost anything



The first heart-lung machine

Glenn Morrow is performing surgery.

done at the time was not only new, but innovative,” says Epstein. The group developed daring catheterization techniques that allowed entry into the left side of the heart, “which until then was essentially a black box”—holding information essential to understanding heart problems, if one could only get to it.

In the first technique, Glenn Morrow advanced a needle (hooked up to a catheter) through an endotracheal tube to a point adjacent to the heart’s left atrium and punctured the left atrium through the bronchus. This formidable achievement allowed measurement of pressures in the left atrium, which launched a series of observations that increased understanding of diseases of the mitral valve and left ventricle.

John Ross, working with Braunwald and Morrow, developed a second technique, for transeptal left heart catheterization. Through a specially designed catheter inserted into the femoral vein in the groin, a very long needle could be advanced into the right atrium; the needle would be passed along, would puncture the atrial septum, and would then be advanced into the left atrium. At the time, this was an extraordinary advance. Through the catheter they injected green dye into the left ventricle. Another catheter in the pulmonary artery was sensing blood. If they detected green dye prematurely, they knew there was a defect in the ventricular septum.

### The carotid sinus nerve stimulator

Many collaborations formed within the cardiology–cardiac surgery group. Glenn Morrow was often at the center of them, but sometimes Gene and Nina Braunwald collaborated, too. “I worked much more closely with Morrow than with Nina,” says Gene Braunwald, “and she worked more closely with Morrow than with me, but there were areas where, without design but also without avoidance, we collaborated. We did not make it a point to work together, and we did not make it a point to not work together.” The Braunwalds coauthored papers on changing the supply/demand ratio to the heart to treat angina, and on how surgical treatments affected heart function.

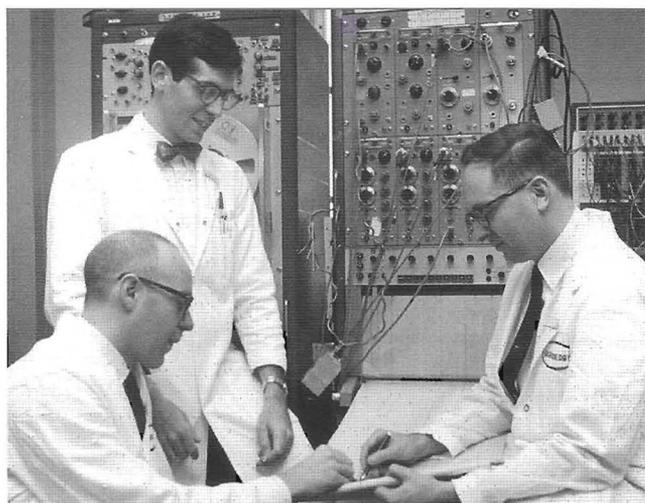
Sometimes even brilliant concepts lead investigators down blind alleys. So it was with the Braunwalds’ collaboration on

pacemaker stimulation to change the heart’s function. In the mid-1960s, investigators had demonstrated that blood pressure could be effectively lowered by applying an electric current through electrodes placed around the carotid sinus nerves (located in the neck) using a radiofrequency pacemaker capable of activating a receiver that had been placed subcutaneously in the upper chest wall. The carotid sinus nerve is the control center for altering the sympathetic nervous system’s support of the heart. When these nerves sense the heart beating too fast or the blood pressure rising too high, they send a signal to the heart—“Hey, slow down! We’re getting too much of an impact here!”—which slows the heart down and lowers the blood pressure. This rather novel approach of applying stimuli to the carotid sinus nerve to treat hypertension had been used with some success in a few hypertensive patients.

Working with dogs in the animal lab, Braunwald and his colleagues had been studying cardiac physiology and how the heart consumed oxygen. Those studies made it clear that the faster the heart beat and the more it contracted during exercise, the more the heart consumed oxygen and used up energy. If the blood supply to the heart was limited because the arteries were narrowed by atherosclerosis, the heart—deprived of oxygen—would become ischemic.

Braunwald reasoned that if you put an electrical pacemaker on those nerves to the heart (as opposed to the heart itself), you could slow the heart and lower blood pressure, diminishing the heart’s work and bringing it into balance with the limited amount of oxygen-carrying blood those narrowed coronary arteries could supply. He hypothesized that stimulating the carotid sinus nerve, by lowering the heart rate and blood pressure, might reduce demand for myocardial oxygen and thereby possibly relieve anginal pain.

He asked three young associates to test the hypothesis: Epstein, Andrew Wechsler, and Gerry Glick. They found that applying an electrode to test animals’ carotid sinus nerves did slow down the heart and make it contract less vigorously. When they were ready for a human test, Nina Braunwald surgically attached the carotid sinus nerve stimulator to a patient with heart disease and, again, the heart rate and blood pressure went down. A few



Stephen Epstein, Andrew Wechsler, and Gerald Glick studying readouts from the carotid sinus stimulator.

days later, in the summer of 1967, the group used the stimulator on an artist from New Jersey who was severely compromised by angina pectoris. They had asked him to exercise on the treadmill several times before, and the artist had always stopped because of the chest pain of angina pectoris. They asked him to exercise on the treadmill again—this time with a carotid sinus nerve stimulator in place, his blood pressure recorded by an intra-arterial needle. And this time when the artist developed angina pectoris, they turned the stimulator on and within 10 seconds the heart rate and blood pressure came right down, the man's pain stopped, and he continued exercising. "It was staggering—a phenomenal result!" says Epstein, "and we published an important paper on it."

Unfortunately for the strategy—though fortunately for patients—coronary bypass surgery came along the following year and was a much more powerful intervention. The coronary bypass allowed the delivery of more blood to the heart, correcting the primary abnormality, rather than making the heart beat more efficiently. "It looked like something that was going to have a huge effect, and it turned out to be sort of a sidebar," says Braunwald. "That's research."

Meanwhile, however, Nina Braunwald had figured out a way to install a pacemaker that the patient could activate manually. They were cumbersome, but they worked. After coronary bypass surgery came along, people forgot about this intervention, but in the meanwhile the research revealed that if a patient had a heart attack while the pacemaker was activated, damage from the heart attack was less severe. And that set off an important train of research in which many, many people engaged—namely, reducing cardiovascular damage in the presence of a heart attack. Together with Steve Epstein, the Braunwalds coauthored several papers on the subject.

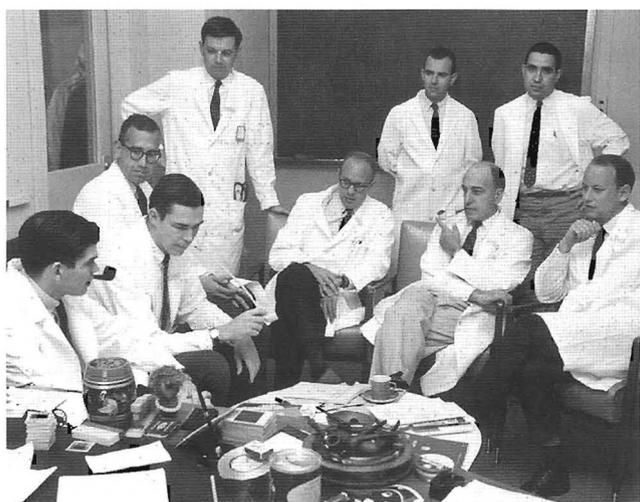
In those days, says Epstein, the breadth of information about how the healthy and diseased heart functioned was far more limited than it is now. There was no ultrasound, no nuclear medicine, no coronary bypass surgery, no angioplasty. Even into the 1960s, you could know almost everything there was to know about cardiology. Not until the 1970s and later, when subspecialties began developing, did it become impossible to

stay on top of everything. "So we were all specialists of the heart: what made the normal heart function, what made the diseased heart dysfunction," says Epstein. "We all worked in the animal laboratory, we all worked in the cath lab, we all worked in the ward, we all consulted with the surgeons—that was an important component of the group's strength." The only real specialist was Edmund Sonnenblick, who was studying the papillary muscle, the heart's only longitudinal muscle (all the others are circular).

### Identifying the risk from sudden death

In 1968 the Braunwalds left NIH, and Steve Epstein was appointed chief of the cardiology branch. NIH remained the world's major referral center for HCM. Over the next two decades, work continued on its diagnosis and treatment and on determining its genetic causes. In the early 1970s Walter Henry and Barry Maron made major advances in the use of a newly developed technology—echocardiography—to diagnose the disease, and, with Lameh Fananapazir, the new team made major inroads into identifying those HCM patients at risk of developing a fatal rhythm disturbance of the heart. This allowed more effective treatment strategies to prevent sudden death in HCM patients—in particular, a rational basis for choosing which patients should have implantable defibrillators that could prevent sudden death. Epstein, Douglas Rosing, and colleagues also explored the use of new drug therapies for this condition. In the process they discovered that blocking calcium's entry into the heart, by using calcium channel blockers, effectively controlled some of the incapacitating symptoms these patients experienced. Maron and Epstein pioneered in defining the characteristics of the athlete's heart and in determining the mechanisms of sudden death in athletes. They used this information to develop recommendations for screening studies to reduce the likelihood of such deaths.

In the 1990s, NIH investigators also helped identify various genetic abnormalities that predispose a family toward developing hypertrophic cardiomyopathy. (Although there are different mutations on multiple genes, one patient in a given family will usually have only one mutation.) In a series of innovative studies, Neal D. Epstein's research group showed that the stretch-



Left to Right: John Potts (who was to become Chief of Medicine at Massachusetts General Hospital), John Parker (front), Louis Sherwood (rear, who was to become Chief of Medicine at Northwestern Medical School), Ray Jamison, Stephen Epstein (who was to become Chief of the Cardiology Branch), Art Gottleib, Robert Berliner (Scientific Director, NHLBI), Robert Levy (who would become Director of NHLBI), Don Frederickson (Clinical Director, NHLBI)

activation response that allows insects to beat their wings rapidly enough to fly may also play a role in the beating of the mammalian heart. The human heart beats something like 3 billion times over a 70-year lifetime, powered by a molecular motor that changes chemical signals into directed movement. Neal Epstein's group identified novel mechanisms on the myosin molecule responsible for cardiac dysfunction, and they demonstrated that the heart's ability to beat efficiently as fast as it does is based on the same molecular mechanism that allows insects to beat their wings rapidly enough to fly! A mutation in the insect gene leads to the insect's inability to fly. A mutation in the functionally homologous genes in humans leads to the heart's inability to perform normally. Studying the two might suggest new ways to modulate human cardiac function. These studies broadened the context of what goes wrong with the heart in HCM by showing related problems in what no one would have ever suspected—the ability of insects to beat their wings!

In addition to researching HCM, the cardiology branch made major advances in developing strategies for treating patients with valvular heart disease and coronary artery disease. With Robert Bonow and Walter Henry, for example, in the 1970s and 1980s the branch pioneered in identifying indices that predict long-term survival in patients with aortic regurgitation and patients with aortic stenosis, and indices that indicate imminent deterioration and death. Hence testing strategies were developed to recommend when to proceed with surgery and when it was safe to delay it—recommendations still largely in use today.

An important part of the evaluation relied on real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise. Jeff Borer, Steve Bacharach, and Mick Green pioneered in the development of this now routinely used technique. The test allowed the investigators to measure how vigorously the heart could pump—not only at rest, but also during exercise. The information provided by this test proved critical to predicting which patients with a leaky aortic valve were at risk of sudden death. Additional studies demonstrated that this test also provided prognostic information critical to deciding whether more invasive therapy (surgery) was warranted in

patients with coronary artery disease. And the technique was used to confirm the clinically important effects of coronary angioplasty.

It isn't generally known that the Clinical Center was one of the early centers to use angioplasty in the treatment of coronary artery disease (CAD) in the United States. In the late 1970s the first angioplasty procedures had been performed in the United States and, after visiting Andreas Gruntzig, the inventor of the technique, in Switzerland to learn how to do the procedure, Kenny Kent performed the first such procedure in the Clinical Center. Using radionuclide angiography, the cardiology branch did the first study to measure the effects of angioplasty on heart function, showing that successful angioplasty had important biological and clinical effects—that heart function during exercise improved after successful angioplasty.

### Using nitroglycerin to reduce damage in a heart attack

In the late 1960s and early 1970s there was a flurry of research about treating acute myocardial infarction—generated by the development of coronary care units, where data about infarcts had begun to accrue. Research in the intramural program reversed two standard approaches for treating patients with acute myocardial infarction.

Standard treatment of patients coming to emergency rooms with an acute infarction in the 1950s and 1960s was to administer narcotics to control pain and generally at the same time to administer intramuscular atropine to counteract the slowing of the heartbeat the narcotics usually induced. The rationale was that atropine's speeding up of the heart rate prevented death from arrhythmia, and it was true that atropine appeared to eliminate extra heartbeats (ventricular premature contractions, or VPCs) that showed up on an electrocardiogram when narcotics slowed the heart beat down. But half a dozen experiments with dogs—conducted in the early 1970s by Kent, David Redwood, Epstein and others—demonstrated that slowing the heart was beneficial and speeding it up was deleterious. With the administration of atropine, VPCs no longer showed up on the electrocardiogram, but the atropine actually

“IT WAS STAGGERING—A PHENOMENAL RESULT!”

increased the incidence of death, ventricular fibrillation, or the amount of damage from the heart attack. It took an hour or two, but sophisticated testing showed that a steady rhythm of 100 would cause fibrillation or a massive infarction. So administration of atropine came to be contraindicated in patients with heart attacks, a reversal of standard procedure!

At the same time a parallel series of observations was made about the role of nitroglycerin in the treatment of acute myocardial infarction. No less an authority than Charles Friedberg, author of the classic textbook *Diseases of the Heart* (1968), stated that although nitroglycerin placed under the tongue was beneficial when a patient was exercising and experienced chest pain, once the diagnosis of acute infarction was made, “nitroglycerin should not be taken for the pain associated with the infarct”—the rationale being that the reduced pressure caused by the nitroglycerin (a vasodilator) would make the infarct worse. Having reason to believe this might not be true, Epstein, Kent, Redwood, Eldon Smith, and Jeff Borer undertook experiments with dogs to determine if the standard approach was valid. Their first studies, in which they produced acute coronary occlusion in dogs for a relatively brief period of time, demonstrated that nitroglycerin actually reduced the amount of damage to the heart muscle. These animal studies led to the first human study, which demonstrated that nitroglycerin administered to patients with acute heart attacks was beneficial. This was published in the *New England Journal of Medicine* in 1975. Those experimental findings about atropine and nitroglycerin are now routinely applied to patients with acute myocardial infarction.

### **Studying the role of angiogenesis, infection, and antioxidants**

Coronary bypass surgery had come along in the late 1960s and angioplasty in the 1970s, so by the late 1970s a powerful array of therapies was available for patients with coronary artery disease, including drugs that helped alleviate symptoms. But a sizeable number of patients didn't respond to those therapies or, for one reason or another, were not candidates for angioplasty or surgery, which are not minimal procedures. Stimulated partly by

a lecture they heard Judah Folkman give on angiogenesis (the formation of new blood vessels), which fed the growth of tumors, Epstein and Ellis Unger became interested in the principle as the basis for a therapy for coronary artery disease. Folkman was studying what made collateral blood vessels grow so he could figure out how to stop tumor growth.

In most hearts tiny blood vessels that normally don't function run parallel to the major functioning blood vessels—some-what like unused country byways running parallel to interstate highways. They're present as the embryo develops, and as the embryo grows, they become residual channels that are present but not functioning until the major highway is closed; then, all of a sudden, a small stream of blood courses through these small country byways. That little stream stimulates the cells lining these tiny roads so that they remodel, causing the vessel to enlarge. The problem is, they rarely get big enough to be functional. When their major vessels become obstructed, most people develop some collaterals, but it's the rare individual with collaterals big enough to take over the failing main vessel's normal function. And some individuals simply cannot develop collaterals. Unger spent several years in the late 1980s and early 1990s developing a reproducible dog model of coronary occlusion—preliminary to attempts to find ways to grow new blood vessels or expand the secondary vessels that existed, to compensate for compromised blood flow.

Not until two kinds of molecules involved in the growth of new blood vessels were identified—vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)—and techniques were developed to produce them in large amounts, could they establish proof of concept that by injecting bFGF or VEGF into the coronary arteries, collaterals could be made to function better over a period of weeks. The results were published in the *American Journal of Physiology* in 1994. The success of those investigations led to clinical trials in several institutions, including two at the NIH, the first led by Unger, Epstein, and Arshed Quyyumi in patients with coronary disease, the second by Daisy Lazarus and other colleagues in patients with peripheral vascular disease.

Edith Speir, Epstein, and others in the cardiology branch also studied infection's role in atherosclerosis (publishing the results of their study in *Science* in 1994). Further studies have suggested that the level infection can be mild and not even evident clinically. Juanhui Zhu and Epstein observed that the presence of multiple infectious agents (such as cytomegalovirus, *Chlamydia pneumoniae*, *H. pylori*, and *Herpes simplex*) may pose an additive risk. The greater the "pathogen burden"—the more such infectious agents an individual harbors—the greater the risk of atherosclerosis and, should atherosclerosis be present, the greater the risk of myocardial infarction or sudden death.

One of the branch's principal efforts in the 1990s was to define the normal role of the endothelium in modulating vascular tone—and to learn what controlled the blood vessels' ability to dilate and contract. It had been shown that nitric oxide is released from the endothelium and relaxes vascular smooth muscle cells, which is important to normal vascular function. Arshed Quyyumi, Julio Panza, and Richard Cannon demonstrated that endothelial dysfunction leading to an impairment of vasodilator mechanisms occurs in several kinds of patients, including patients with hypertension and patients with hypercholesterolemia, postmenopausal women with estrogen deficiency, and patients with either coronary atherosclerosis or risk factors for atherosclerosis (even if atherosclerosis has not yet appeared). They also found that such dysfunction was caused in part by a decrease in the availability of nitric oxide—a condition that could be improved by administering antioxidants—or, in postmenopausal women, estrogen.

### **Making new uses of imaging technology**

New technologies constantly change the field. According to Bob Balaban, scientific director of the laboratory research program of what had become the National Heart, Lung, and Blood Institute, the use of advanced magnetic resonance imaging equipment in emergency room settings could bring life-saving treatment to 20 percent more patients with acute coronary syndrome than are currently being treated. MRI results were shown to be more effective at detecting patients' heart attacks than were three standard diagnostic tests: an electrocardiogram

(ECG or EKG), a blood enzyme test, and the TIMI risk score, which assesses the risk of complications or death in patients with chest pain based on a combination of several clinical characteristics. MRI detected all of the patients' heart attacks, including three in patients who had normal EKGs. It also detected more patients with unstable angina than the other tests did.

"MRI is a noninvasive imaging tool that we can now interact with in 'real time,' allowing us to see soft tissues, such as the wall of a diseased artery or the heart muscle itself while measuring physiological functions such as contraction, blood flow, and viability," says Balaban. "The future of MRI is to go from diagnostic uses to therapeutic applications. MRI can be used to guide minimally invasive procedures, including cardiac catheterization to open blocked arteries, direct the injection of therapeutic agents such as gene vectors or stem cells into damaged areas of the heart, replace heart valves, or remove cells that are causing arrhythmias."

The essence of an intramural investigator's job is to go where the science leads, which means that research is constantly changing directions. In the early years, the work done collaboratively between cardiac surgery and the cardiology program was some of the most important work done in the Clinical Center. When the time came that cardiac surgery had become primarily a technical business, with little going on scientifically, Claude Lenfant, the director of NHLBI, suspended cardiac surgery in the Clinical Center. Without a huge patient base, it is difficult to sustain a skilled cardiac surgery unit, and after the death of Glenn Morrow in 1982, there was little desire to do so. In any case NHLBI wanted to invest more of its resources in an important new technology: bone marrow and stem cell transplants. NHLBI's new scientific director for clinical research, Elizabeth Nabel, wants to bring cardiac surgery back. Compelling reasons to revisit interventions in cardiology and heart surgery include the ability now to study what's going on at the molecular and cellular level.



The proximity between research labs and clinical facilities is what makes the Clinical Center special—what permits, as one investigator puts it, “if not renaissance scientists, renaissance departments, where the same group is doing both basic science and clinical trials.” Investigators are free to explore ideas and to concentrate on their research, made easier by the hospital’s ability to bring in patient groups with rare and instructive diseases, without the patients having to pay for their stay or worry about reimbursement through health insurance. The Clinical Center has always been a place where one could learn in the corridors; if you aren’t an expert, you can very quickly become one. And it is not uncommon for an investigator to move from one institute to another, or for staff to come to the Clinical Center expecting to fill one role and finding themselves mastering another. “What you know is more important than who you are,” says scientist Ed Rall. This holds true at all levels of staffing in the Clinical Center.

## Nurses who are paid to think

In the 1950s, when the Clinical Center opened, there were three ways to become a registered nurse: through a four-year baccalaureate program, the last two years of which offered clinical experience; through a three-year diploma program from a hospital-run school of nursing; or through a two-year program run by a junior college. Junior colleges had just begun to flourish, and a nurse with an associate degree could

get a state license. The three-year programs were expanding less as hospitals became less willing to finance them as part of the cost of running the hospital. The four-year nursing baccalaureate programs were scarce but growing in importance, as science became more important in nursing and women increasingly went to college. The leadership in nursing began to come from the nurses with baccalaureates, partly because the diploma schools offered relatively little basic science and the junior colleges provided relatively little clinical experience—principally in the last six months of training.

So the nurses hired by the Clinical Center in 1953 tended to come from the baccalaureate program or to be diploma graduates who had gone on to college. And the tradition of well-educated Clinical Center nurses has persisted. “The nursing force at the Clinical Center is truly unique, in my experience,” says David Henderson, deputy director for clinical care. “The nurses here are the smartest, the best trained, and the most knowledgeable about science of any you’ll ever find. And they’re unbelievably well educated. Most of them have bachelor’s degrees, 18 percent have master’s degrees, and 1 or 2 percent have Ph.D.s. It’s easy to educate them about a new study because many of them have spent years here and are knowledgeable about clinical research. They are always thinking about the processes of both science and nursing care.”

Ann Plunkett was working as a nurse in Boston, earning a little over \$2,000 a year for a 44-hour week, when the father of a

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The remarkable thing at NIH, from a patient’s perspective, is that you not only have the best and the brightest and the best possible medicine that you can have but you have the best care that you can have, and that is largely the responsibility of the nurses. The nurses are incredibly intelligent and responsible and happy to be there. . . .because they are given a great deal of responsibility and respect.

—Cokie Roberts, congressional analyst for ABC News

(Left) Nurse with pediatric patient shown in laminar flow room, which opened for the first cancer patient in 1969. Originally designed for use assembling space capsules and instruments in a particle-free atmosphere in NASA’s space program, the laminar flow room was adapted for patient isolation by the National Cancer Institute and was made famous by stories about the “boy in the bubble.”

classmate, a postmaster who got civil service announcements, told the two young women about openings in the Clinical Center, where they could make nearly twice the amount. "I came to the NIH and made \$3,638 and I thought I was wealthy," says Plunkett. Another nurse remembers becoming a GS-6, pulling down \$4,080 a year, and having \$86.50 a month deducted from her pay slip for rent in an efficiency apartment in Building 20, where nurses lived next door to heart surgeons and physicians on call. It was an advantage to have some of the staff nearby and easily available.

From the start, the quality of patient care was the highest priority, says Pat McIntyre Griffith. "Nurses took pride in what they did: collecting samples and specimens and data, weighing everybody every day at a precise time, and collecting their 24-hour urines." The patients' care was never compromised for a protocol. If the patient got sick, the protocol stopped.

"It was a wonderful place to work because you could give the kind of care that you were taught to give in school," says Maureen Estrin. "You had all the resources you needed, and you developed relationships with the patients and their families, who came back year after year—which would never happen in a general hospital. It was tremendously rewarding—like working in fantasy land."

At first, nurses' patient care duties were limited to changing bed linens daily, washing patients on bed rest, giving them a back rub, easing their pain, comforting and talking to them, giving them medications, prepping them for surgery, and changing their dressings. Sometimes just changing the dressings could take hours, especially for cancer patients who had had radical surgery. One patient had had his face removed, recalls Ann Plunkett. "He had no nose, no teeth, no chin, no nothing—just the tongue and where the nose used to be. But he still smoked—through the hole in the nose of a mask he wore! He was so good, so patient." The nurses got to know their patients well, because the patients were there a long time—some of them a year or longer.

Physicians' orders controlled everything. Because at first nurses could neither hang an IV bag nor alter the rate at which drops of fluid came through a serious intravenous drug infusion, the doctor couldn't say, "Make it 20 drops if their blood pressure is 120/80, and 40 drops if goes below X." But very soon the nurses began to take on additional responsibilities. To some extent, their strengthened role at the Clinical Center paralleled widespread changes in the medical community. But also the clinical associates—now called medical fellows—were at the Clinical Center only for two years, often with only an internship under their belt. They weren't as well-trained in some specialty areas as the nurses, and a well trained nurse might take more seriously the rigor of having a sample done at precisely the right time, so eventually the role of the nurses expanded and became more important. Nurses became partners with doctors in the research effort and their team efforts became an important feature of clinical research done in the Clinical Center. Many of the things the nurses do now were once done by clinical associates. Nurse practitioners in particular have taken on some of the functions once handled by junior physicians, including admission assessments, management, routine orders, and the like.

Before a particular nursing duty changed there would sometimes be skirmishes. Blood-drawing became an issue in the 1960s and 1970s. Nurses on the night shift would set up a blood cart, with the tubes all labeled, and the clinical associate on duty was expected to be there by a certain time in the morning to draw blood from patients. The young doctors began balking at this duty and the director of the Clinical Center told Louise Anderson, the chief of nursing, that the nurses should start drawing blood instead. Finally, in 1976, the clinical pathology department launched a phlebotomy service and technicians took over the duty.

Now nurses do a huge amount of independent decision-making, always under the supervision of the responsible physician and senior investigator. "In many ways, they do better than the medical fellows do," says immunologist Tom Waldmann, "because this is their prime job and responsibility. The medical staff fellow, especially in our branch, wants to rush off and work in the laboratory." Now nurse practitioners and



Building 20

In this apartment building across the street from the Clinical Center, nurses lived next door to cardiac surgeons and other healthcare workers who might be needed at a moment's notice. Without such quarters nearby, it was felt some nurses might hesitate to accept employment because the NIH was so far out of town.

research nurses play a dominant role in patient care, are knowledgeable about protocols, write their own research papers, and understand the scientific basis of protocols, which prevents errors and helps give them insights into what's going on with patients.

"We're actually paid to think," says nurse Tye Mullekin, "and I think that's the thing that's really made a difference, for me. When I have a patient who comes in on a protocol and I look at the patient and say, 'We should be doing daily weight—let's make this part of the protocol,' or 'We need to be drawing amylases because there's the potential for having pancreatitis,' the physicians are very open. They let us have input into these protocols. I hear from my colleagues outside the Clinical Center how burned out they are because they're so task-oriented, and not able to think about what they're doing with their patients. They don't even have time to look at their labs, let alone think about what they're hanging, sometimes. So it's a wonderful place. I'll probably be here till I'm ninety, if they let me."

Clinical Center nurses have always had to be educators, too—all the more so after the shift to outpatient care, when patients and their families have to undertake more of their own care. When patients are discharged, it's the nurses who educate patients and their families about medicines and their side effects, and what to do and expect when they've gone home. Nurses also handle much of the informed-consent education. In the early days, people wouldn't even say the word cancer aloud, recall the early nurses. "Even families of some of the leukemia patients requested that the patients not be told, so the doctor couldn't tell them. It was all hush-hush." One of the biggest changes over 50 years of clinical research has been a shift toward fully informing patients not only about their medical condition and the medical research being done to address their problem, but also of the risks associated with the research.

Clare Hastings, the current chief nurse, encourages nurses to develop a portfolio of work that tracks along a theme, which puts them on a par with other investigators on campus. One nurse was in charge of 200 families whose children had precocious puberty—a Child Health Institute study, trying to

understand what was going on in the systems of children who, at extremely young ages, develop signs and symptoms of puberty. One day she might meet with investigators, work on the study documents, and keep the study books up-to-date; another day she runs a pediatric clinic, screening new patients. One day she might do serial sampling on two or three children, trying to keep them busy while she draws blood from their IVs. Another day, she's on the phone all day, calling families. "So the work is varied but focused," says Hastings. "People love that."

At first the nursing department practiced team nursing, and registered nurses were helped by licensed practical nurses and untrained male attendants. (Male nurses would come along later; none were available at first.) The nurses worked under and reported to a team leader, who made assignments. When more nurses were needed, especially during nursing shortages or cutbacks in hiring permanent staff, the service would bring in part-time nurses called WAEs ("while actually employed"), to fill in as needed. Many nurses became WAEs when their children were small and they could only work occasionally. Later the same functions were served by a float pool. There was a shift from team nursing to "primary nursing," in which a single nurse took charge of and developed an ongoing relationship with a long-term patient.

All of the nurses (and everyone employed directly by the NIH) worked for the Public Health Service—the NIH being a PHS agency. They also had a choice between being civilians or applying to be commissioned officers, and an average 10 percent of the employees in nursing and patient care have chosen to become commissioned officers. Alice Duncan, a formidable early leader in the nursing service, became a commissioned officer because it meant she got better pay and was able to retire sooner than she would have as a civil servant. (PHS retirement is based not on age but on number of years. The civil service considers both age and years; one might have to work longer to collect a full government pension.) Officers were on duty 24 hours a day, subject to being called in during an event that left the hospital shorthanded. They could also be moved to another part of the PHS.

“The Clinical Center was considered the Mecca of the Public Health Service,” says Alice Duncan. “In those days, if you had to work and you were in nursing, it was probably the best place to work, because nursing care was good there.”

The higher the nurse’s government status, the more she earned. When the Clinical Center opened, nurses’ status ranged from GS-5 to GS-7. Vernice Ferguson fought for the right for (primary) nurses to be a GS-10; many were upset that she didn’t fight for a GS-11, the top of the ladder at the time. Today nurses can go as high as GS-14.

A patient care unit was defined by geography and was usually in a single physical area. It might be an inpatient ward, a day hospital, or a procedure room. An inpatient area of the hospital—8-West, for example—was staffed by a group of nurses supervised by a nurse-manager. Each nurse was assigned to care for certain patients. Depending on the admission pattern, they might have 15 admissions on a Monday, almost no patients by Friday, and the next Monday start all over again. On some protocols patients come back over and over, in which case a patient might be assigned both an attending physician and a primary nurse, to work with them regularly as they progressed through the protocol. One memorable long-term study (done for the U.S. space program) put a number of normal volunteers at some risk over a period of months to determine the effects of total bed rest on calcium absorption.

### Outpatient care gets its own home

For ten years or more, the regular hospital nursing units provided staff to work in contiguous clinics—not realizing, at the time, that outpatient nursing was a specialty. “Those were the days when a nurse was a nurse was a nurse,” says Joyce Harris, “so an RN could move anywhere, do anything, fill any void. As time went by, things got more specialized.” Pat Kelly, who worked with acute leukemia patients in the very busy unit on 13-East (before administering platelets became popular and while many patients were still hemorrhaging), recalls being sent to work in the clinic and considering it R&R—“Mrs. Anderson’s rest and relaxation.” Nurses in the cancer clinics still administered chemotherapy but didn’t have to work evenings or weekends.

The opening of the Ambulatory Care Research Facility in 1981 allowed nurses to move their clinic work into a proper facility. Before that, clinics were tiny areas ill equipped for outpatient care. The ACRF—with its many exam rooms, built-in treatment areas, and consultation space—was really designed for ambulatory research. Nurses began taking care of patients in a coordinated way. The ACRF opened at about the same time the AIDS epidemic was becoming known, and named. Gay men in the hepatitis B clinic began telling the nurses about this new “plague.” They were some of the Clinical Center’s first subjects when HIV became a protocol. In some of the work NIAID did, looking at the characteristics, progression, and treatment of the disease, the nursing department began establishing a model of care that’s still used in some of the institutes, in which the nurse is case manager for a group of patients, working with the investigator on the study. One kind of nurse will do clinical work (such as administering drugs), partnered with a study coordinator in the institute, who manages data and research. A study nurse, or research nurse, on the other hand, will handle data management, protocol consenting, patient recruitment—whatever the investigator asks—and may not have much clinical encounter with patients at all. In between are nurses who combine clinical and research functions.

In 1982, surgery moved from the 10th floor of the hospital into a new surgical wing on the second floor of the ACRF, with larger operating suites, more space for equipment, two viewing galleries, and better delivery systems. C-arm fluoroscopy provided a live, continuous x-ray on a TV monitor during surgery. The ophthalmology operating room was equipped with ceiling-mounted instruments that rotated to either side of the operating table, eliminating the need for cart-mounted equipment. Outpatient waiting and dressing rooms facilitated outpatient surgery. The *NIH Record* reported that Surgical Services performed more than 2,000 cancer, eye, and general surgical procedures a year.



AND HERE, THEY COME BECAUSE THEY FEEL LIKE THEY MIGHT BE MAKING A DIFFERENCE FOR EVERYONE.

In the 1980s there was a shift to the concept of day hospitals, so patients who didn't have to be in the hospital could be treated. Day treatment programs evolved to the point where patients who needed pre-treatment and post-treatment for infusions that took 8, 10, or 12 hours could return to the hotel or wherever they were staying between treatments.

### A wonderful place to practice nursing

Several things make the Clinical Center a wonderful place to practice nursing. First, the Clinical Center is fully staffed, with a high nurse-to-patient ratio so investigators don't have to worry about whether a staffing crunch will impair their ability to take in new patients or collect research data. The level of patient care needs to be predictable, not a variable that can affect the research results.

Second, as a group, the nurses are smart. They have to be on the ball because often they are helping with therapies, medications, treatments, technologies, and procedures that others have not yet used. They have little or no reference material to fall back on and in fact may be creating reference material for others as they go. They have to document much more of what they see and do than they would if they were learning about something tried and true. This is attractive to some nurses, but not to those who depend on a step-by-step nursing manual. In clinical work, the nurse has to be able to discuss with the investigator what's going on with a patient in terms that require knowledgeable judgments: Is this a manifestation of something related to the treatment? Is it an adverse event? Is it something that was expected? And so on.

Clinical Center nurses enjoy a collegial relationship with physicians. Institute investigators depend on the nursing staff to make observations, collect data, administer tests and treatments, and implement many of the things being done in their clinical research. They generally acknowledge that and respect what the nurses think. As a result, the Clinical Center can attract and retain highly qualified nurses.

### VERNICE FERGUSON, A CHIEF NURSE WITH A BATTLE PLAN

Louise Anderson, the stern and starched chief nurse through the 1960s and early 1970s, always had a five-year plan. If she spotted a potential head nurse, she would let her know that she might advance to the position if, within the next two years, she had (for example) spent a year working with the open-heart surgery patients. Many a nurse asked not to serve a rotation on the cancer nursing service; she invariably put them there anyway, on the principle that it was good for them. A Corps officer from the old school, Anderson would send a nurse home to change if her uniform, hairstyle, and shoes weren't up to standards. She expected order and precision, and often checked for proper hospital corners on the bed linens. Anderson followed Ruth Johnson as chief nurse and was followed in turn by Vernice Ferguson, Mary Thompson (acting chief), Rena Murtha (whose Christmas gift to the nurses in the 1980s was to dispense with official uniforms), Janice Feldman, Kathy Montgomery, and Clare Hastings.

Vernice Ferguson, the chief nurse from 1972 to 1980, is widely credited with professionalizing nursing in the Clinical Center. Ferguson (who had a sense of humor, but always referred to herself in the third person, as in "Vernice Ferguson says,") expected a lot from unit chiefs and from nurses and was adamant that they document their observations about patients. But she insisted that the nurses were not going to carry the keys for everyone else in the hospital—were not going to be weekend pharmacists and dietitians, for example—and during her tenure a new phlebotomy unit took over the duty of drawing blood from patients. She articulated a clear view of the nurses' role, grounded in values one couldn't really argue with, and got the nurses behind her. She was a strong advocate for the nurses, had them read Machiavelli's *The Prince*, and viewed each day as going into battle. At a time when nursing was opening up, she gave nurses money to travel to meetings and got them more involved in protocols. She insisted that all the nurses be kept under the nursing service (at a time when at least one of the institutes thought it could do a better job of overseeing the nurses than the Clinical Center did), reasoning that only if all of the nurses were under her supervision could she make sure they were competent. "She made a good nursing department into a great one," says Joyce Harris.



Vernice Ferguson says...

“The Clinical Center is clearly not a match for everybody,” says chief nurse Clare Hastings. “The people who tend to like it here are the people who like the intellectual pace and don’t mind that, even on some of our most intense units, the pace is more deliberate. Even with acutely ill patients, as in surgical oncology or an intensive care unit, the nurses are not crazed like they are in the community. A born-and-bred trauma nurse is going to need a much more steady diet of crises than the Clinical Center offers. Some nurses also want to feel more connected to the local community.”

Nurses who care for patients in a research setting not only help investigate health problems today but also help develop knowledge with broader implications. Nurses in clinical research know they have probably helped add decades to the average American lifespan and improved the quality of life of those who survived critical illness. Their rewards may include the smile of a child leaving the hospital because his life and health were extended by procedures or medications unavailable only weeks before, or the knowledge that a new vaccine has been developed that can prevent a disease for which there was previously no satisfactory response.

Periodic nursing shortages around the country inevitably have an impact on the Clinical Center. During an acute nursing shortage in the mid- to late 1980s, when it was difficult to staff oncology units, the nursing service ran focus groups around the country to find out what would make the opportunity of working with AIDS patients more attractive. They learned that what nurses wanted most was recognition of their role and contribution. Title 42, a special pay authority, allowed the Clinical Center to offer more competitive pay; if the nursing service was recruiting someone with specialty experience, it could recognize that in pay. More important, in the long run, is the psychic payoff from working at a hospital with the mission of improving health care overall. “Nurses in general come to nursing because they want to make a difference for someone,” says Hastings. “And here, they come because they feel like they might be making a difference for *everyone*.”

## NURSE TYE MULLIKIN, MAKING A DIFFERENCE

A lot of research happens before people can go to their local physician, learn what their problem is, and get a prescription to take to their local drug store, so they can get better. Whether it’s new treatments or medications, or new diagnostic tests and diagnostic imaging, everything medical that people have access to becomes available only because someone, somewhere, did research. That research might have started with a scientist looking at cells in a Petri dish, or studying an animal model of a disease, which led to an understanding of the disease or the identification of drugs that might be useful in therapy. Then the drugs had to be tested for safety first in animals and then in humans, followed by testing to find out how the body handles the drugs, followed by testing to learn if the drug was in fact effective for the condition for which it would be prescribed. (If it’s an antihypertensive agent, does it indeed lower blood pressure? If it’s an antiretroviral drug for HIV, does it reduce levels of the virus? If it’s a cancer chemotherapeutic drug or a tumor vaccine, is there evidence that it actually reduces the tumor burden?)

Research at the Clinical Center allows the nurses to have a say in what nurses on the outside will be practicing. “As a nurse at the bedside, I am giving drugs or innovative surgeries that have never been done with human populations,” says nurse Tye Mullikin.

“I think about the practical side of how to implement something—about how outside nurses will someday be getting a drug we’ve been doing in a clinical trial.

“Phase one is very hard because we know that the patients are coming not for treatment necessarily—that they’re looking at doses and toxicity,” says Mullikin. “Working with that patient population is something most nurses in regular hospitals don’t have the opportunity to do. We have the opportunity to sit and counsel those patients on what it means to be in a clinical trial. When patients come to us in a phase two trial, the researchers are looking at whether the drug is going to work on a specific population—maybe melanoma patients or patients with renal cell cancer. We have a pretty good suspicion, based on the animal models. Then, when we hit phase three, we feel like we’re hitting pay dirt. We’re studying, is it better than what’s out there in the real world. And we have a pretty good chance of seeing some of our patients respond quickly, which



**Martha Quayle, dispensing medications**

In the 1950s and 1960s, drugs were dispensed in bulk from the pharmacy on the Clinical Center’s first floor and were sent up to the nursing units on three dumbwaiters. The nurses would count pills, draw medication from vials, and generally measure out all the medications patients were to be given, based on doctors’ orders. Narcotics and controlled drugs were kept in the pharmacy safe, along with alcohol, the nutrition department’s silverware, and the occasional celebrity patient’s stash of champagne. During the evening, as patients watched movies in the hospital auditorium, the pharmacist could also watch from the auditorium’s back row, where people knew to find him if they needed a special prescription filled. In 1974 the pharmacy introduced the “unit dose,” modernizing the system for dispensing medications.

is very satisfying. We have the satisfaction of seeing some patients coming back years later disease-free, when they were told that they only had three months to live—patients who went on and had babies and raised families. We've had patients call us and say, 'You made such a huge difference. I never thought that this would work for me.' And we have some patients who say, 'I know this may not work for me, but this could be genetic and it will help my kids or other people like me.'

"It's a whole different realm of nursing," says Mullikin. "My unit's an oncology unit and for patients who come here, this may be their last resort. We have the initial hope of a cure, and if our treatments don't work we hook them up with hospice workers in their own community to help them through the process of dying.

"The collaborative effort makes a huge difference in the Clinical Center," says Mullikin. "Without that, we wouldn't be able to implement some of the research. We have to take into consideration the patient's wants, needs, or desires. If a patient tells us 'I'd rather take these medicines during waking hours, not sleeping hours, so I can

get some sleep, so my quality of life is better,' we have input. As nurses we will lobby for patients. Physicians at the Clinical Center are open about what nausea meds or pain medicine may be needed, and the pain and palliative care service will provide acupuncture, massage therapy, spiritual counseling, or other kinds of holistic care. And the nutrition groups send nutritional supplements home with them to see them through their final stages."

Tye Mullikin, with patient



## Cleaning up the blood supply

The Clinical Center's Blood Bank (renamed the Department of Transfusion Medicine in 1984) had published its first research paper delineating the problem of post-transfusion hepatitis in 1957. Years later, a clinical associate named Harvey Alter would play a crucial part in solving that problem, though doing so would take decades. His story once again illustrates how easily collaborations form in the Clinical Center and how unexpected and long the paths to success in research may be.



In the 1960s, Alter was trying to figure out why patients developed high fevers in reaction to transfused blood. "We knew that some people reacted to white cells and to red cells, but a lot of people seemed to be having febrile transfusion reactions that weren't explained. My theory was that people might be reacting to plasma proteins that were different from their own." Alter had set up a method for testing the serum of repeatedly transfused patients against the serum of donors, which produced a milky white line in agar, reflecting the presence of antibodies. One day a colleague told Alter that he'd just heard a lecture by Baruch Blumberg, a geneticist with Arthritis and Metabolic Diseases, and that Blumberg was studying analogous precipitant lines.

"The beauty of NIH is that I went to talk to him the very next day and by that evening we had established a collaboration," says Alter. Their work together led to the discovery in 1964 of the Australian antigen, which Blumberg later showed to be the surface coating of the hepatitis B virus. This discovery led to the isolation of this medically important virus.

In the 1950s and 1960s, the technology for open-heart bypasses was in its infancy, and several units of blood were

## Life Island

Jay Freireich introduced the first clinically usable germ-free environment, the Life Island, in 1965. A bed with a plastic canopy over it, the Life Island protected immune-suppressed patients from pathogens.



required just to “prime” the oxygenator used in surgery, so cardiac patients typically received 14 to 17 units of blood. There was much less concern then about the risks of blood transfusion, and blood was used liberally. The Blood Bank was concerned that this might lead to a high rate of transfusion-transmitted infection, especially hepatitis. Alter took specimens from each of the donors for open-heart surgery. He also took samples from the surgery patients, before and after surgery and then continually for their lifetimes—the frequency of the sampling depending on whether or not he found any evidence of transfusion-transmitted hepatitis. Unfortunately, about a third of those patients had received tainted blood, which eventually inflamed their livers, producing hepatitis.

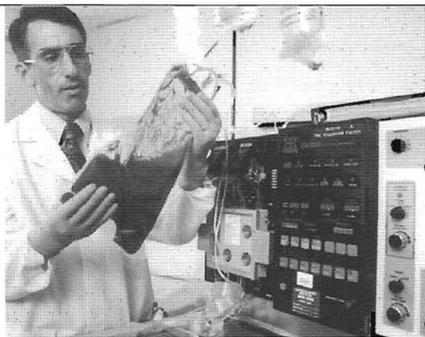
Alter froze and stored those donor and patient specimens, which required an enormous serum repository. Initially he put the samples in freezers in the Clinical Center, then in a rented meat locker in Tyson’s Corner, Virginia, and eventually in a professional facility from which specimens could easily be retrieved when needed. “At the time such a repository was quite expensive and didn’t exist. It turned out to be a gold mine,” says Harvey Klein, who became department director in 1984.

Studies done in 1970 had shown that patients who got one unit of paid-donor blood had about a 50 percent chance of getting hepatitis, whereas if they got only volunteer blood, that chance dropped to 7 percent, a dramatic difference. The Blood Bank had been buying about half its blood from outside sources—classic commercial blood establishments in Baltimore and Memphis, at which donors often sold their blood to buy alcohol and perhaps other drugs as well. So in 1970 the Blood Bank switched to an all-volunteer system, at the same time adding a test for hepatitis B surface antigen. Prospective studies done later showed that those two measures alone reduced the hepatitis rate from 30 percent before 1970 to about 11 percent after. “In truth,” says Alter, “nothing we’ve ever done since that time has had that dramatic an impact.” When they added more sensitive tests, hepatitis B virtually disappeared as a problem in the Blood Bank. These policies were soon made national standards.

In collaboration with Bob Purcell and Stephen Feinstone (NIAID), Alter determined that whatever was triggering the rest of the transfusion-associated hepatitis was neither hepatitis A nor hepatitis B. From 1975 to 1989 they called the unknown agent(s) “non-A, non-B hepatitis” (NANBH), showed that it produced antibodies in a chimpanzee, and searched for a simple serologic test to distinguish those who carried the infection from those who didn’t. So many laboratories claimed to have produced tests for NANBH that from his warehouse of frozen samples Alter developed a coded, well-pedigreed panel of specimens, some of which were known to be non-A, non-B cases, and some of which were controls. It was a tricky panel, and only Alter held the code to it. Roughly 40 labs asked to have their test applied to the panel, and none had produced a successful test. In 1989 a commercial firm named Chiron, which had secretly been working to clone the non-A, non-B agent since 1983, told Alter they had developed a test to run against his panel. Their test worked.

The beauty of having a repository of well-followed, highly pedigreed patient specimens, says Alter, was that they could truly show they had found the marker for what they now named “hepatitis C.” They published a paper in the *New England Journal of Medicine* (“the fastest paper I ever wrote”), and by 1990 had a first-generation test in place in all of the blood banks in the country.

“This kind of long-term, nondirected research could really only have been done here at the Clinical Center,” says Alter. “If I had gone to a granting authority in 1970 and said, ‘I don’t know what hepatitis agents are, but I think there are some out there and I want to find them, and I want to follow patients long term because the natural history of hepatitis C or non-A, non-B, is 20, 30, 40 years—it’s a very slowly evolving infection—so I’d like to be funded for about 30 years and really study this . . .’ I couldn’t do it! But here at NIH each year I would get some money to do something and just kept going.



Harvey Klein, chief of Transfusion Medicine



Harvey Alter, left, and Baruch Blumberg  
“The beauty of NIH is that I went to talk to him the very next day and by that evening we had established a collaboration,” says Alter. The collaboration would bring Alter a Lasker Award and Blumberg a Nobel Prize.

“THIS KIND OF LONG-TERM, NONDIRECTED RESEARCH COULD REALLY ONLY HAVE BEEN DONE HERE AT THE CLINICAL CENTER.”

“It’s an amazing place in which to engage patients and particularly to strike up collaborations,” says Alter. “It’s so easy to work with other people, to get expertise you don’t have, to get patients who are interested and grateful and participate in studies with great enthusiasm. There’s no money involved, and you don’t have to discharge a patient at a given time. Both you and the patient know that you’re here to find out what’s wrong, to study many patients, and to publish the results. So both patients and physicians come in with a totally different perspective than in a regular hospital. The ability to do studies depends on the patients’ confidence in the people taking care of them, and the nurses play a dramatic role in this. Increasingly nurses really run studies, so it’s way more than just peripheral involvement—they’re very heavily involved. The whole place is geared to work that way and also to work between institutes, between departments—whatever it takes to make information evolve and to help the patient at the same time.”

In 1976, Baruch S. Blumberg received a Nobel Prize for his work on the Australian antigen and hepatitis B. In 2000, Harvey Alter and Chiron’s Michael Houghton shared a Lasker Award for their work. Alter, elected to the National Academy of Sciences, has been widely recognized for reducing the risk of blood transfusion-associated hepatitis from 30 percent in 1970 to virtually zero in the year 2000. According to the FDA, the risk of contracting hepatitis B from a pint of blood is now 1 in 200,000; the risk of contracting hepatitis C, about 1 in 2 million.

When, in the early 1980s, a new disease came along, an acquired disease of severe immunodeficiency, there was a suspicion it might be transmitted by blood, but no one was really sure. The work done in the Blood Bank—and that repository of frozen blood specimens—became important both for AIDS generally and for the safety of the nation’s blood supply. And so would work done elsewhere in NIH’s intramural program.

## From MIS to CRIS—adventures in computer systems

In 1974 three Clinical Center doctors (Tom Lewis, Roderick Prior, and David Swedlow) and a hospital-oriented industrial engineer (Gerald “Jerry” Macks) began exploring the possibilities of a large-scale computer-based medical information system to keep track of the hospital’s clinical research and patient-care data. They wanted a system to replace hand-written medical orders—a system nurses, physicians, and lab staff could use as easily as they used a telephone. (The term “user-friendly” hadn’t been coined yet.) Some hospitals had begun using computers to keep track of billing; the Clinical Center wanted a system to keep track of clinical research and patient care, to convert manual operations and information handling to a computerized system.

Earl Laurence, who was then executive director of the hospital, remembers a total lack of bureaucratic oversight, committees, and consultations about the system. “In retrospect, we were outrageous. Scottie Pratt, the director of the Division of Computer Research and Technology, thought it was a *dreadful* idea. But we didn’t ask anybody. We just decided, ‘This is what we need,’ and did it.”

The main champion of the medical information system (MIS), Tom Lewis, was a physician who became a computer scientist but remained convinced that science and clinical practice should drive the technology and not the other way around. Vernice Ferguson, the visionary chief of nursing, put together a cadre of nurses to help determine the system’s information requirements and later to help with training and the conversion from a pen-and-paper to a computerized process.

At the time, says Carol Romano, part of that original team of nurses (and eventually an expert in clinical informatics), nurses were part of information processing across all departments. They sent requisitions to other services, such as pharmacy and diagnostic radiology; they knew what was involved in medical orders, what signatures were needed, who had to be notified of what, and what reports had to be generated. The nurses were at the patient site, and involving them from the start meant that the computer system would produce a patient-centered flow of information.

### O’ Say Can You CC

For 50 years this building has been the portal  
To understand illnesses that make us all mortal  
To study the diseases that our lives constrain  
To partner with patients to alleviate pain

To amplify knowledge like a polymerase chain  
To bring new concepts from the bench to the vein  
And above all, to approach each patient in a manner humane

For my life, the very pinnacle  
Has been to work in this Center so Clinical  
Of this fact you may be cynical  
But I have a fervor for it just short of rabbinical  
I’m addicted to the CC in a manner nicotinical

Through these doors for half a century  
The most perplexing diseases have made their entry  
In this giant red brick tower  
Translational medicine began to flower  
As disease after disease lost their power

Today it’s gene arrays and stem cells with which we’re enchanted  
Tomorrow, life will be extended as we’re routinely transplanted  
We’ll become mixed organ beings with internal diversity  
There’ll be a plethora of new ways to face medical adversity  
At the heart of these advances will be the world’s  
best scientific fermenter  
The entity whose values we cherish and honor—the Clinical Center  
—Harvey J. Alter, MD

One thing the development and implementation of MIS did was make people think about systems. In looking for information needs, the MIS team learned that the departments weren't talking to each other. When a physician ordered an x-ray that required some kind of medication, pharmacy was involved, medicine was involved, nursing was involved, and x-ray was involved—but nobody recognized all that. When you're designing a computer system, says Romano, you have to bring all those players to the table. The technology forced them to recognize that they had to start thinking in *systems*. Many people had something to do with a patient's chart in the course of a week, and MIS made them realize that they needed to pull their information management together to avoid duplication and fragmentation of effort.

After an intensive period of questioning to identify probable user needs, in 1975 the Clinical Center awarded a contract to a firm called Technical Medical Information Systems (later Eclipsys Corp) for the hospital's medical information system (MIS). The mainframe system would handle clinical orders, online retrieval of results, and charting for all Clinical Center inpatient and outpatient visits for three decades. The Clinical Center was the sixth hospital to install the "Technicon Medical Information System" but the first to install a system configured and enhanced to facilitate protocol-based clinical research. Most hospital systems were billing systems. As configured for the Clinical Center, MIS was one of the first systems in the country to offer online care planning, assessments, clinical documentation, and retrieval of results.

In 1976, MIS began going live for inpatient documentation, one nursing unit at a time. Anxiety was nearly universal, but most of the nurses were on board from day one, recalls Romano. A cadre of nurses trained in the system took the lead in training multidisciplinary teams in the new technology. One of their tasks was quelling resistance from doctors. "Believe you me," says retired nurse Alice Duncan, "nursing was the one, it landed on them to learn all that, and the doctors wouldn't use the thing."

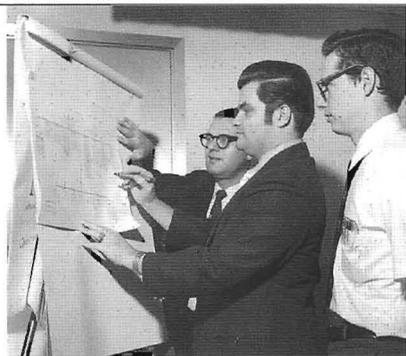
The first nursing unit to go online was neurology, a unit in which physician's orders flowed heavily. "Neuro," it was felt,

would be receptive to the new system, but Duncan remembers one doctor in neurology saying, "I am NOT going to use this computer. This is for a bank! This is not for a medical professional!" Medical history quickly proved him wrong, of course.

For the older doctors, especially, the introduction of MIS was traumatic. Young doctors today grow up with spreadsheets and other software, but at the time the computer gave people headaches. "I saw a surgeon hit the computer, he was so frustrated," said one nurse. She watched the doctor key in a whole list of orders, all the patient's vital signs, activity, diet, medicines, everything, and *then* an order, and the computer wouldn't take what he was entering. He hadn't learned first to enter something to see if the computer would take it, and his frustration was intense. An oncology doctor, "who changed IV orders as often as he blinked," ordered an agent without specifying the vehicle (dextrose or a saline solution) in which to dissolve and deliver it intravenously. He didn't get what he wanted, had to reorder it, and "had a fit and a half." More than once the MIS team adapted the system to make it more palatable to doctors and more responsive to the needs of a research protocol.

When MIS was implemented, Vernice Ferguson insisted that the nurses would not transcribe physician orders—that physicians must enter their own orders, to avoid introducing another level of errors. Considering that this was at a time when other hospitals weren't even *implementing* clinical systems, the level of compliance with Vernice Ferguson's insistence on physician-entered orders was astonishing—for a while, as high as 80 to 90 percent.

"It's also a credit to Mort Lipsett's personality that they were able to get the system out," says Earl Laurence, referring to the physician-scientist who became Clinical Center director after MIS had already been designed and ordered and who pushed the system despite wide resistance. "Glenn Morrow



Before "user friendly" became part of the world's lexicon, Clinical Center staff, including (from left) Jerry Macks, Anthony J.J. Rourke, and Thomas Lewis, began exploring the benefits of a computerized medical information system as easy to use as a telephone.



MIS uses multiple workstations throughout the hospital to provide quick, confidential access to patients' lab test results, biographical information, diagnoses, medication summaries, and diagnostic test results.

didn't want the system on his nursing unit in cardiac surgery and he would literally go up there at two o'clock in the morning, unplug the equipment, and take it off the ward. And no wonder. People didn't have computers in those days—e-mail didn't exist.”

Between Mort Lipsett, Vernice Ferguson, Tom Lewis's team, and the nurses, somehow MIS had become operational in most hospital nursing units by the second half of 1978. On April 21, 1979, just before the afternoon shift in staff, a fire started in the solarium on the ninth floor and soon spread to the 9-West nursing unit. Luckily, it was a Saturday so the patient load was down. All of the patients in the building were evacuated and because the hospital was on MIS, they were all quickly and easily accounted for. The food service people managed to serve dinner to all 300 patients by eight o'clock.

After a lot of handholding and one-on-one training, most of the doctors grew accustomed to the system and realized that although the computer wasn't perfect and didn't do everything they wanted it to do, it provided a resource with a memory for protocol orders. At one point a cat or a squirrel on a high wire in New Jersey got electrocuted, temporarily shutting down the mainframe the Clinical Center shared with St. Barnabas Hospital, and although there was a complex backup system for Clinical Center data, there was a period when everything had to be done manually, and the staff realized they had gotten used to looking at the screen, which would tell them what to do, and few were willing to go back to pen and paper recordkeeping.

Because it started with a clinical focus, designed to support patient care (unlike hospital systems, which were mainly billing systems), the Clinical Center had some catching up to do on administrative applications, such as keeping track of the number of patient stays, the cost of implementing a protocol, and integration into the budget process of information about how much the different institutes used Clinical Center services, as a basis for reimbursement.

It was ahead of its time, and with continual customization it lasted for more than a quarter of a century, but “some of the dreams people originally had for it—having a data warehouse

and those kinds of things—were never realized,” says Earl Laurence. In the meantime, the world caught up and got hooked on computer technology, and instead of one terminal per nursing unit there was a computer on every desk and then a laptop to carry on trips.

By its nature, MIS was never built to support research, says Steve Rosenfeld, chief of clinical research informatics. “It was a hospital information system, not a research system, and that's all it was.” The MIS team's goal had been to support the research process by automating data retrieval. It had designed a system that would collect patient data, so they could keep track of the clinical research and patient care. But support for research protocols was limited by the vendor technology, which was a proprietary database—a closed system—and not very flexible. Over time the vendor software was adapted to handle chemotherapy, antibiotics, and other applications. But the expectations the software generated were quickly disappointed, and as research studies and clinical care became more complex, the old technology couldn't meet the Clinical Center's changing needs.

In 2002 the Clinical Center accepted bids for development of a clinical research information system (CRIS) to replace the MIS installed in 1976. CRIS represents the next generation of medical information technology. Two dozen distinct information systems will plug into two broad CRIS hubs: a clinical data repository (for patient care) and a clinical data warehouse (for research). The repository will keep an electronic medical record, housing information about patient care and hospital operations—such things as a patient's lab results, pharmacy orders, doctors' notes, and information about nutrition, radiology, surgical services, and critical care, with links to patient images. (MIS was text-based; CRIS will be able to display images.)

One feature of the new system will be protocol mapping. Think of a protocol map as a matrix, with certain requirements along the left axis—such as medications, treatments, diet, education requirements—and along the horizontal axis Day One, Day Two, Day Three, and so on. Protocol mapping will allow a protocol to become a set of care plans for a patient but will also generate data that ends up in the research database.

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THE TECHNOLOGY FORCED THEM TO RECOGNIZE THAT THEY HAD TO START THINKING IN SYSTEMS.

The clinical data warehouse will collect historical patient data for use in research (while protecting patient privacy and confidentiality). The two systems will be separate so that demand on the research system won't slow down the fast delivery of information on the patient-care system.

### Critical Care becomes a department

In the mid-1950s there were only two or three cancer nursing units, but it wasn't long until the service had very sick patients, including many who had had extensive radical surgery. The length of the patients' stay began decreasing, but the intensity of their care started to increase—a change that was happening all over the country. The Clinical Center's hospital hadn't been built for people who were so sick and wasn't equipped to care for them—wall oxygen and wall suction had to be added, for example. If a nurse had a patient who needed a ventilator, she basically emptied the other bed in the room and managed it herself, even if she had never managed a patient on a ventilator before. They took down a wall in 10-East and made it into a four-bed intensive care unit and did the same to make a four-bed recovery room for cardiac surgery patients in 6-West.

The concept of critical care and intensive care departments developed nationally only in the 1970s—beginning with surgical recovery rooms and then expanding as hospitals realized that other patients, especially after myocardial infarction and stroke, could use the benefits of critical care. In 1977, the Clinical Center began creating a Critical Care Department on 10D.\* Initially they hired three clinicians, with no training program or research agenda, who quickly became burned out doing patient care and left. The Clinical Center then created a more traditional academic department in which the leadership would have trainees and research opportunities, the hope being to create a stable model that was more like what NIH investigators were accustomed to and that academic physicians could better relate to. As chief of the department, Joe Parrillo brought in Henry Masur, son of the Clinical Center's first director, who came to deal especially with the infec-

tious complications from AIDS. Under the more academic arrangement, and with Masur as current director, the departmental staff has remained remarkably stable, providing crucial support to the institutes and developing important research on its own—including the study of new approaches to the diagnosis and management of patients with pneumocystic pneumonia. The department's presence also changed nursing practice, because patients who needed intensive care were transferred to Critical Care and doctors and nurses skilled in intensive care took over.

### The quality-of-life team

"We are the quality-of-life team," says Ann Berger, chief of the Clinical Center's relatively new Pain and Palliative Care consult service, whose focus is the "whole patient." Palliative care, says Berger, is a combination of active and compassionate therapies that focuses mainly on the "physical, psychological, social, and spiritual suffering of the patient, family, and caregiver."

Because so many patients come to the Clinical Center as a last resort, after exhausting all standard treatments, the unit is an obvious and extremely important addition to Clinical Center services. As Berger puts it, "the Cancer Institute may cure 20 percent of its patients with melanoma, but 80 percent are going to die—and even those who are cured have serious symptoms that need to be controlled." Although palliative care is usually considered a service for patients who are dying or in pain, Berger and her team prefer to work with them from their first day at the Clinical Center.

The team members are prepared to tackle a long list of ills (nausea, vomiting, mouth sores, hair loss, anxiety, sadness, loss of appetite, lack of energy, shortness of breath, and sleeplessness, to name a few), using an equally long list of weapons (including massage, Reiki, acupuncture, acupressure, hypnosis, music therapy, art therapy, biofeedback, stress management, relaxation, and pet therapy). An anesthesiologist specializes in pain management, a spiritual minister does grief counsel-



(left) Critical care nurse checking a patient.

ing. An anesthesiologist specializes in pain management, a spiritual minister does grief counsel-

Harvey Masur, center, with part of the critical care team. The concept of critical care and intensive care departments developed nationally only in the 1970s.



\* A perinatal unit had been slated to study neonatal infants there, but the unit couldn't get enough families to participate.

ing, and the team also provides the services of recreation therapists, the pharmacist, and social workers.

Because the team is present from the beginning, they develop a close relationship with both patients and their families, which is especially helpful in difficult situations. And at positive moments—such as a transplant or a birthday—they often throw a tea party, bringing a teacart to the patients’ bedside and “life into unhappiness.” Clinical Center staff also benefit from their services. Many who are used to holding their feelings inside have taken to dropping in for cookies or chats and joining the fun at the tea parties.

The service is now running its own clinical trial to examine the efficacy of what it is doing. During the three-year study, some patients will receive the unit’s services and others won’t, although, at the request of the principal investigator, patients who are randomly assigned not to receive palliative care can opt out of the study if they need to.

In a very short time, Berger and her team have become indispensable, an integral part of the culture of the Clinical Center, and they are actively taking their message—and training—all over the world. “We can’t always cure illness,” she says, “but we can heal people. This is what we do.”

### Clinical Center volunteers

The year the Clinical Center opened, the Montgomery County chapter of the American Red Cross began providing volunteers to help patients; it has been providing volunteers ever since. Volunteers provide patient support of many kinds—welcoming patients and visitors, helping them find their way, making them feel at home in the Clinical Center, and bringing them tea and coffee and cookies.

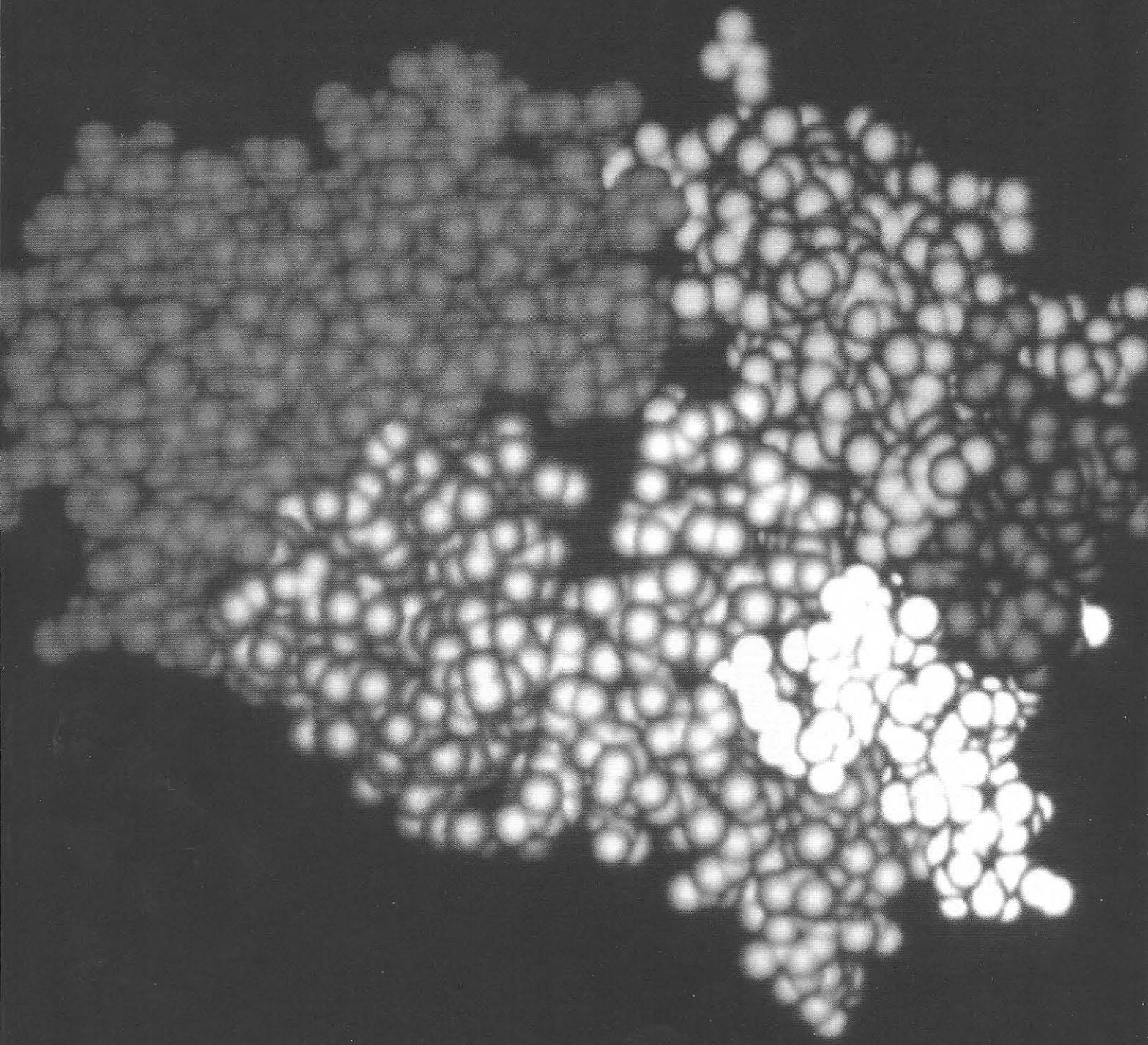


Nancy Pond on left and Floride Canter on phone and bottom right. Nancy Burke, top right.

Some of the volunteer greeters at the south entry

In the group photo, clockwise from far right: Ruth Jones, Aushkon Foroutan, Kim Mitchell, Evelyn Bendersky, Peg Wintz, Aurora Cruz, Lee Kush, and Janet Salkey. Not pictured are Ruth Graves, Feven Kiflu, Mary Meikle, Jean-Luc Pierre-Louis, Maribel Ruiz, Susan Stevens, and Melissa Turgusen.

“WE CAN’T ALWAYS CURE ILLNESS, BUT WE CAN HEAL PEOPLE. THIS IS WHAT WE DO.”



Monoclonal antibodies

**P**aralleling the intramural cancer program's leadership in chemotherapies for cancer has been a track in biological approaches, based on deepened understanding of how the body's immune system works. Tom Waldmann (in the National Cancer Institute) and Bill Paul (in the National Institute of Allergy and Infectious Diseases) were pioneers in figuring out how interleukins (cell-signaling molecules) were involved in immunological responses. The NIH became a center for researching interleukins and establishing new approaches to the treatment of both cancer and immunological diseases. Research in the 1960s defined the survival of all the classes of immunoglobulin (antibody) molecules: which parts of the molecule controlled survival and how long they survived. Learning about the very long survival of an IgG molecule provided the scientific basis for the use as therapeutic agents of monoclonal antibodies—antibody substances developed from a single line of B cells, targeted to a specific disease.

Clinical research is easier in the Clinical Center, says Tom Waldmann. You don't have to worry about getting paid for your patient's stay in the hospital bed so you can bring in patients with rare and instructive diseases in ways that are not financially damaging to them. Experiments are often designed on the basis of a hypothesis, but experience, serendipity—a chance observation in a patient that cannot be explained by the way we presently think about a disease—can open up a whole field of research that had not been there before, says

Waldmann. There was, for example, a single patient with a leukemia that was somewhat different, which permitted the discovery of the first retrovirus, HTLV-I (which came before HIV), which was cloned. An antibody was made to the patient's cells, which turned out to be to a cytokine receptor (cells use receptors to communicate with each other) called the IL-2 receptor (IL standing for interleukin). That receptor, to which we could make an antibody, ultimately told us how T cells divide, says Waldmann. The antibody to the receptor is now sold commercially to prevent rejection of kidney grafts. "None of these discoveries had been anticipated," says Waldmann. "They couldn't have been part of an experimental design because they were truly novel."

So this chance observation revealed by a patient to an observant scientist-clinician opened up the fields of retroviruses and of antibodies to cytokine receptors, and led to the discovery of new cytokines such as IL-15. This new cytokine will be of great importance in vaccine design. There are now 400 monoclonal antibodies in clinical trials. Things that had not been anticipated were possible because patients came to the Clinical Center and were seen by physician-scientists. That patient was important not only because of the study he came for, but for many other studies that have followed, because of what his condition revealed.

Nowhere else in the nation can you so easily do basic science and then take it to preclinical drug development and into the

clinic yourself, says Waldmann. “The Clinical Center is clearly a treasure—the dominant place for doing translational research,” by which he means converting what basic scientists study into practical ways of diagnosing, treating, or preventing human disease. In his case, he wanted to use basic scientific insights into immunology as the basis for making new biological agents—monoclonal antibodies, cytokines, the chemicals our cells use to talk to one another—and, after approval by the FDA and other regulatory groups, use those in new therapies for patients. “It is exciting to see your patient get better with an agent that you’ve developed yourself,” says Waldmann. “I cannot tell you how exhilarating the feeling is that you’ve made a difference.”

With work like Waldmann’s, the NIH became phenomenally strong in immunology. Some researchers began studying genetic immunodeficiency diseases, not because they are big public health problems but because they involve a single genetic defect, so they can provide a lot of information about what is essential for immune system responses, such as T cells, B cells, and antibodies. For decades, researchers in the National Institute of Allergy and Infectious Diseases (NIAID) have been developing immunosuppressive therapy for nonmalignant diseases such as lupus. In the late 1960s, Shelly Wolff and Tony Fauci produced the first “cure” of a formerly lethal non-neoplastic disease, Wegener’s granulomatosis, by using low doses of cytotoxic agents. Wolff, who did classic studies of fever and who as clinical director brought the NIAID clinical program into the modern era, was one of NIH’s most beloved and influential mentors. Among those who trained with him were David Dale, Charles Dinarello (who discovered pyrogen and later the first interleukin, interleukin-1), Ray Dolin, Tony Fauci, John Gallin, Bart Haynes, Harry Kimball, Mark Klempner, Peter Lipsky, Herb Reynolds, Robert Rich, and Richard Root.

There have been many long-term studies (over thirty years), helping to define the phenotype, genotype, and treatment of orphan diseases of the innate immune response (inflammation), such as Chediak-Higashi syndrome, chronic granulomatous disease of childhood, Job’s syndrome (hyperimmunoglobulin-E and recurrent infection syndrome), leukocyte adhesion deficiency, neutrophil-specific granule deficiency, and IRAK-4

deficiency. John Gallin and his colleagues applied immunotherapy to boost host defenses to prevent infections in patients with chronic granulomatous disease (CGD) of childhood, using interferon gamma. This led to the licensing of interferon gamma to boost host defenses and reduced infections in CGD by 70 percent—to the extent that researchers increasingly drop “of childhood” from the disease’s name, as patients live to adulthood. Further studies showed that prophylactic itraconazole prevents fungal infections in CGD patients, and Harry Malech has made important advances toward gene therapy for the disease. Studying the pathophysiology and genotype of these orphan diseases often opens areas for further investigation and can lead to treatments for common diseases.

As director of NIAID, Richard Krause predicted in his book *The Restless Tide*, completed in 1980, that we had not seen the last of infectious diseases (at a time when many scientists felt it was time to move on to more pressing health problems). Krause had built NIAID into an institute with strength in basic and clinical immunology. Many investigators studying human immune deficiencies had significantly advanced understanding of how the immune system works and how it goes awry. That knowledge would be useful when HIV and AIDS came along.

BUILDING TEN AT FIFTY  
70



Shelly Wolff did classic studies of fever and, as clinical director, brought the clinical program of the National Institute of Allergy and Infectious Diseases into the modern era. Wolff was one of NIH’s most beloved and influential mentors.

WITH THIS CRITICAL MASS OF TALENT AND ABILITY, YOU CAN REALLY STAY SCIENTIFICALLY ALIVE.



On any list of the world's great clinical immunologists, Tom Waldmann is certainly among the top three, say his peers. He started as an MD, got infected with the research bug by a 50-dollar grant to do research on erythropoietin at Harvard Medical School, and the doctor draft did the rest by bringing him to the Clinical Center. He came between the Korean and Vietnam wars—like many others, thinking it was for a two-year stint, after which he would return to Mass. General Hospital at Harvard Medical School—and now, nearly 50 years later, he's still here.

His boss in the Cancer Institute quit, he became de facto a tenured investigator, and like others who suddenly found themselves in the position of having more authority than they had expertise, survived by what he learned talking to other scientists in the corridors. Indeed, they all learned together. Having been at the Clinical Center longer than most, he looks back on the last 50 years with astonishment at how enormously biology and medicine have changed. When he arrived at Building 10, Watson and Crick had just defined DNA. No one had any idea what a lymphocyte was, much less any idea about B cells and T cells, receptors, cytokines, retroviruses, restriction enzymes, genetic errors, and knock-out mice. "Now we have molecular understandings of leukemia, of malignancy, and of autoimmunity, and these provide molecular targets for therapy. We have moved clinically from chance observations—a kind of

crude serendipity—and crude efforts to targeted therapies that have a rational scientific base."

Waldmann studied the cellular immune response in the human immune response—dissecting how T cells actually work. He identified the Tac receptor on T cells, figured out how to make monoclonal antibodies against it. Having discovered that people with HTLV-I infections express an enormous amount of the alpha subunit of the interleukin-2 receptor identified by his anti-Tac monoclonal antibody, Waldmann wondered if the antibody could be used therapeutically—if biological agents could be used to treat disease. They could, and

were—eventually with patients with leukemia as well as those with autoimmune diseases. He helped the Clinical Center's Nuclear Medicine Department hook that antibody to a radioactive compound so it could be delivered to where it would do the most good. Both a basic and clinical scientist, he is considered a treasure at the Clinical Center.

"Thomas Waldmann is the latter-day equivalent of the dedicated microbe hunters who built the Public Health Service and started the National Institutes of Health," wrote Edward Shorter in his history of health care in the twentieth century. "But bravery in the late 1980s frequently consists of renouncing the overwhelming material abundance of a consumer society in favor of dedication to what Waldmann calls 'bringing molecular science to the bedside.'" You will always get gripes about the place, says Waldmann, but "here there is less of the intense competition you might see at Harvard, where doors may be closed because people are competing for resources. Here, the tendency is to collaborate, and there are so many people with so many skills that groups tend to work together. With this critical mass of talent and ability, you can really stay scientifically alive. I'm as enthusiastic and excited as I was 47 years ago when I came here. I would never consider leaving the Clinical Center of the NIH."

"The National Institutes of Health is not only the largest institution for biomedical science on earth, it is one of this nation's great treasures. As social inventions for human betterment go, this one is a standing proof that, at least once in a while, government possesses the capacity to do something unique, imaginative, useful, and altogether right. . . .

[At] the center of the NIH scientific effort, driving the whole

vast enterprise along, is the research conducted on the Bethesda campus itself—the so-called Intramural Research Program. Although this represents only a minor portion of the total NIH budget—around 10 percent—for sheer excellence and abundant productivity, the institution cannot be matched by any other scientific enterprise anywhere."

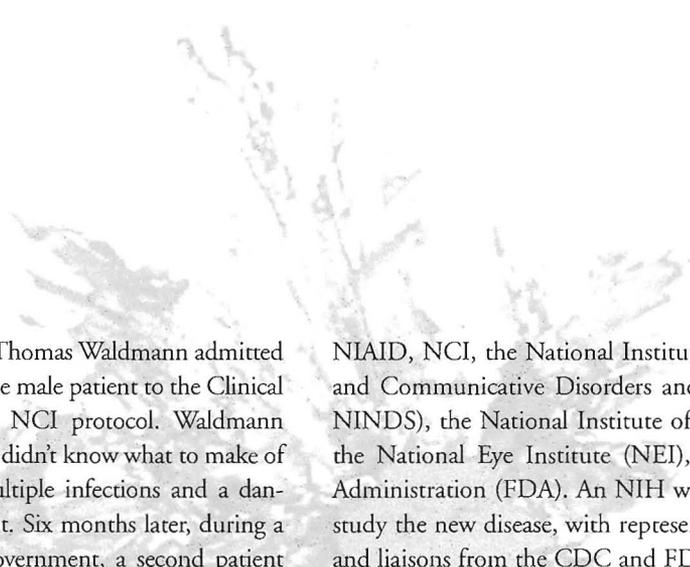
—Lewis Thomas, 1984



Anthony Fauci

As the government's semi-official spokesman on the AIDS crisis, Fauci became the visible face of the greatest team effort the Clinical Center ever marshaled. As a complex syndrome of opportunistic infections and other diseases brought about by a failing immune system, AIDS drew intramural NIH researchers from many disciplines. A "grass-roots" team of scientists worked together, routinely sharing observations. That AIDS was so complex made it both difficult and fascinating to study.

# ADDRESSING THE AIDS CRISIS



**O**n June 16, 1981, Thomas Waldmann admitted a 35-year-old white male patient to the Clinical Center under an NCI protocol. Waldmann and his colleagues didn't know what to make of his condition: multiple infections and a dangerously low white blood cell count. Six months later, during a snowstorm that shut down the government, a second patient with similar symptoms was admitted and was seen by Tony Fauci, a senior investigator with NIAID. There would be many more before scientists knew exactly what they were dealing with.

In 1981, nobody had the faintest idea how this strange new disease worked, except that it appeared to be transmitted by blood and through sex. Early reports convinced Fauci that the emerging disease could become a disaster, spreading well beyond the community of gay men and drug abusers where it had first appeared. He quickly redirected his branch's work almost totally toward studying the disease. Most of the investigators who joined him put aside most of the work they had been doing on other diseases, to help with what could clearly become a medical crisis. The institutes could mobilize an intramural army of researchers to attack the problem faster than other institutions because the infrastructure was in place and funding could be rapidly shifted. The intramural staff did not have to write grant applications.

In June 1982, a Clinical Center protocol was approved to study the etiology of immunoregulatory defects in the new disease as a collaborative effort among Clinical Center departments,

NIAID, NCI, the National Institute of Neurological Diseases and Communicative Disorders and Stroke (NINCDS—now NINDS), the National Institute of Dental Research (NIDR), the National Eye Institute (NEI), and the Food and Drug Administration (FDA). An NIH working group was set up to study the new disease, with representatives from each institute and liaisons from the CDC and FDA.

Fauci converted his lab from one that explored fundamental questions of immunology to one that focused on understanding this new disease. Joe Parillo, head of the Clinical Center's new critical care department, agreed to take patients if he could hire a specialist. Henry Masur had been working in New York when he observed a strange increase all around the country in *Pneumocystis carinii*, a rare cause of bacterial pneumonia usually seen only in patients with severe immune disorders. Masur agreed to join the Clinical Center staff because he sensed it would be easier to tackle a complex emerging disease in a place with experts on almost everything, a place where physician-scientists were free to follow their own interests.

The Clinical Center began admitting more patients with this complex array of symptoms. The hospital focused on only a few patients first, providing intensive care but always in a setting of clinical investigation. It "was like living in an intensive care unit all day long," says Fauci. Most of those first patients eventually died, despite the best efforts of NIH's dedicated and initially anxious doctors and nurses.

IT "WAS LIKE LIVING IN AN INTENSIVE CARE UNIT ALL DAY LONG."

Scientists describe as “elegant” the work Fauci, Clifford Lane, and others did in figuring out the pathogenesis of AIDS. In their laboratories, they proved that during long periods when the infectious agent was lurking, silent and invisible, it was nevertheless wreaking havoc in the molecular architecture of the human lymph nodes, destroying the immune system. They worked on strategies to restore immune defenses. Lane observed that patients with AIDS lacked helper T cells but had markedly hyperreactive B cells—the cells that make antibodies. Lane concentrated on understanding the immune system abnormalities in AIDS patients and looked for ways to stop the disease. He and his colleagues tried white blood cell transfers from healthy twins to their identical siblings with AIDS. They tried alpha interferon, interleukin-2, and other agents.

As a complex syndrome of opportunistic infections and other diseases brought about by a failing immune system, AIDS drew intramural NIH researchers from many disciplines. Soon a “grassroots” team of scientists was working together, routinely sharing observations. That AIDS was so complex made it both difficult and fascinating to study. Scientists in dental research, for example, showed that the AIDS virus could infect not only T4 lymphocytes but also macrophages.

David Henderson, the hospital’s first official epidemiologist—and now deputy director for clinical care—led the team charged with reducing the risk of health professionals becoming infected with the disease, even before the virus and its mode of transmission were identified. For a while it was a full-time job keeping hospital staff up to speed on what the known and unknown risks were and how to reduce them. Aided by nurses such as Barbara Fabian Baird and Christine Grady—and many others on the front lines of the AIDS crisis—Henderson developed guidelines for protecting healthcare workers from infection.

In some ways previous decades of research at the Clinical Center—before AIDS came into public awareness—had prepared its physician-scientists to deal with the problem. Had it come along 30 years earlier, they would not have known enough to be able to look for the retrovirus that caused AIDS or to be able to grow continuous cell lines so they could study it. In 1979 Robert C. Gallo Jr. in the Cancer Institute had

discovered the first human retrovirus, human T-cell lymphotropic virus, or HTLV-I—at a time when most scientists believed retroviruses occurred only in cats, mice, and other animals. To be able to do this, he had first developed methods (based on the discovery by others in his lab of the interleukin hormone IL-2) for growing human T cells in culture. Because HTLV-I caused an obscure cancer of the immune system, little attention had been paid to the discovery.

In 1982, Gallo had proposed, and was working under the assumption, that the new disease was caused by a retrovirus. By 1984, research groups led by Gallo and investigators in Paris and California had all simultaneously identified a retrovirus as the cause of AIDS (calling it HTLV-III, LAV, and ARV). Renamed human immunodeficiency virus, or HIV, the virus provided a target for research. Gallo’s laboratory developed a diagnostic antibody test, which allowed researchers to get a sense of the scope of the epidemic and gave healthcare workers the ability to screen blood donors and protect the blood supply. Gallo’s location on the NIH’s main campus and his constant interactions with the Clinical Center, from which his lab received tissue samples and peripheral blood specimens, unquestionably accelerated his seminal discoveries.

When Fauci took over as NIAID’s director in 1984, in addition to overseeing laboratory and clinical research, he helped convince Congress to dramatically increase funds for AIDS research. NIAID’s scientific director, John Gallin, who helped create the first AIDS clinic at the Clinical Center, coordinated NIAID’s on-campus fight against AIDS when (in 1986) Congress gave them the funds they sought. An important spin-off of the AIDS epidemic was stronger patient advocacy and activism. As unofficial spokesperson for the government during the crisis, Fauci drew the public ire of playwright Larry Kramer, co-founder of Act-Up and a proponent of theater tactics. By engaging in a productive dialogue with Kramer and other protesters, Fauci helped introduce more active patient representation in NIAID decision-making. Gallin, who went on to become Clinical Center director, strengthened that emphasis by creat-



“IF YOU TAKE AN INSTITUTIONAL CLIMATE OF INFORMALITY AND UNLIMITED SUPPORT, AND BRING THE RIGHT PEOPLE ON BOARD, SOMETHING IS GOING TO HAPPEN.”

ing the Patient Advisory Group, which plays an important role in advising the director on patient-related issues.

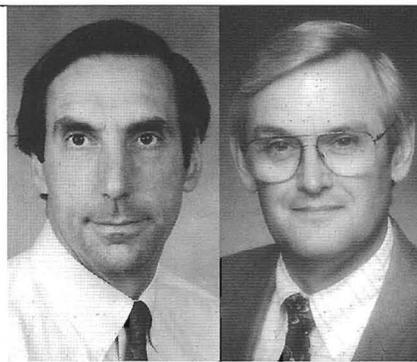
When the epidemic started, NCI was the only institute involved in drug development in areas the private sector ignored. Most of the institutes looked down on drug development, and most scientists insisted that viruses were unaffected by drugs. But Sam Broder, a physician-researcher at NCI, began testing several agents for their effectiveness in blocking replication of the AIDS virus. Working with him were Hiroaki (“Mitch”) Mitsuya (who “could grow anything in tissue culture”), Robert Yarchoan, and others in the intramural program. There was a window of two to three years, says Broder, between 1984 and 1987, where “everything sort of clicked in and the bureaucracies were not there to do what bureaucracies usually do.... Among the reasons why I think bureaucracies stayed away is that there was a strong presumption that the project would fail quickly or self-destruct.... I was also willing to accept that it is better to make some progress quickly than hold back and wait for a cure before acting or before trying to implement a new therapy.” He had the full support of NCI’s director, Vince DeVita, who, says Broder, “had a belief that you can do things without having to wait for perfect knowledge, and he was not afraid to act.”

One of the agents Broder’s team tested was a chemical that had been rejected as an anti-cancer agent: Broder and his colleagues pulled AZT off the shelf and tested it against AIDS. Yarchoan recalls being particularly impressed by AZT’s dramatic effect on one patient, a nurse from New York, “who had gotten AIDS through a blood transfusion and had a horrible fungal infection of her fingernail. Her nail was quite ratty. When we gave her AZT, the infection cleared up, and you could see where the normal nail was starting to grow.” Children whose mothers had infected them with HIV at the time of delivery looked flaccid and nearly dead. Infused with the drug over several days, they were soon sitting up and behaving like normal children. That caught the attention of the pharmaceutical firm known then as Burroughs Wellcome, which became interested in developing the drug. In March 1987 the FDA approved AZT as the first

antiretroviral drug to be used as a treatment for AIDS. Broder’s group led studies on AZT’s antiretroviral cousins, ddI and ddC.

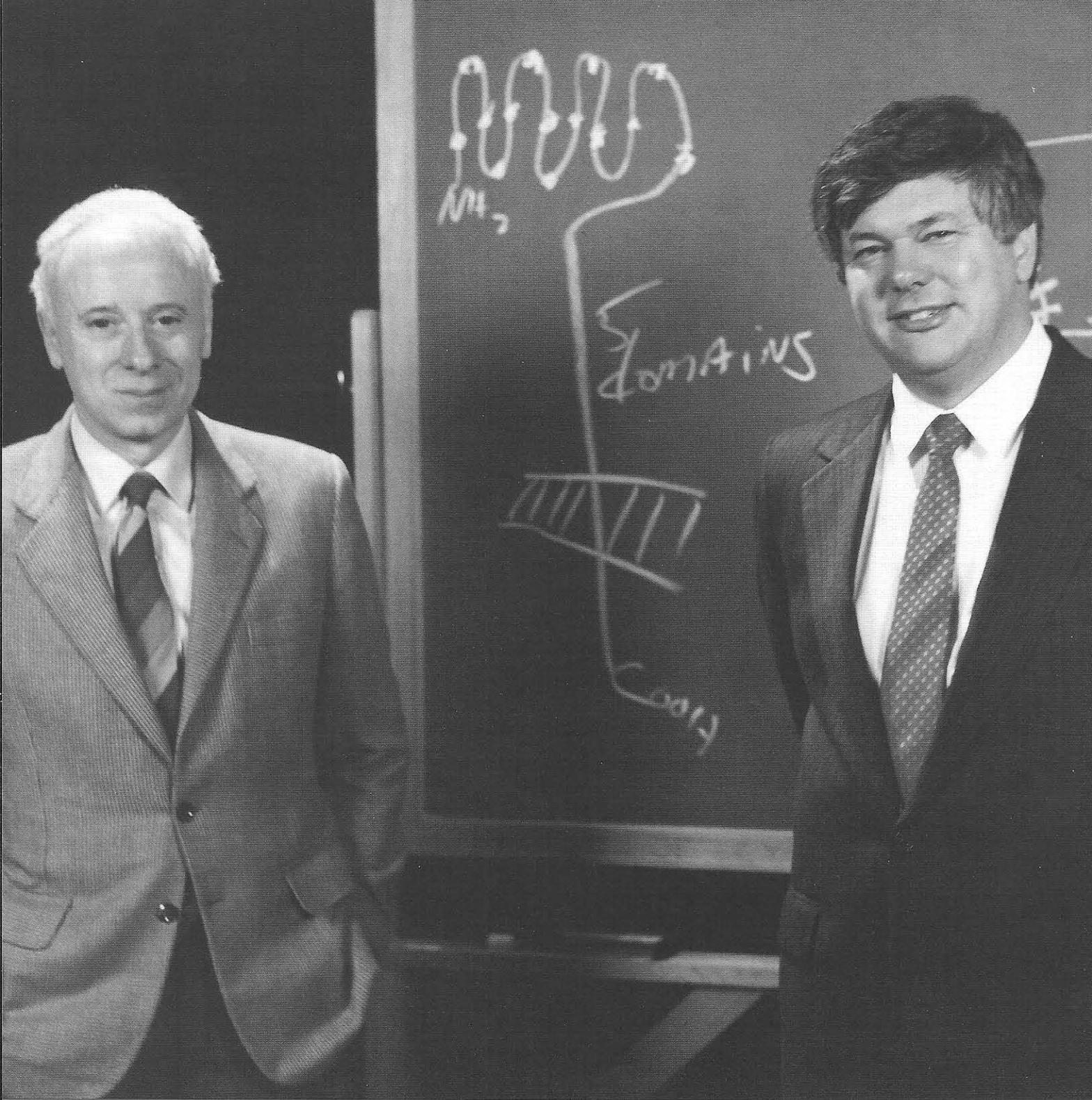
In many ways, the Clinical Center’s handling of the AIDS crisis was no different from its handling of earlier disease problems, including the first attempts to cure cancer with chemotherapy: A few interested investigators simply dug in and attacked the problem from as many angles as necessary. “The great thing about the Clinical Center,” says David Henderson, “is that it can turn on a dime. You could say, ‘This is a national public health problem. Deal with it,’ and we could figure out how to restructure our resources and get started the next day.” Because intramural researchers are free to follow their interests—to go where the science leads them—it was relatively easy to redirect resources to the new crisis. Once more it had been shown that, given enough funding, scientists and clinicians could address even so large a problem as AIDS. And the work continues—in particular, efforts to develop a vaccine.

“The very compactness of the Bethesda campus and the willingness of its immunologists to work together, to have seminars constantly, and wander in and out of each others’ labs gave them a leg up,” observed Edward Shorter, commenting on the NIH’s intramural program in his book *The Health Century* (1987). “At centers where in-house competition was fiercer, such as Harvard, people were more secretive. At the state universities, the sheer number of researchers, however excellent they were individually, did not achieve that critical mass. But the NIH, like Baby Bear’s porridge, was just right. An AIDS researcher at the NIH explained... ‘if you take an institutional climate of informality and unlimited support, and bring the right people on board, something is going to happen.’”



left to right:

Sam Broder,  
Bob Yarchoan,  
Henry Masur, Dave  
Henderson, and  
Christine Grady



Joseph Goldstein and Michael Brown

As clinical associates from 1968 to 1970, Joseph Goldstein (left) and Michael Brown (right) were exposed to patients with a rare disease, the memory of whom led them later to study the regulation of cholesterol metabolism. Their subsequent discoveries led to new principles for preventing and treating atherosclerosis. Speaking of their training at the Clinical

Center, Brown says: "We all shared the same experience—coming out of a clinical background and suddenly being exposed to incredibly clear and rigorous thinker[s] and to science at a level where you could really reduce a problem down to simple questions that could be answered by elegant experiments. For all of us, it molded our future lives. We just wanted to keep doing it again and again."

# STUDYING GENETIC DISEASES

**A**fter the development in the 1970s of recombinant DNA techniques for cloning genes and of techniques for identifying and sequencing DNA fragments, intramural protocols aimed increasingly at elucidating the pathophysiology and treatment of genetic diseases. But some of the earliest studies of genetic disorders were done before these tools were developed. Among the most important of these were studies in the Heart Institute of the disorders of lipid metabolism and the pathogenesis of arteriosclerosis.

## Studying lipid abnormalities and genetic disorders

Among the most beloved of NIH and Heart Institute researchers—and for a period NIH director—Donald Frederickson brought attention and understanding to a rare genetic disorder that he named Tangier's disease, for an island where it occurred with some frequency. He, Robert Levy, and Robert S. Lees developed a clinically useful biochemical and genetic classification of blood lipids and lipid abnormalities. Their classification of hyperlipidemias did not stand up to the test of time, but their important work led to the current classification of risk factors for coronary artery disease, and to popular understanding of things like good cholesterol and bad cholesterol. For this work, the Clinical Center was invaluable not only because it is one of the few places in the world that conduct long-term studies of rare diseases, but also because it brings patients with these diseases to the Clinical Center from all over the country and sometimes all over the world.

Experiences with such patients at the Clinical Center often affected young physician-scientists long after they completed their training there, indirectly generating important biochemical research later and elsewhere. As clinical associates from 1968 to 1970, for example, Michael S. Brown (working in Earl Stadtman's laboratory in Arthritis and Digestive Diseases) and Joseph L. Goldstein (working in Marshall Nirenberg's lab in the Heart Institute) were intrigued by two young patients of Donald Frederickson's.

As clinical associates, the two men spent one year taking care of NIH patients and a second year doing research. One of Brown's patients in the Arthritis Institute was a long-time Clinical Center patient, Al Cohen, who because of an inherited condition (abetalipoproteinemia) had no LDL in his blood (LDL being a low density lipoprotein, the major cholesterol-carrying particle in human blood). Among patients of Donald Frederickson's, they also saw a brother-sister pair with excessive levels of LDL (their total blood cholesterol levels of about 1000 milligrams per hundred milliliters being nearly 10 times above normal for children aged 6 and 8). These siblings' condition, known as homozygous familial hypercholesterolemia, 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 1972, they began to collaborate on studies of familial hypercholesterolemia at the University of Texas Southwestern Medical School, where they made use of Al Cohen's plasma and of cells from patients with familial hypercholesterolemia. “We could only have seen these patients at NIH, because both genetic diseases are extremely rare, and only the NIH would have been able to bring these patients together,” says Brown. In 1985 they won the Lasker Award and the Nobel Prize for their discovery of mechanisms regulating cholesterol metabolism.

“Somebody could go through the National Academy of Sciences membership roster, especially of the MDs, and count how many had actually been at NIH,” says Brown. “I imagine it's a very significant percentage. One could go through the list of people who trained with Stadtman and Nirenberg, as an example, and that would give you an incredible who's who in modern medical science. Dr. Stadtman alone, the person I trained with, has had two Nobel Prize winners, me and Stanley Prusiner, [and a long line of exceptional physician scientists]. We all shared the same experience—coming out of a clinical background and suddenly being exposed to this incredibly clear and rigorous thinker and to science at a level where you could really reduce a problem down to simple questions that could be answered by elegant experiments. For all of us, it molded our future lives. We just wanted to keep doing it again and again.”

## Al Cohen, the hospital's longest-term patient

Mike Brown's patient, Al Cohen, was one of many who both benefited from medical research at the Clinical Center and contributed to it. NIH investigators—starting with Leonard Laster—have been studying Al for more than 40 years. Al presented with neurological symptoms, the indirect result of his body being unable to secrete the major cholesterol- and triglyceride-carrying lipoproteins—although it took the Institute of Diabetes and Metabolic Diseases a while to diagnose the problem. The complications from his unusual disease, abetalipoproteinemia, arose from the lack of lipoproteins to carry fat-soluble vitamins throughout the body. Once Clinical Center investigators had determined what the core problem was, they tried addressing it by giving him megadoses of the oil-soluble vitamins A, E, and K (because his body doesn't absorb them all). He still takes 36 capsules of vitamin E, 50,000 units of A, and 10 grams of K daily, which have doubled his life expectancy.

Al may be the Clinical Center's longest-running continual patient. Born in 1941, he didn't become sick until his second year of high school. He came to the Clinical Center in 1959, after his first semester as a high school senior, for what they thought would be a two-week visit, and he left 12 years later. Teachers from Montgomery County taught him in the tenth-floor schoolroom of the Clinical Center, from which he was the first student to graduate. (He was officially a graduate of Bethesda-Chevy Chase High School, without having been there.) He also attended American University.

During his first six months at the hospital, he was afraid to be seen in public. When his roommate finally took him to a movie in the auditorium, Al insisted at first on being taken in a wheelchair, because he had a tremor and a problem walking and was self-conscious about his gait. When he got to the auditorium, he saw patients who were visibly worse off than he was, and stopped feeling sorry for himself, and “took over the place, becoming Peck's bad boy,” as he and others recall—smoking in the elevators, staying up too late, and generally breaking hospital rules. When he first came, it felt traumatic to be away from home and his friends, to be probed and stud-



Al Cohen, long-term patient  
The Clinical Center is one of the few places in the world that conducts long-term studies of patients with rare diseases. Al Cohen's rare problem with lipid metabolism, and his willingness to be studied on strange diets, led to deeper understanding of both his rare condition and more common cholesterol problems. On one diet, Al and a normal volunteer ate a pound of butter a day—with saltines.

ied, but in time it became home to him. “In the mornings I was busy with tests, and in the evenings, I was free. It was like a big hotel to me, and I knew everybody, from the secretaries on up: all the housekeeping staff, the elevator operators, the nurses, the doctors—they were like my aunts and uncles.”

After Arnold Sperling started a recreation program on the hospital’s fourteenth floor in the 1960s, Al became active in drama. The recreation department played an important role in sustaining the morale of patients like Al and normal volunteers who had to undergo extensive, often demanding, tests—and often tedious experimental diets. He spent his time with young patients and with college students who came as normal volunteers (controls in the research) for three-month periods.\* The hospital arranged for them all to go bowling and swimming once a week, to the Shady Grove Music Fair, Washington Senators baseball games, and Rehoboth Beach. They did crafts and played bingo. Al became a master bridge player. “Bethesda was a one-horse town,” says Al, and the grounds of the NIH still seemed almost rural. “It was a joy to take a walk around the grounds in the evening. In the summer, it was heaven.”

While living out his adolescence and young adulthood in the hospital, Al became something of a legend, especially in the metabolic kitchens. One institute passed him on to another—his body being such a beautiful experiment in nature—and Al would joke about the nuisance of breaking in new investigators. He was studied by Arthritis and Metabolic Diseases, by Child Health and Human Development, and by the Heart, Lung, and Blood Institute. Forty-some years later he still comes to the hospital twice a year for follow-up studies. He is seen now by Robert Shamburek.

Richard Gregg, who came to the Clinical Center as a clinical associate in 1978 and stayed on as a senior investigator in the Molecular Diseases branch of the Heart, Lung, and Blood Institute until 1988, explains both how the study of Al’s disease reflects change in scientific understanding over fifty years

and how working with patients like Al has produced continuing discoveries both in and out of the Clinical Center. When Don Frederickson was working with Al Cohen in the late 1950s and early 1960s, says Gregg, scientists were doing what he calls descriptive biology: looking at individuals with health problems and describing their abnormalities. In the case of Al Cohen’s disease, abetalipoproteinemia, the abnormalities were very low levels of cholesterol, pigmentosa, spinal-cerebellar degeneration, abnormal-looking red blood cells, and a tendency to bleed. “That was a description of the syndrome, but we did not have the technologies at that point to understand at a molecular level what genes and proteins were involved in the process,” says Gregg, who is now in charge of early clinical studies of new drugs for Bristol-Myers Squibb.

Through the late 1960s, 1970s, and 1980s, scientists began to understand more about the proteins involved, and are still learning. When gene cloning technologies developed, they could clone and sequence genes and identify the genetic mutations associated with the disease. By identifying the causative gene and the causative protein for the disease, they knew where the disease started and could start building the sequence of events that led to the abnormalities. By knowing that it was a microsomal triglyceride transfer protein (MTP) abnormality, they knew it was an alteration in the assembly of lipoproteins, which confirmed that it was the body’s failure to absorb the fat-soluble vitamins from the gastrointestinal tract that led to the vitamin deficiency that caused the neurological and ophthalmological problems in patients like Al.

A similar sequence of events occurred in many areas: After a period of doing descriptive biology in the 1950s and 1960s, scientists were able in the 1970s and 1980s to study cell biology and proteins and in the 1980s and 1990s to get down to root molecular causes.

“Once we knew that the MTP mutation led to the disease,” says Gregg, “we then knew that if we could inhibit this protein it would cause a lowering of cholesterol, so we set up a

\* “When I first came, they had federal prisoners as normal volunteers,” says Al Cohen. “The prisoners were basically in for bad checks and stolen cars, nothing serious. They would have maybe a couple of months left on their sentence, and they would get a week off their sentence.” The prisoners were confined on 11-East, allowed to attend movies and concerts in the hospital but not to join other volunteers on trips. They had the gym to themselves an hour a day, with a guard on the door.

A SIMILAR SEQUENCE OF EVENTS OCCURRED IN MANY AREAS: AFTER A PERIOD OF DOING DESCRIPTIVE BIOLOGY IN THE 1950S AND 1960S, SCIENTISTS WERE ABLE IN THE 1970S AND 1980S TO STUDY CELL BIOLOGY AND PROTEINS AND IN THE 1980S AND 1990S TO GET DOWN TO ROOT MOLECULAR CAUSES.

program here at Bristol-Myers Squibb to identify small-molecular-weight compounds that would inhibit MTP.” That research, based partly on an understanding of Al’s disease, provided them with a drug discovery target: potent inhibitors of MTP that would produce a tremendous lowering of cholesterol and triglyceride. Unfortunately, in some individuals, this causes fat accumulation in the liver, some elevation in the liver enzymes, and malabsorption of fats (causing diarrhea), which precludes it from becoming a broad-based drug for lowering cholesterol and triglycerides. However, they are working with another former NIHer, Dan Rader, now at the University of Pennsylvania, on whether the dose can be titrated so that the drug can be used with patients with familial hypercholesterolemia, the disease patient Diane Dickinson has. The work goes on even after investigators leave the NIH and the Clinical Center.

### Counting their peas and carrots

NIH interest in nutritional research dated back at least as far as Joseph Goldberger, who in 1915 demonstrated that a nutritional deficiency was the chief cause of pellagra, a disease that killed thousands of Americans early in the twentieth century and was widely believed to be spread through germs. Nobel laureate Arthur Kornberg, among other notable early NIH scientists, considered himself a “vitamin hunter” before he became an enzyme biochemist involved in the study of genetics. In the early decades of the Clinical Center, the research tended toward biochemical analysis and many investigators were studying the rates at which the body metabolized various products.

Edith Jones, chief of the Clinical Center’s nutrition department for 33 years, set up several metabolic kitchens to provide research and test diets to selected inpatients. “One of the things that was so wonderful about coming to the Clinical Center in 1954 was that there was room for expansion,” says dietitian Elaine Offutt, who came to the NIH as a dietitian in 1954 and helped set up the first metabolic kitchens. “Many areas were not yet occupied, and I had come from the University of Iowa, where everything was jammed.”

Meals for up to 500 hospital patients a day were prepared in the main kitchen and delivered in bulk to satellite kitchens on each of the patient care units, where food service aides would spoon individual servings onto food trays and serve patients in the nursing services. The first two metabolic units were set up under Donald Whedon in Arthritis and Metabolic Diseases (with Gordon Samson Fry as dietitian) and Frederic C. Bartter of the Heart Institute (Merme Bonnell, dietitian). A third unit opened later in the Cancer Institute, under Donald Watkin and then Nat Berlin. When doctors did patient rounds, a nurse, dietitian, and social worker accompanied them. In a research hospital, it was important that everyone understood both patient care and research needs.

Specially trained metabolic cooks managed the kitchens. Although some patients were on a regular diet, some were on a controlled diet. The metabolic cooks would weigh the food served to patients and weigh what they didn’t eat, and then the dietitians would calculate the nutrients consumed from the food that was actually eaten. Other patients were on a metabolic diet, which meant every item was carefully weighed and measured, and the patient had to eat every bite—actually licking the plate.

On many of the protocols involving controlled and metabolic diets, the same food was served to both patients and normal volunteers. Soon after the Clinical Center opened, arrangements were made with two church organizations (Mennonites and Brethren) through which healthy young men and women would volunteer to participate as normal subjects in the NIH research programs, and the normal volunteer program expanded later. Patients were also volunteers, of course—they were providing their own cases for clinical research; but the normal volunteers served as controls for scientific test purposes. Normal volunteers on metabolic diets were not in danger, but they often did have to deal with boredom, discomfort, and inconvenience. On the metabolic diet, for example, they had to eat the same thing every day and to eat every single crumb.

For comparison, the researchers made the same measurements in normal volunteers as they did in the patients.

Diane Dickinson, shown here with her husband, Glenn, came to the Clinical Center in 1976 with angina so severe she had to undergo a coronary artery bypass. Her life expectancy was six months. Hypercholesterolemia, a genetic disorder, caused too much LDL (the “bad cholesterol”) to accumulate in her body. The recommended level is 100; her LDL levels were typically 600 to 800. Since 1977, she has come to the Clinical Center every two weeks, first for plasma exchange and then, since 1989, for LDL apheresis—filtering the bad cholesterol out of her blood. Researching such extreme conditions has led to knowledge and treatments—including drugs called statins—that benefit many Americans at risk from high cholesterol.



Al Cohen and a normal volunteer followed every diet the scientists came up with: low fat, no-fat, and normal diets; a quart of carrot juice a day, four milkshakes, a dozen eggs. (This was before everyone knew about good and bad cholesterol, and Al contributed to what we know about that.) Once Al and the normal volunteer ate a pound of butter a day (with saltines).

Patients on a metabolic diet had to keep their weight constant, so dietitians would calculate their caloric need and their need for protein, carbohydrate, and fat—checking every day, as part of rounds. The idea was to keep the food intake constant, so that any change could be attributed to the medication or treatment being offered the patient. To keep the nutrient value constant, the main kitchen would bring in a certain amount of meat and divide that into enough individual portions to last a whole study. They would use canned fruits and vegetables from a single source, all canned at the same time. A sample of the entire day's diet would go to the lab, which would analyze for nitrogen (representing protein content) and for electrolytes (sodium, potassium, calcium, and phosphorus).

The lab would also analyze output. Clinical Center nurses on some wards became famous—or infamous—for measuring everything that went into a patient and everything that came out. Part of the reason the diet had to be precise was to enable scientists to find meaning in what the lab learned from a patient's urine, feces, sweat, and blood. (Patients and controls weren't allowed to leave air-conditioned spaces during such tests, to avoid sweating—but if they did sweat, they wiped the sweat with tissues and the nurses collected the tissues, too.) Nurses would gather “output” during what they informally called “collections.”

To get the information scientists needed to understand the metabolism of whatever was being measured, patients on metabolic diets had to be given the same food at very specific intervals. For a certain time, patients and volunteers literally had to eat the same food every day at the same time and eat all of it. If one pea fell on the floor, the nurse or dietitian had to replace it with a pea the same size. “The metabolic cooks would sometimes sit with the patients that were having trouble getting the last morsels in, just to distract them so that

they could get the food down,” says Elaine Offutt. The analysis of the fecal fat collected from Al, other patients with lipid disorders, and normal volunteers advanced understanding of both lipid disorders and normal lipid functioning, among other things.

The kitchen also had to accommodate special diets for varied purposes, and variations in diets were sometimes extreme. Some diets had to be vitamin free, because the vitamins might be antagonists for medications the patients were taking. Other diets might be low-purine, or gluten-free, or low-sodium (or varying ratios of calcium and phosphorus). Diets changed as protocols changed. In the 1960s, dietitians had to calculate saturated and unsaturated fatty acids, for example. Lipid Research Clinics had been set up all around the country, for participants with various types of hyperlipidemia, depending on their levels of cholesterol and triglycerides. Some patients would be on high-fat diets for a couple of weeks, to see how their bodies processed fats—which the staff could tell by checking changes in the levels of their blood fats.

One of the teachers in the NIH school, Margaret Gilbert, wrote a little book of poems (*Dawn's Song*) about experiences in the Clinical Center. One of the poems reads:

All my food is boiled,  
Complains a lad, a Sikh.  
Please sprinkle some curry powder  
And make this bland stuff reek,  
Reminding me of Delhi,  
Hot, colorful and smelly.

#### Counting every bite

On many of the protocols involving controlled and metabolic diets, the same food was served to both patients and normal volunteers. Patients on a metabolic diet had to keep their weight and food intake constant, so that any change could be attributed to the medication or treatment being offered.



The Mental Health Institute also performed all kinds of studies. Patients on MOA inhibitors, for example, were given diets that eliminated certain foods. With patients who were bulimic or anorexic, the dietitians' goal was to get them to eat. On the other hand, patients who were obese were given 500 calories a day and isolated from their home community, to prevent food being smuggled in. "Dr. Berlin would tag the blood cells in the obese patients, so researchers could count the isotopes," says Offutt.

"The thing I used to find exciting was seeing a patient come in very, very ill and getting well and walking out," says Offutt. "Many patients would come with a very unusual problem, find something that helped them recover, and go out and be productive again."

Metabolic studies were expensive and, with healthcare costs rising rapidly, the trend in the 1970s was to change from metabolic to controlled diets. Then, in 1981, when the Ambulatory Care Research Facility opened, the nutrition department began serving food from a centralized kitchen, and the satellite kitchens were closed. The one remaining metabolic kitchen on the eighth floor moved to its current home on the second floor in the late 1980s. The nutrition department computerized its food procurement, inventory, and distribution systems, and research dietitians began using computerized data banks to assess dietary intake for research studies.

Metabolic studies are still conducted. In the 1990s, the metabolic kitchen provided a research diet low in vitamin C for a study that led to revision of the recommended dietary allowance for vitamin C.

## MARIAN PAYNE, A NOT-SO-NORMAL VOLUNTEER

Marian Payne, born in 1933, was one of the Clinical Center's original normal volunteers, who later developed symptoms that weren't diagnosed until almost 50 years later, as being a rare genetic disorder. At 70, Marian has been, in turn, a volunteer control, a patient, a volunteer patient on an investigational protocol, and an author advancing the cause of an "orphan" genetic disorder—so rare that only 40 people in the world are known to have it, mostly among Scandinavians and the Amish population in Lancaster County, Pennsylvania. Listen to part of her own account of life with a rare, unknown disease, written for a special issue of the British medical journal, *Lancet*, containing patients' perspectives:

"At the age of 19, my heels became so swollen and stiff that I couldn't walk. A visit to the local doctor brought "good news and bad news." I didn't have rheumatic fever, but he didn't know what was wrong. He recommended that I soak them in magnesium sulphate mixed with hot water (Epsom salts water). In 1956, I volunteered myself as a 'normal control patient' in a clinical trial. The doctor who did my exit physical examination noted that I had rheumatism in my knees and ankles with swelling in my ankles.

"For several years, my heels would periodically swell and become stiff and sore, making walking painful and sometimes impossible. They were getting so large that to wear a shoe that curved in at the top of my heel became impossible. Aside from the lumps growing on my heels, nodules began to form on the tendons of my fingers. I also had a growth on my left knee, which was diagnosed as 'housemaid's knee.'

"Two weeks after my wedding in June 1957, I was unable to walk. My husband and I consulted another doctor, who was baffled. As a mother and homemaker, I hobbled on sore feet and coped with painful joints, relying on the Epsom salts water for relief during flare-ups. Every family doctor I visited examined my ever-enlarging heels, the lumps on my fingers and my left knee, and the swelling emerging on my right elbow, and shook their head in amazement; none could diagnose my condition.

"In the summer of 1961, I went to the Vanderbilt University Medical Clinic for a checkup. The doctor there noted the large nodule on my

CLINICAL CENTER NURSES ON SOME WARDS BECAME FAMOUS—OR INFAMOUS—FOR MEASURING EVERYTHING THAT WENT INTO A PATIENT AND EVERYTHING THAT CAME OUT.

elbow, and suggested that I have it removed. As he extracted it, the surgeon remarked, 'Hmmm! That looks like chicken fat!' A biopsy revealed that the growth wasn't cancer, so I forgot about it.

"In 1970, I began teaching. And in 1972 our family doctor suggested that I have the lumps removed and analyzed. I was referred to a surgeon. After surgery, he explained that he had removed two of the lumps, but that the rest were intertwined with my tendons. At that point I was referred to a specialist, who finally gave the lumps a name—xanthomas, caused by type-II hyperlipoproteinaemia. With a blood cholesterol over 10 mmol/L, I was put on a low cholesterol diet and various cholesterol-lowering drugs, with little effect.

"At the age of 40, I had a heart attack that wasn't diagnosed until 2.5 weeks later when the specialist admitted me to hospital. Unfortunately, I was unable to have bypass surgery because of the fatty deposits clogging up my system. I learnt that my disease was hereditary, and that I was unlikely to live to old age. Blood tests revealed that our son's cholesterol concentration was fine, but our four daughters have raised cholesterol. While I was in hospital our doctor apologized for his misdiagnosis, explaining that I was the wrong sex and too young to have a heart attack."

For 18 days in 1956 Marian had been a volunteer control for the Heart Institute, participating in early studies on steroids and electrolytes in Dr. F. Bartter's Metabolic Studies service. A year later he published his results on "Bartter Syndrome." Her clinical associate was Eugene Braunwald, who would later become a leader in cardiology. Marian wanted to enroll in a Clinical Center study on cholesterol, but she lived in Pennsylvania, too far away to participate. She had had many attacks of angina by the age of 50, at which point a heart catheterization revealed a severe narrowing of the right coronary artery. Successful angioplasty reduced the angina and in 1989, at the age of 55, she retired early on disability because she was having so much chest pain. Because her life might be cut short, her husband took early retirement, too, and they moved to Virginia's Chesapeake Bay area.

There her new family doctor was as perplexed as the earlier ones had been about how to reduce her cholesterol, which was still very high despite diet and drugs. She was referred to a lipid specialist and researcher at the Medical College of Virginia, who consulted with

researcher Charles Schwartz. She was finally diagnosed with a genetic disorder called Sitosterolemia, in which the patient hyperabsorbs plant cholesterol (sitosterol) and is unable to excrete it into the bile for removal from the body. The plant cholesterol accumulates in the xanthomas and in the arteries, causing heart disease, just as animal cholesterol often does.

"Charles Schwartz investigated me," she writes, "and discovered that the bodies of individuals with sitosterolaemia search out all cholesterol ingested, recycle it in the bloodstream, and deposit any excess within the body."

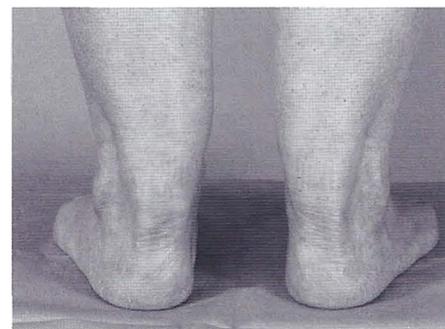
In 2001, Marian participated in a Clinical Center protocol in which the genetic cause was elucidated: a deficiency of ABCG5 and ABCG8, genes in the intestinal and liver bile ducts. (Both parents must carry the disease for a child to be born with it.) She volunteered that year for a Clinical Center protocol investigating a drug designed to block absorption of both plant and animal cholesterol in the intestinal tract. Because of positive trial results, FDA approved the drug, called ezetimibe (Zetia). It was the first medication approved for sitosterolemia but was also approved for use in lowering cholesterol in the millions of patients with ordinary cholesterol disorders.

With proper medication, her total cholesterol plummeted. Today, at 70, she is healthier than she was when she retired on disability at 55. "I used to pray that I could watch my children grow up," she said one evening as we spoke by phone—after she had cooked dinner for 15. "Now I pray I can watch my grandchildren grow up."



Marian Payne in 1972, at about the time she had a heart attack

The xanthomas on Marian Payne's ankles are no longer as bad as they once were, but the Achilles tendon is still enlarged.



## Studying inborn errors of metabolism

Some of the most important work in the Clinical Center has involved the concept of inborn errors of metabolism (biochemical reactions in the body). Many metabolic diseases lead to the buildup in cells of toxic products that cause cell abnormalities known as “storage” diseases. Features of these diseases vary depending on the biochemical pathway affected—in the patients Frederickson and his colleagues studied, they were lipid storage diseases. Much of this research is conducted in laboratories, where NIH scientists work with patients’ cell lines and with tissue cultures. But the presence of patients in the Clinical Center is a constant reminder of the NIH mandate to improve the nation’s health, not just its science.

One of the first NIH researchers to investigate storage diseases was Roscoe Brady (NINDS), who in 1956 began studying a rare inherited disease called Gaucher’s disease. In 1964 Brady discovered and the next year described the underlying enzyme defect in Gaucher’s disease (for which he later developed an effective enzyme therapy). Brady went on to describe the enzyme deficiencies in Niemann-Pick disease (1966) and Fabry disease (1967) and with colleagues the specific defect in Tay-Sachs disease (in 1969).

### Marathon man Roscoe Brady

New medical treatments are often a relay race—one scientist or group makes a key discovery, then hands off the baton to other researchers to develop, refine, clarify, extend, and apply. Each person involved makes a contribution to the final result. But Roscoe Brady is running a marathon. The physician-scientist has been working on Gaucher disease since he joined NIH as chief of the section on lipid chemistry at the National Institute of Neurological Disorders and Stroke in 1954.

As a Harvard medical student, Brady was so unnerved by his dying patients that he didn’t want to wait until they got sick to help them. Once he’d finished his internship, he took a postdoctoral position in a biochemistry lab at the University of Pennsylvania, determined to do significant basic research. There he found his calling: lipid metabo-

lism. (Lipids, along with proteins and carbohydrates, are a principal component of living cells.)

It seemed a natural step from there to Gaucher disease, an inherited disorder in which lipid metabolism goes wrong. Instead of being broken down and recycled, a fatty lipid substance called glucocerebroside builds up inside the cells, causing bone damage, an enlarged liver and spleen, and blood problems such as anemia and low platelets. In infants and severe cases, Gaucher disease produces neurological damage as well.

Scientists had known for decades that accumulating glucocerebroside was the culprit in Gaucher disease, but Brady wanted to find out why it accumulates. He started out by examining the chemistry of the spleen, the organ most affected by the disease. It can swell up to 35 times its normal size, giving patients a huge pregnant-looking belly, and doctors sometimes remove it in order to treat the disorder. As a result, Brady and his team found a ready supply of tissue to study—tissue loaded with lipid-filled cells. They soon established that Gaucher patients form cerebroside (both glucocerebroside and galactocerebroside) normally. Moreover, they form glucocerebroside at the same rate as other people.

If the metabolic flaw wasn’t in the construction of the lipid, where else could it lie, Brady wondered. Perhaps it was in the lipid’s destruction—the enzymatic breakdown that is crucial to reduction of material in the body. This was unknown territory in the late 1950s and early 1960s, and Brady experimented with several methods, trying to find one that would show precisely how enzymes and glucocerebroside interact. Nothing panned out.

Then he read a paper involving another lipid storage disorder, Niemann-Pick disease, by chemist David Shapiro of the Weizmann Institute in Israel. If they collaborated, Brady thought, maybe they could find the metabolic defect for both illnesses. He arranged for Shapiro to join him at NIH, and in 1964 the pair succeeded in making the first chemically synthesized glucocerebroside. With its radioactively labeled molecules to guide the way, they identified the enzyme glucocerebroside for the first time. It has an extremely important

#### Roscoe Brady

It took Brady 5 years to discover the enzyme defect that causes Gaucher disease, 8 more years to get enough enzyme for trials in enzyme replacement, and another 16 years to make enough enzyme and to target it to storage cells for effective treatment of patients. At least 3,500 patients are alive and well because Brady didn’t give up. “NIH is for the long-term, difficult projects that couldn’t be supported elsewhere,” says Brady.



IN THE 1960S THEY FOUND THE METABOLIC DEFECTS IN GAUCHER DISEASE, NIEMANN-PICK DISEASE, FABRY DISEASE, AND TAY-SACHS DISEASE.

## MOVING AND STORAGE

Gaucher disease is one of a group of genetic diseases known as metabolic storage disorders, so named because they influence how substances are stored in the cells. In Gaucher disease, the metabolic defect is in the lipids, so it is sometimes also called a lipid storage disease. So far scientists have found about 40 storage disorders, including some that involve carbohydrates. Gaucher disease is the most common.

In the 1960s, Roscoe Brady and his colleagues discovered the enzymatic defect in four inherited lipid storage diseases: Gaucher disease, Fabry disease, Niemann-Pick disease, and Tay-Sachs disease.

There are three types of Gaucher disease, depending largely on how much of an enzyme called glucocerebrosidase the body can produce. Patients have the most residual enzyme activity in type 1, for which the symptoms are the least severe. Adults and young adults typically have an enlarged liver and spleen, bone pain, fatigue, and blood problems such as anemia, nosebleeds, and bruising. The disease occurs in 1 person in 40,000 to 60,000 worldwide. Patients with type 1 Gaucher disease respond well to enzyme replacement therapy.

Much rarer, type 2 is the most severe. It attacks the nervous system of infants, who usually die before age two. Type 3, also rare, affects children and young adults. Symptoms include seizures, eye movement problems, lack of coordination, and neurologic deterioration. Although they improve systemically in response to enzyme replacement therapy, they may have some neurological problems, such as difficulty moving their eyes horizontally and, more rarely, devastating myoclonic seizures.

Fabry disease is a sex-linked disorder, passed from mothers to sons, who have a 50 percent chance of inheriting the full-blown version of the disease from their carrier mothers. Daughters of carriers, who have a 50 percent chance of becoming carriers, may have an attenuated form. One person in 40,000 suffers from Fabry disease.

The metabolic defect in Fabry allows lipids to clog up the blood vessel walls, reducing blood flow to the skin, kidneys, heart, and nervous system. The disease begins in childhood with reddish-

purple skin blemishes and a painful, burning sensation in the hands and feet. Between ages 30 and 45 other symptoms may appear: early heart attacks, strokes, neurological signs, and kidney problems. Many patients eventually need a kidney transplant. Positive benefits have been obtained in enzyme replacement trials now under way, and gene therapy is also on the horizon.

There are four types of Niemann-Pick disease. Type A, the most common, affects infants, who rarely live beyond 18 months. Symptoms include feeding problems, a large abdomen, the loss of early motor skills, and a cherry red spot in the eye. Type B, which has the same enzyme defect, occurs in the childhood or preteen years, causing an enlarged liver and spleen and breathing difficulties.

A different enzyme defect creates type C, causing lipids to pile up in the brain and cholesterol to accumulate in the spleen and liver. Although it may begin in infancy or adulthood, it usually affects school-age children, who are sometimes misdiagnosed with learning disabilities, developmental delays, or retardation because the symptoms—clumsiness, difficulty with upward and downward eye movements, slurred speech, and learning problems—are so similar. Type D is a variation of type C specific to the Nova Scotia region. One in 80,000 people is affected by the various forms of Niemann-Pick disease.

In Tay-Sachs disease, accumulating lipids affect the developing infant brain, destroying mental and physical abilities and causing death by the age of five. Children develop normally for the first few months, then begin to startle abnormally and lose their peripheral vision. By the age of two, they may suffer from seizures, and the skills they've acquired gradually diminish.

Although Tay-Sachs is most common among Ashkenazi Jews (1 in 27 in the United States is a carrier), many babies born with the disease today are born to families who aren't believed to be at risk. In the general population, 1 in 250 is a carrier.

Because of the difficulty of crossing the blood-brain barrier, enzyme therapy hasn't been a solution for Tay-Sachs. Preimplantation or prenatal diagnosis offer reprieve from the disease, and carrier screening programs have greatly reduced the frequency of this disorder.

job, they observed: It splits glucose off from glucocerebroside and is present in almost every cell in the body.

Brady's next step was to extract and purify the enzyme so he could measure its activity. Beginning with rats and moving on to normal human spleen, he finally tested enzyme extracted from the spleen tissue of Gaucher patients in 1965 and at last confirmed his hunch: He had found the metabolic defect in the disease. The enzyme's activity was a mere 15 percent of normal, not nearly enough to clear away the lipids piling up in the cell. But some activity was better than none. It meant that if they ever managed to create an enzyme treatment for Gaucher disease (which they would, decades later), the body wouldn't block it by producing antibodies against it.

Over the next few years, Brady's team went on to find the defective enzymes in a series of lipid storage diseases using the same radioactive-labeling techniques. In 1966 they found the metabolic defect in Niemann-Pick disease, in 1967 the defect in Fabry disease, and in 1969 the fault in Tay-Sachs disease.

During the same period Brady began using the enzymes they'd found to develop much-needed diagnostic tests for these diseases, which are sometimes hard to distinguish from one another. This work also made it possible to identify non-symptomatic carriers and to offer them prenatal diagnosis. (In 1982, this body of work would earn Brady the prestigious Lasker Award for "solving an enigma that had confounded medical practitioners for nearly a century.")

In 1972, Milton Shy, NINDS' scientific and clinical director, brought Brady's lipid chemistry section and Anatole Dekaban's child neurology section together to form the new Developmental and Metabolic Neurology Branch, which Brady headed. The reorganization gave Brady a chance to work more closely with patients in the NIH Clinical Center, an opportunity he welcomed because he was beginning to think about how to replace their defective or missing enzymes with healthy, fully functional ones.

To do enzyme replacement therapy, he had to have a source of enzymes, so his group set to work extracting several

enzymes from fresh human placenta. First the researchers purified the enzyme that is defective or missing in Fabry disease, in which the buildup of lipids affects the heart and kidneys and nerve involvement causes severe pain. Two patients received injections of the purified normal enzyme, and in the blood of both the accumulating lipid level fell to the normal level for several days.

In Gaucher disease, the lipid level in the blood is 3 to 4 times higher than usual—but in tissue like spleen or liver the lipid level can soar to several hundred times above normal. In his next study, Brady wanted to measure the enzyme's effect on tissue as well as blood. As soon as the lab readied the enzyme for Gaucher disease, he secured his patients' permission to insert a small needle into the liver and obtain a tiny sample of tissue before and after they received their intravenous enzyme infusion. In both patients, the biopsies showed that the liver's lipid level had decreased by 26 percent after the injection of enzyme. In the blood it had dropped to normal, where it stayed for three months. These long-lasting effects convinced Brady that he could really help these patients—if he could give them enough glucocerebrosidase.

But that was easier said than done. After the team spent a year purifying the enzyme to test on a third patient, they concluded that they needed an entirely different and quicker purification process. They went back to the lab and devoted two more years to developing a new procedure, but just when they thought they had found the right formula they hit yet another roadblock: Their newly purified enzyme worked only some of the time. It turned out that the revamped method removed too many lipids normally associated with the enzyme—including ones that sent the enzyme to the right cells in the body and activated it. Now they had to figure out how to redirect the precious enzyme to the overstuffed storage cells of the liver, spleen, and bone marrow where it was needed.

Frustrated and discouraged, they went back to the lab. Not until 1984 did they emerge with a new purified enzyme, but this time they were so sure of its strength and ability to reach its target that they rushed straight into patient trials. Once a week seven adults and one five-year-old boy came into the

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“WE TRIED AND FAILED MANY TIMES. IT'S THE SUPPORT EVEN WHEN THINGS GO WRONG THAT MAKES THIS PLACE SO SPECIAL.”

Clinical Center to get an intravenous infusion of 190 units of glucocerebrosidase.

Nothing—good or bad—happened to the adults. But the little boy, who was desperately ill and likely to die by the age of eight or nine, began to get better. Because his platelet level was so low, his blood didn't clot and he often bled from his nose, lips, or gums. But after three months of weekly infusions, his platelet level rose enough to stop the bleeding episodes, and his hemoglobin rebounded from severely anemic to near normal.

Why did he respond when the adults didn't? Brady and his team of researchers soon realized that the difference was in the magnitude of the dose. The boy was receiving far more enzyme per pound of body weight than the adults had. The team then gave Clinical Center Gaucher patients a wide range of enzyme doses—from minuscule to massive—preceded and followed by liver biopsies, to ascertain exactly how large a dose was required to reduce the lipid stockpile consistently.

At that point Brady and the team knew they could give the boy more enzyme. To their delight, his hemoglobin rose to normal, where it has remained ever since, his platelets increased, and he has stayed out of the bleeding danger zone. After two and a half years of weekly enzyme replacements, his spleen, which had ballooned to 26 times its normal size, shrank to just one third of its former volume. "We had no way to predict this organ would get smaller," says Brady. The boy's liver, which was four and half times the normal size, shrank to only double the normal size; and the abnormality in his Gaucher-weakened bones cleared up entirely. Since then he has led a normal life, marking a lot of milestones he would have missed, had he gone untreated: a bar mitzvah, a college education, a marriage, a job, and on October 12, 2002, fatherhood. Brady attended the bar mitzvah and wedding. Still taking his infusions, he has no sign of bone, spleen, or liver damage or involvement. He no longer comes to the Clinical Center, but Brady follows up on him regularly, keenly interested in the long-term effects of treatment.

With the appropriate dose level now well established, Brady began a clinical trial with a dozen patients with Gaucher dis-

ease. All 12 improved dramatically, showing almost the same changes in hemoglobin, platelets, liver, spleen, and bones that his child patient had shown. Although enzyme injections don't provide a permanent cure, patients taking them experience far less pain and disability. Based on these impressive results, the FDA approved enzyme replacement therapy for Gaucher disease on April 5, 1991. It was a big day for Roscoe Brady: More than a quarter century of work had finally borne fruit.

Now Genzyme Corporation—which paid the \$10-million bill for the 12-patient clinical trial—makes the enzyme glucocerebrosidase using recombinant DNA technology, and at least 3500 patients with Gaucher disease are alive and well because Roscoe Brady wouldn't give up.

Brady credits the NIH intramural program for backing him during all those years when things went wrong. "This work couldn't have been done anywhere else," he says. "Long-termness is the beauty of NIH. We tried and failed many times, and NIH supported us adequately enough to get the job done. It's the support even when things go wrong that makes this place so special. Would a corporation or university have supported me during the 25 years between the enzyme discovery in Gaucher disease and making the enzyme work? Maybe, maybe not. NIH is for the long-term, difficult projects that wouldn't be supported elsewhere."

Brady is still going strong. In the last few years, he has collaborated with nephrologists Jeffrey Kopp, J. Howard Austin, and James Balow of the NIDDK on a clinical trial at the Clinical Center of enzyme replacement therapy for patients with Fabry disease, one of the lipid storage disorders whose genetic defect he discovered so long ago. The new enzyme regime has improved kidney and heart function, reduced pain, and significantly improved the quality of life of Fabry patients. Already approved in 30 countries around the world, the therapy has received accelerated approval in the United States.

Brady's consuming interest in Gaucher disease continues. Although enzyme replacement is an extremely effective therapy for patients with type 1 Gaucher (affecting young adults and adults), there is still no treatment for the nervous system

AFTER TWO AND A HALF YEARS OF WEEKLY ENZYME REPLACEMENTS, HIS SPLEEN, WHICH HAD BALLOONED TO 26 TIMES ITS NORMAL SIZE, SHRANK TO JUST ONE THIRD OF ITS FORMER VOLUME.

in children with type 3 and infants with type 2 Gaucher disease. Because the brain develops so rapidly during the first few years of life, lipids accumulate in the infant nervous system at a furious pace in Gaucher disease (as well as in Tay-Sachs and type A Niemann-Pick disease). When the enzymes are delivered to patients by intravenous injection, as they are at present, they can't cross the blood-brain barrier to rid the brain cells of their stockpiled lipids. With NINDS neurosurgeon Edward Oldfield and Stanley Rapoport of the National Aging Institute, Brady has been trying to figure out how to deliver the enzymes to the brain in this critical early period so that brain development can go forward unimpeded.

And then there is Brady's hope of the ultimate cure, gene therapy. If normal genes could replace the defective ones in these storage diseases, afflicted patients wouldn't need enzyme therapy for the rest of their lives. Although replacing the defective gene in Gaucher disease still seems a marathon away, work on inserting a normal gene in a mouse model of Fabry disease has produced excellent results. And Brady hasn't stopped running.

"It took five years to discover the enzyme defect, eight more years to get enough enzyme for the first Gaucher trials, and then another 16 years to make enough enzyme" and to target it to storage cells for effective treatment of many patients, writes Lewis P. Roland in his account of Brady's career in the book *NINDS at 50*. "NIH was designed, he thinks, for that

kind of high-risk, long-term research as opposed to the short-range, quick publication projects needed by university investigators to qualify for tenure and obtain grants. He is an outstanding model of the physician-investigator."

### Studying other storage disorders

Many researchers have followed Brady's lead. In 1983 he shared a Lasker Award with Elizabeth Neufeld (NIDDK), who was recognized for identifying the enzyme defect that causes mucopolysaccharide (carbohydrate) storage disorders (and with Robert Gallo, for his work leading to isolation of the retrovirus HTLV-I). Approaches to treatment being developed for these storage disorders include enzyme therapy, protein therapy, and gene therapy. Bill Gahl (formerly of Child Development and now with the National Human Genome Research Institute) has saved many children from early death for his work on a rare disorder called cystinosis, a lysosomal storage disorder for which he has developed effective small-molecule therapy. Here's one mother's story of how Gahl's work saved her daughter's life.

# A DESPERATE MOTHER FINDS HOPE

Marybeth Krummenacker knew in her gut that something was wrong with her daughter Laura. She was different from Marybeth's son, Brian. Laura was a picky eater with strange cravings for salty and spicy foods, so tiny for her age that her measurements didn't even make it onto the growth charts.

On Laura's second birthday, in 1988, the pediatrician in her hometown of Hicksville, New York, thought she was "failing to thrive" and sent her to an endocrinologist for tests. But the tests were inconclusive, and the specialist told Marybeth not to worry; Laura would probably outgrow whatever it was. That winter Laura landed in the intensive care unit of the local hospital, severely dehydrated from a bout of flu. For a week the doctors tested, poked, and probed, and even when she seemed better, her lab results remained frighteningly out of kilter. Finally the puzzled doctors called in a pediatric kidney specialist.

Nephrologist Frederick Kaskel was an inspired choice. He had recently attended a lecture by William Gahl of the National Institute of Child Health and Human Development—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, where no one even knew transporters exist. Lysosomes, tiny bag-like 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. Gahl was spearheading a national collaborative effort to find an effective treatment for the disorder.

As soon as he heard Laura's story, Kaskel suspected cystinosis, but he needed more information to make the diagnosis. He ordered additional tests and asked her to visit a pediatric ophthalmologist who could confirm the presence of telltale crystals on her corneas. After an anxious few months, the results came in. Kaskel reached for the phone, and Laura's parents found themselves talking directly with Bill Gahl.

They knew at once they were in capable hands. "Instead of calling me an overreactive mother, instead of saying 'Don't worry about her, she'll probably outgrow this,' he asked questions and listened carefully to my answers," Marybeth recalls. "I started to realize that my instincts were right, and I really needed to worry about her."

Gahl offered them the opportunity to bring Laura to the Clinical Center. For seven days in September of 1989 he and

Bill Gahl

Studying rare diseases is an intellectual challenge, says Gahl. It is worthwhile to help people who have nowhere else to go, but it also advances understanding of more basic health problems.



"I CANNOT SAY ENOUGH ABOUT THE NIH CLINICAL CENTER. IT RESTORED MY FAITH IN MEDICINE."

the staff on 9 West recorded her history, examined her, and performed innumerable tests. Three-and-a-half-year-old Laura was scared, but she took things in stride. Marybeth was another matter: She was angry. Suddenly all the pent-up worry, the months of frustration, the feeling of not knowing and not being heard, exploded inside her and directed itself at Dr. Gahl. Later in the day she apologized for her outburst, but Gahl was unperturbed. “I hear these stories all the time,” he said.

Marybeth soon realized that if the people in this building were not going to help her, nobody could. Her job was to stay focused and pay attention. “For the first time in my daughter’s life I felt I had met up with people who really cared about my child, not my insurance. I truly felt these were individuals—each and every one of them, from the nurses to the social workers to the physicians—who cared about what was wrong with my daughter and how to make it better.”

Gahl and his collaborators, Jerry Schneider in San Diego and Jess Thoene in Ann Arbor, Michigan, had been testing a treatment for cystinosis since 1978. When he had enough information about Laura, he accepted her into his protocol (research study).

Marybeth and Laura were in the playroom at the end of the hall in the Clinical Center when a nurse approached with a sheaf of consent forms. She explained that the doctors wanted to start Laura on an experimental medication, but because it was just that—experimental—there were risks involved, and they needed parental consent before Laura could join the clinical trial. “That was one of the scariest moments of my life,” Marybeth says. “I knew that experimental means you’re a guinea pig. But I also knew I had no choice. I had to sign it for my daughter’s survival, and I did.”

One of Laura’s new medicines—phosphocysteamine—would help dissolve the destructive crystals forming in her cells; oth-



Making medical history

Left to right, medical chemist Isa Bernardini, Heidi Hughes, Laura Kruppenacker, and Amelia Douglas (the three “cystinosis sisters”), and their doctor, Bill Gahl.

ers supplemented the essential nutrients her damaged kidneys couldn’t redirect back into her body. There were eight medications in all and from then on Laura had to take them every 6 hours, day and night. Sulfur-based, the liquid phosphocysteamine tasted and smelled horrible (“like the worst science experiment,” says Marybeth), and it made Laura smell, too. Laura had a mind of her own and an iron will and was determined not to participate in this drug regimen. But Marybeth knew it would keep her daughter alive and did not give in. Nor did she back down when it came to the cysteamine eye drops Laura needed 12 times a day to prevent her eyes from becoming hypersensitive to light. Over time Marybeth learned tricks to make the process easier, but battles over medication remained part of their lives for years.

Laura had to return to the Clinical Center for monitoring and medication adjustments every four months. Because the Center provides secure funding for research, first-rate laboratories onsite, and free service to patients, it can provide exceptional data collection and continuity of care. Physician-scientists like Gahl can see their patients frequently and respond rapidly and aggressively to changes in their condition. The result is more effective treatment.

“I cannot say enough about the NIH Clinical Center,” says Marybeth. “It’s the place that restored my faith in medicine. They cared about my daughter, they cared about me, they cared about how we were treated, and offered any help in any way. It’s the kindnesses that really stood out—certainly that first week that we were there. They call it the place of last resort because if the people there can’t help you, nobody can.” When Laura and her family came to Washington the following May, they discovered another Clinical Center bonus: the cystinosis family conference, an annual event at which they learned about the latest research and had a chance to meet other families struggling with the disease.

It was exciting to realize they were not the only ones in the world with cystinosis, and it was even better to meet Heidi Hughes and Amelia Douglas. Although they lived in different parts of the country, the three girls were almost exactly the same age. They became fast friends—“cystinosis sisters”—who



At the Clinical Center, Laura Kruppenacker and her family were excited to learn that they were not the only ones in the world with cystinosis. Laura, Heidi, and Amelia lived in different parts of the country but were the same age. They became fast friends—“cystinosis sisters”—who gave one another strength to bear the travails of the disorder. One was good at blood draws, one at eye drops, and one at taking her medications. They developed a lasting friendship.

gave one another strength to bear the travails of the disorder. “One was good at blood draws, one at eye drops, and one at taking her medications,” says Heidi’s mother, Carol Hughes, of Vero Beach, Florida. “It was and is a beautiful friendship.” Gahl allowed them to schedule their appointments at the Clinical Center at the same time, so the girls felt as if they were visiting friends, not going to the hospital. They brought one another gifts and picked up where they left off the last time, making full use of the Children’s Inn (on-campus housing for pediatric patients) to have fun and live as normal a life as possible between tests and treatments.

The parents supported each other, too, and eventually founded a more formal support group, the Cystinosis Research Network, which Marybeth calls “my lifeline, the key to my survival.” Parents network at the annual family conferences, meet when their children come to the hospital for follow-up, e-mail and telephone one another, and run an online support group that answers questions and gives advice to more than 200 people. It is like family.

Like many others in the group, Marybeth now knows more about cystinosis than most doctors. (“I tell people I failed biology in high school and I’d have paid more attention if I knew I was going to give birth to this science experiment.”) She follows the research closely and acts as an advocate not only for her own child but also for other people’s children and the scientists and physicians who’ve helped them so much. “We’ve shown the researchers that we have a community of people out there who need their help, and we want to help them as much as they want to help us. They want to understand what’s wrong and how to fix it, and that’s what we want, too. It is a collaborative effort.”

The parent group, Cystinosis Research Network, networks with the National Organization of Rare Disorders (NORD) and the Genetic Alliance. Last year, thanks partly to their efforts, NIH’s Office of Rare Diseases, which promotes the investigation and care of patients with disorders such as cystinosis, got a boost in its budget from \$2 million to \$10 million per year, in a bill sponsored by Senators Ted Kennedy and Orrin Hatch. The parents have also become advocates

within the research community, actively trying to interest young scientists in cystinosis work. “That’s the key to our survival, that’s my hope, and that’s my daughter’s future,” Marybeth says.

In addition, the support group reaches out to the greater medical community so that doctors without a close connection to the NIH can learn to recognize and treat the disease—just as Laura’s doctor did.

For patients, physicians at home remain crucial. Laura now visits the Clinical Center every two years and counts on Dr. Kaskel to follow up, deal with problems, and maintain her health on a daily basis. Says Marybeth, “There are two people in this world whose judgment I trust implicitly, Dr. Gahl and Dr. Kaskel. I know if those two men are communicating about my child’s health, she’s fine.”

Kaskel and Gahl stayed in constant touch during the year-long period in 1998 and 1999 when Laura’s kidneys began to fail. After keeping a close eye on her lab results for months, they finally recommended a transplant. Laura’s father, Larry, matched as her donor, and on September 29, 1999, father and daughter underwent surgery simultaneously at Montefiore Hospital in the Bronx.

Although a transplant is a relatively common event for cystinosis patients, even among those like Laura who’ve taken phosphocysteamine and the newer FDA-approved CystagonR since they were toddlers, it is still rare. The doctors couldn’t predict how the cystinosis medication would interact with the anti-rejection and transplant drugs, and Gahl and Kaskel conferred often and proceeded cautiously, relying on Marybeth’s reports on Laura’s condition as well as the unremitting lab tests. “They knew if I called them it was because I needed them,” Marybeth says. “They knew that if they asked me to do something, I would do it. There is trust and respect on both sides.”

When she turns 21, Laura will officially become a grownup, no longer eligible for Dr. Kaskel’s services. Marybeth, hard-headed as always, is already searching for an adult nephrologist. Because of the drug therapy developed by Gahl and his

IT’S THE KINDNESSES THAT REALLY STOOD OUT—  
CERTAINLY THAT FIRST WEEK THAT WE WERE THERE.

collaborators, Laura belongs to the first generation of cystinosis patients who have been treated successfully enough to live to adulthood, so adult nephrologists have little or no experience caring for them. Marybeth has instructed Dr. Kaskel to be on the lookout for someone he can educate to take care of Laura.

No one knows what the next 20 years will bring, or what quality of life Laura and the other young adult cystinosis patients will face. Clinical Center scientists have addressed many practical aspects of disease management, but their research continues. For example, they are doing swallowing studies, because cystinosis causes muscle wasting, the esophagus is a muscle, and many older patients not treated with Cystagon have trouble eating and talking. Gahl, who recently became clinical director of the National Human Genome Research Institute and director of the intramural program of the Office of Rare Diseases, still sees his patients every two years, to study whether long-term therapy will prevent late complications such as diabetes mellitus, digestive problems, central nervous system destruction, retinal damage, and infertility in males. The Clinical Center is still producing and studying the cysteamine eye drops so vital to the patients' quality of life—but unavailable commercially. And Gahl dreams of a newborn screening test that will enable patients to start Cystagon therapy early, avoid kidney damage, and obviate the need for renal transplantation entirely.

Now 17, Laura is assuming more and more responsibility for her own care. The doctors talk to her, not to Marybeth, and she tells them exactly what she thinks. Always able to speak her mind, she is her own best advocate, forceful and clear without being fresh or obnoxious, her mother says.

She is a normal, productive young adult. Early on, her family developed a philosophy for living with the disease: "We can't change what you have," her parents told her. "We have to learn to live with it. So you have to do what you have to do, and get on with what you want to do." Right now, that's to finish high school. All things considered, that will be a remarkable achievement.

## A protocol of their own

Patients—and families of patients—like Laura are increasingly in touch with each other, sharing information and giving each other referrals to people who can help. This is how Donna Appell found the Clinical Center and persuaded Bill Gahl to do the first research ever on her daughter's rare disease.

Ashley, now 16, has Hermansky-Pudlak syndrome, a type of albinism that comes with a bleeding disorder and blindness. Diagnosed at the age of 2, she was one of only 23 people in the United States known to have the disease, which often led to death in young adulthood. Her mother, 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.

Donna quickly realized that she was the only one who was going to help her daughter and she set to work. She founded the Hermansky-Pudlak Syndrome Network, collected everyone she could find with the disease, put her organization into directories, and started a website. She kept her ears open at all times and at meetings of families with sick children she heard about the NIH. It occurred to her that she, too, might be able to get help there. She soon had a primary investigator on the phone, Bill Gahl. She was not only Ashley's mother, she explained, but also the founder of an organization of patients "who could definitely use research." Gahl asked her to send a letter about the group and some patients' stories.

In September 1993, Gahl 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 two 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.

### Why study rare diseases?

Bill Gahl, now Clinical Director of the National Human Genome Research Institute and head of the intramural program of the NIH Office of Rare Diseases, has spent 21 years researching cystinosis—and several even rarer disorders, including Hermansky-Pudlak syndrome.

Why do such work?

First, it is an intellectual challenge. Not only has it given him a unique opportunity to understand the human body—because cystinosis affects so many systems—but it has also allowed him to do pioneering research into normal functioning, a pursuit with broad applications. As he puts it, "A block in the metabolic path-

way often reveals the normal state. In fact, it reveals it best and most easily." Because of Gahl's research, we now know that a genetically faulty transporter in the lysosomal membrane can be the underlying cause of disease.

A second but no less important reason for Gahl is that it permits him to work with a group of patients who have been abandoned by the medical system. There are only three experts in cystinosis in the United States, and Gahl is one of them. (He is the only expert in the clinical aspects of Hermansky-Pudlak syndrome.) He finds great satisfaction in being able to help people who have nowhere else to go, and no doctor is more beloved or has more grateful patients.

The great day came in 1995. “Dr. Gahl met me in the hall of 9-West, the children’s ward, and he 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. “This is such a momentous occasion, they should have announced it on the P.A. system,” she said. “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.”

### Supporting patients with 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. Her department provides support for all of the institutes, generating questions about each patient’s function and performance and helping investigators understand their patients’ problems better. By encouraging researchers to visit them on the sixth floor, Gerber tries to broaden their horizons and induce them to think not only of prognosis but also of tangibly improving their patients’ daily lives. “Even if they are looking at VEGF or other growth factors or what influences endothelial proliferation, they ultimately want to know how the patient is doing. In fact, ultimately they probably want to know if the patient has less angina or less shortness of breath. I tell them to measure it. That’s one of my themes.”

Quantifying is essential to finding the appropriate treatment—“if we can’t analyze the data it’s useless to us,” says Gerber. The rehab team measures such physical parameters as oxygen consumption, endurance, strength, forces, and joint motion. But they have also developed valid, reliable ways to measure softer, more subjective variables, including comfort, appearance, and self-esteem. “Subjective is not a dirty word in rehabilitation,” says Gerber. “It’s required.”



One area in which Gerber and her colleagues—physical therapist Holly Cintas and pediatric physiatrist Scott Paul in rehabilitation medicine as well



as Joan Marini in the Child Health and Human Development Institute—have made an enormous difference is 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 that gives it strength and flexibility), children with OI don’t grow normally and are born with bones so fragile they can break during a hiccup or an encounter with a family pet. Brianne Schwantes, a 23-year-old 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 six 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; they used to be carried around on pillows. Question number 1 in rehabilitation, says Gerber, is what the pros and cons are of helping them to stand early in life. “Can we get them up safely? What is the cost in terms of fracture? Are they at greater risk for developing scoliosis (curvature of the spine) or other bony abnormalities? What is the emotional cost?” To answer those questions, Gerber and Marini ran a randomized trial of long-leg bracing. The study showed that braces (which go 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—best of all—allow them to be more active. Both parents and patients feel safer and more comfortable and children are willing to take more chances.

Brianne, the first patient with OI to be studied at the Clinical Center, naturally took part in the study and wore her braces religiously. “I love my long-legged braces,” she says. “They were my best friends when I was growing up. They were with me everywhere—in the sandbox, on the playground. When I was eight years old I carried a crescent wrench in my backpack to fix them if necessary. Nowadays kids who have OI are told that braces are one of the main ways that they can get stronger and 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.

## IN FOR THE LONG TERM

Brianne Schwantes is one of a cohort of patients for whom a multidisciplinary team is observing a long-term natural history. With sophisticated testing the team keeps track of the emergence, timing, and severity of different symptoms, so that they know their patients both clinically and molecularly. By studying a stable but specialized population over a long time, the team can make correlations that it would be impossible to make otherwise: For example, do neurological and pulmonary complications from the disease (a major problem) occur in the same population? How fast do they progress?

Having a stable population return regularly to the Clinical Center has given the staff expertise in the disease, much of which can be applied to other musculoskeletal and other developmental problems. It has also helped the OI patients and their families, who have formed a cohesive community. The patients in this study support each other, networking constantly by phone and e-mail and coordinating their visits to the Clinical Center.

As babies, the OI patients come to the Clinical Center every three months, and as they grow older their visits become less frequent—the older teens coming once a year. Some of the protocols are very demanding. In the most invasive—a study of a drug that may or may not help the fragile bones of OI—the team brought in orthopedic surgeons to perform bone biopsies, after which the patients recuperated in the Clinical Center hospital. This is asking a considerable commitment from the patients, all the more so because the protocols are controlled, which means some patients were undergoing procedures even though they may not be receiving the drug. Most patients and their families stick with the long-term study out of their desire to contribute to important research, learn more about the illness, and be on the cutting edge of research leading to new treatments. They also have a sense of the NIH's commitment to them, of the unique multidisciplinary clinical care and research program, and of the strength of the community they have built, which helps them get through difficult times.

Following these patients over many years has been extremely interesting, says senior investigator Joan Marini. "This is a wonderful population of kids. Trapped in fragile bodies, they fight hard to gain ground, and then there'll be some event and they lose that ground, and they have to climb the mountain again. They generally just don't give up—climbing and re-climbing the mountain. It would be hard for me to walk away from that."

Another recent study in rehab medicine showed strong links between patients' temperaments, family support, and their physical progress. Brianne took an active part in her own rehabilitation: "I had as much say in what was going to happen as the doctors did. They would change decisions and make the treatment work for me." But she also gives a lot of credit to the department: "They helped me to become the person I am, to walk when nobody thought it was possible, to be independent when nobody thought it would happen, and they were always there to say, 'You can beat it if you want to.' Because I grew up saying 'I can achieve any goal I set for myself,' I'm living a life I never expected.



Brianne Schwantes,  
Cherry Blossom princess

The first patient with osteogenesis imperfecta to be studied at the Clinical Center, Brianne Schwantes says of the rehab medicine department, "They helped me to become the person I am, to walk when nobody thought it was possible, to be independent when nobody thought it would happen, and they were always there to say, 'You can beat it if you want to.'"



Lynn Gerber, chief of rehabilitation medicine, fit Brianne with her first leg braces when she was a toddler

"I LOVE MY LONG-LEGGED BRACES," SHE SAYS. "THEY WERE MY BEST FRIENDS WHEN I WAS GROWING UP.

## THE CHILDREN'S INN—A HOME AWAY FROM HOME

The Children's Inn came into being because everyone knew that the less time children spend in a hospital, the better they do psychologically. It speeds recovery if they can be with their families in a homelike environment. Physicians caring for children with complex diseases were often torn about whether to keep patients in the hospital or discharge them. The problem was, there was no comfortable place for children to stay where, if they became ill in the middle of the night, it would be relatively easy to bring them back to the Clinical Center. If a child staying in a hotel developed a high fever or other serious symptoms in the middle of the night, it was a challenge to transport him back to the Clinical Center. And so the Children's Inn, which opened in 1990, was born. It was the brainchild and labor of love of Phil Pizzo, a strong leader of NCI's pediatric infectious diseases program and now a dean at Stanford University.

Outpatient scans, blood work, and treatments can be frequent and intense so it helps that children can now return to the Inn's safe environment and play with other children or be with their families. "It's also important for children suffering with critical illness to know they don't stick out," says immunologist Lauren Wood, who works with pediatric AIDS and HIV patients. "Everybody in the Inn has something going on. One child is

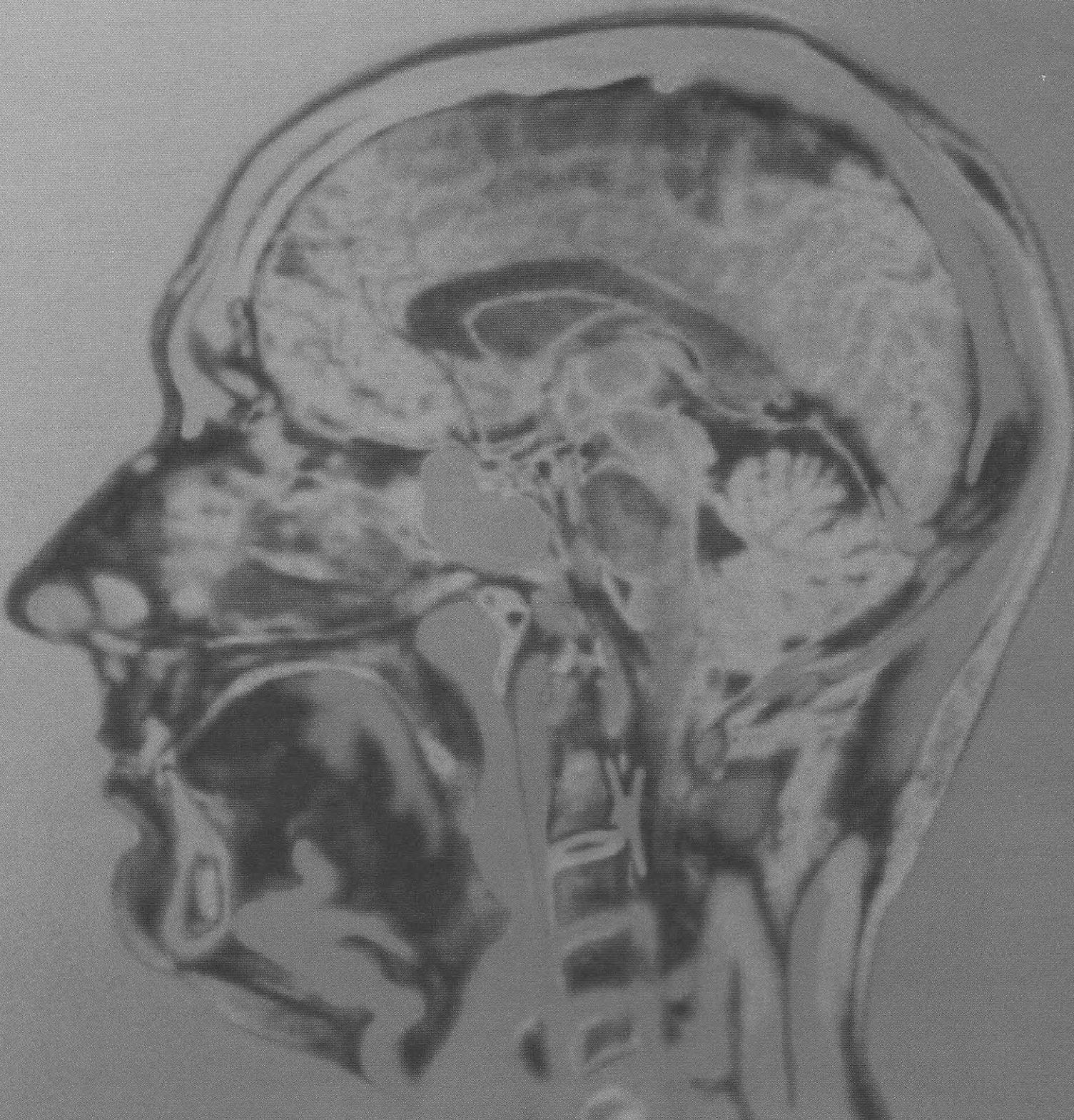
missing hair, another is missing an arm or a leg, one is funny-looking, another has to take ten times as many pills as they do, and many are facing life-threatening illnesses." Being a sick child is what the children here have in common, so they can get that out of the way and get on with the business of being children.

They can sleep in the same room with their parents and siblings, bring their favorite pillows and stuffed animals, sit around the dining room table eating meals cooked by their parents, and if they get sick in the night, it's just a short trip up the hill to the Clinical Center for evaluation.

The Inn also provides a supportive environment for parents. There they naturally develop support networks, comforted by having someone with whom to discuss the financial strain of a severely ill child, the burden of therapies and medications, and the problems of the healthy children in the family.

As investigators realized how helpful the Inn could be, the number of pediatric protocols by different investigators and institutes increased. During the summer months, when many children come, the Inn couldn't handle everyone, so now it's expanding—adding 22 new sleeping rooms, to house a total of 59 families.





In the 1950s, investigators in the National Institutes of Health—led by Seymour Kety, John Eberhart, Bob Felix, and Robert Cohen—put together the basic and clinical programs from which much work on pharmacological therapies developed. NIMH shifted away from an emphasis on psychoanalysis toward more of an emphasis on psychopharmacology as well as on imaging and studies of brain function. Led by Julius Axelrod, who would receive a Nobel Prize for his work, organic chemists did pioneering laboratory research in the 1950s that led to important clinical work in the 1960s and 1970s. Scientists were discovering that chemicals alter the mind—and the NIMH was moving, as Irwin Kopin puts it, “from psychoanalysis to urinalysis.” Many of the institutes were studying basic aspects of how the body works—especially how it metabolizes whatever substances enter it. Scientists looking at catecholamines in the brain were developing the basis for a more biochemical approach to therapy for mood disorders. As a locus for intramural work, the Clinical Center was an ideal place to study the pharmacological treatment of psychiatric problems, including mood disorders.

### **Trials of lithium’s effect on depression**

In the late 1960s, the Clinical Center was the first site of controlled trials of lithium’s effects on depression. Lithium had been discovered earlier in Australia and Denmark to treat mania, but it had not been shown to have any effects on depression. At the time depression and mania were assumed to be opposite states, and nobody thought a single drug

would have the same effect on both of them. “The observation that lithium had at least modest antidepressant effects was an important cornerstone in re-thinking what was going on in the biology of manic-depressive illness,” says Fred Goodwin, who directed the NIMH study. Now we know that in manic-depressive illness the manic and the depressive phase have many factors in common and that lithium was interacting with some of those common factors.

It was the kind of observation that could be made only in the Clinical Center, says Goodwin, because it required careful daily observations of patients by doctors and well-trained nurses working in close collaboration—with the kind of intensity possible only in a dedicated research ward in which everybody’s job is basically research. The investigators spent a lot of time training the nurses, who became experts at what they were doing and were full-fledged members of the research team and coauthors of some papers. Both doctors and nurses—none of whom knew which medication the patients were taking—noted an antidepressant effect with lithium. “It was easier to trust the results because the nurses’ ratings confirmed the doctors’ ratings,” says Goodwin, “the nurses tending to observe behavior more, and doctors tending to rate more the psychological content of what the patients were saying.” Goodwin and his colleagues (including Dennis Murphy and William “Biff” Bunney) published their first paper on lithium as an antidepressant in 1969. In 1972 they did an extension of the first study.

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SCIENTISTS WERE DISCOVERING THAT CHEMICALS ALTER THE MIND—AND THE NIMH WAS MOVING “FROM PSYCHOANALYSIS TO URINALYSIS.”

It was also important that the research team could keep a patient as long as they needed to at the Clinical Center: They didn't have to worry about the patients' insurance running out—especially in today's climate, with hospitalization for psychiatry tending to run about seven days and people forced to complete their research in a very limited time (unless they have an NIH-supported clinical research unit).

### Studying childhood schizophrenia

Judith Rapoport, chief of the NIMH Child Psychiatry Branch, is credited with bringing child psychiatry back to the NIH Clinical Center and the NIMH intramural program—after a false start in the 1950s. An earlier program had attracted talented investigators, but the children and adolescents enrolled in the program were from tough backgrounds, the approach was psychoanalytical, and there was inadequate concern for things like locked doors and close behavioral monitoring. After several adverse events, the child programs closed for a number of years.

When Rapoport was recruited in 1976, there was more concern about containment than there was enthusiasm for child psychiatry. That has changed enormously. Today outpatient and inpatient child programs deal with a spectrum of disorders, including boys with Klinefelter's syndrome (an extra Y chromosome and specific learning and behavior problems) and children with anxiety, depression, attention deficit disorder, early onset bipolar disorder, and childhood onset schizophrenia.

One strength of doing such studies in the NIMH intramural program and in the Clinical Center is the ability to conduct long-term research that involves bringing patients with rare cases in from all over. This is certainly true of childhood-onset schizophrenia, which Rapoport's branch is studying now. In adults, the rate of schizophrenia is about 1 in 100—and 1 percent is not a rare disorder. "But the onset before age 12 is 1/300th the rate of adult onset—we think about 1 in 30,000. Schizophrenia tends to be a disease of late adolescence. We're interested in that because often, very early onset of any illness is more genetic, and it's a good way to hunt for genes. And

these kids are terribly ill, so there's a lot to learn about how to treat them, anyway."

The initial goal of the program was the diagnosis and neurobiology of childhood-onset schizophrenia: describing it and making sure it's the same as adult schizophrenia. "Some adult practitioners who have never seen cases questioned whether we might not have a different disorder that superficially looked like it, which was a reasonable question. We wondered that ourselves." The main study is to characterize the children: do tests to see that they have traits of the illness, to look at family members' functioning, to get the pedigrees straight. Then there are individual treatment protocols, depending on the family's interest in being in them—most of them are. Recently the study has begun examining DNA more closely to see if the genes found to increase susceptibility to adult-onset schizophrenia are the same as those for the childhood form of the disease. That work is just starting, in collaboration with Richard Straub and Daniel Weinberger, who are studying the genetics of adult schizophrenia patients.

Drug treatment protocols for psychiatric disorders require uniquely trained and understanding nurses, which the Clinical Center provides. "When a child comes in with a diagnosis of schizophrenia, part of our protocol calls for taking them off drugs," says Rapoport. "I should say, parenthetically, that this is treatment-resistant"—meaning that although the children may be somewhat better off taking a particular antipsychotic medication (they are better on it than they are on nothing), they haven't shown what would be considered a good response. "It's an enormous act of faith in the research project to have the dedicated research beds—beds the patients' families are not paying for—and the ability to take children off medication for three weeks, during which time they get worse." Nurses have to deal not only with the physical, emotional, and behavioral problems associated with changing a schizophrenic child's medications but with the rigid reporting requirements of a clinical trial.

"Ten years later, the stories are so impressive," says Rapoport. "Although most patients with schizophrenia are so clearly schizophrenic that it's not a hard diagnosis, one out of five of

IT'S AN ENORMOUS ACT OF FAITH IN THE RESEARCH PROJECT TO HAVE THE DEDICATED RESEARCH BEDS—BEDS THE PATIENTS' FAMILIES ARE NOT PAYING FOR—AND THE ABILITY TO TAKE CHILDREN OFF MEDICATION FOR THREE WEEKS, DURING WHICH TIME THEY GET WORSE.

the 90 children we've studied either had no problem off meds (short for medications) or, in some cases, did not have the problem any more! We had two or three children who we now think may have experienced an unusual drug toxicity and it was only by taking them off all their medications that we learned that they no longer needed treatment. We are following up on those patients so we can understand what happened and see how they are managing long term. Much more important and more common is that, after the children are admitted and have been off all medications for several weeks, 20 percent of them change, and it becomes clear that they have another psychiatric illness: bipolar disorder. That's also a serious illness but, in general, a child who is bipolar and on the right medication has a better prognosis than a child with schizophrenia." So changing the diagnosis or, in a handful of cases, finding out the children no longer have a psychiatric disorder, has seemed a miracle to parents in these subgroups. Rapoport's team is still getting letters, calls of thanks, and Christmas cards and presents from these families.

"Twenty years ago with puzzling or treatment-refractory cases a drug-free observation period was absolutely the very first thing you did at a very good academic treatment or research center," says Rapoport. "You wanted to see an unusual, atypical, and treatment-refractory patient off medication. Now no academic center has the luxury of doing that, because it's so expensive and insurance now pays for less—and is particularly bad in psychiatry. We have the resources here to support the drug-free period. If we were working anywhere else, we wouldn't even have tried this study."

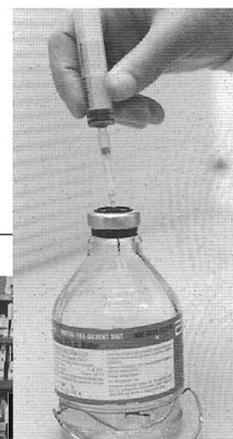
## THE CLINICAL CENTER'S RESEARCH PHARMACY

In protocols involving immunosuppression, drugs play a vital supporting role—and so does Clinical Center pharmacist Chris Chamberlain. When patients suffering from diseases such as diabetes, hypertension, and cataracts come to the Clinical Center for a kidney transplant, they are already using a large number of medications—ten is not unusual. Then they receive powerful new drugs to suppress their immune systems. The pharmacy keeps track of them all, informing medical staff about interactions and side effects, even if they appear unrelated. This reporting is especially crucial with new drugs, because no one yet knows what the side effects will be. Transplant surgeon Allan Kirk values his pharmacy colleagues because the setup in the Clinical Center, by giving them dedicated research time, allows them to be extremely attentive, with an emphasis on thoroughness.

The Clinical Center's research pharmacy is equally valuable for research like the current NIMH study of childhood schizophrenia. On double-blind drug studies (in which doctors, nurses, and patients have no idea which drug is being administered), the pharmacy takes charge of the treatment and control drugs, sometimes produces drugs, and runs blood levels. The pharmacy often handles drugs that aren't on the market yet, interacting with the company supplying the compound, sometimes literally making up the pills and making matching placebos. "In an ordinary medical school, there are few pharmacists dedicated for research; there's too much pressure for them to provide services," says NIMH's Judith Rapoport. "On our drug treatment protocol for these very sick children, there's a representative of the Clinical Center pharmacy at our weekly meetings. They are research partners, coauthoring papers with us on whether children metabolize drugs differently, a side focus of the study."



The pharmacists in the Clinical Center have dedicated research time, which allows them to be extremely thorough and attentive research partners. This is especially important in double-blind clinical trials involving experimental drugs and in protocols on which patients require as many as ten drugs.





Judith Rapoport, chief of child psychiatry Rapoport is credited with bringing child psychiatry back to the Clinical Center and the NIMH intramural program. With childhood-onset schizophrenia, a rare disorder that Rapoport's branch is studying, the Clinical Center provides the resources for a drug-free observation period in which to study unusual, atypical, and treatment-refractory patients off medication.

# HOW ONE FAMILY FOUND ITS WAY TO THE CLINICAL CENTER

In most respects Max\* looks like a normal kid, a good kid, the kind with whom a parent happily tosses a ball back and forth. But after an uneventful childhood, Max developed early-onset schizophrenia, a disease so rare in young children that his parents had trouble getting a diagnosis. Most child psychiatrists have no experience with schizophrenia, and few specialists in schizophrenia have experience with patients as young as Max.

His parents, Diane and John, had been vaguely aware of problems. They had started him in school a year late because his birthday was late in the year and he was less mature than his peers. At eight and nine, according to his teachers, Max “zoned out” in class. He didn’t zone out at home, where he was active and enthusiastic. Diane asked the school board for a psychological evaluation and was shocked when the board psychologist, who wouldn’t answer many of their questions, concluded that Max was autistic. A psychologist they consulted for a second opinion concluded that Max was clearly not autistic. When she asked, “What is your favorite TV show?” he responded, “I like *The Simpsons* but I am not especially addicted to it.” She found him to be somewhat uninhibited for an eight-year-old, “bright as a button,” and basically delightful.

Two years later, when Max was ten, she was shocked at the change in him and saw it as a psychiatric emergency.

It was January when his family noticed a dramatic change in his personality. Suddenly his short-term memory wasn’t very good, he couldn’t concentrate, and he seemed emotionally flat. Hearing tests revealed normal hearing. His behavior on a family vacation in March confirmed that things were definitely wrong. His brother and sister noticed that Max, who had played on three hockey teams, was no longer physically active. He was withdrawn and had begun muttering to himself. When the family returned home, he paced and was agitated. In April he stopped attending school. He was falling apart.

As April passed, Max became increasingly agitated and began to perseverate (get stuck and repeat himself). “We were floundering and desperately looking for help, and nobody would take the problem on,” says Diane. “The pacing and muttering were the first signs of schizophrenia. The disease progresses. He wasn’t gone yet, but we were losing him. He still knew what he wanted, but he didn’t seem to have any sense of time, and he wasn’t sleeping.” What he most wanted was to play hockey and to see his friend Tommy, a child who lived two doors down. At 2 or 3 in the morning he would ask Diane repeatedly to go play hockey—at first passively, then with agitation, and finally in anger. Grabbing his hockey bag he would try to walk out of the house. They couldn’t reason with him and had to restrain him. This kind of behavior increased in frequency.

\* The story is true but the names of the patient and his family have been changed.

MAX WAS TEN WHEN HIS FAMILY NOTICED A DRAMATIC CHANGE IN HIS PERSONALITY. SUDDENLY HIS SHORT-TERM MEMORY WASN'T VERY GOOD, HE COULDN'T CONCENTRATE, AND HE SEEMED EMOTIONALLY FLAT. HE WAS WITHDRAWN AND BEGAN MUTTERING TO HIMSELF.

## Desperate for help

Diane and John spent March and April looking for professional help. Three times before he was hospitalized, they took Max to a highly respected children's hospital. The first psychiatrist who saw him there told them it was a behavioral problem and sent them on their way; he didn't seem interested in the case. "Max had never been a behavior problem, and I knew the behavioral modification he was suggesting wouldn't work on Max because he didn't have any sense of reason," says Diane, who for six years had run a vocational rehabilitation facility for former psychiatric patients. "I was happy to hear that he didn't think Max was psychotic, but things didn't improve; they got worse."

Their pediatrician, who is affiliated with the children's hospital, saw there was a problem with Max and insisted he be given another psychiatric appointment. "He was probably the first person to mention schizophrenia. He actually followed up, using our case, trying to make some changes at the hospital. You can't assess a child like Max in an hour; you need more time than an office visit allows." Partly as a result of his efforts, there is now a centralized system for finding a bed fully dedicated to assessments of psychiatric patients in the city where they live.

On the first of May, Max had been at his friend Tommy's house and wanted to go right back—forgetting that Tommy was busy. "For several hours we had to restrain him, and once you start doing that, it just gets uglier," says Diane. "Finally we phoned an ambulance to come pick him up, thinking maybe this would get them to take us seriously. I guess too we didn't know that we could get him to a hospital on our own. By the time the police and ambulance came, Max was calm and sitting on the couch. He agreed to go in the ambulance. My husband went with him and I followed in the car to our neighborhood hospital." They had just set up psychiatric units at local hospitals.

"You know how hospitals are," says Diane. "They take your name and number and make you sit and wait. Max, who had been very athletic, was doing pushups and had reached 100

when I walked in the door, when he decided to leave. John had to hold Max in his lap. Max tried again to leave, John grabbed him, and Max became a ball of fire. John said, 'Can somebody come and help us?' An orderly took it upon himself to lecture John on how this was his responsibility—apparently assuming this was an abuse case. We were literally at our wit's end. We were right by the emergency room door and I said, 'John, when those emergency doors open, just let him loose, because he'll go in there and they'll have to take this seriously.' Meanwhile, the nurse who had been trying to get a room ready apologized that it was taking so long, saying she had not realized the seriousness of our problem. An old woman who must have been there waiting with her husband came up to me, put her hand on my shoulder, teary-eyed, and said, 'Oh God bless you,' and I felt at that point that the only person who knew what was going on was this old lady."

Finally it became obvious to the staff that Max needed to be hospitalized. "If he'd remained calm—if he hadn't finally blown up—we'd probably have had to take him home," says Diane.

Max was in the local hospital for six weeks. There he was diagnosed primarily as multidimensionally impaired (MDI), a diagnosis that may be neurobiologically related (or possibly a precursor) to schizophrenia—researchers aren't certain yet. Diane felt that Max didn't quite fit the criteria for MDI, one symptom of which is terrible temper tantrums by the age of seven. "He was very combative at the hospital when he was restrained, but before he was ill Max never, never lost his temper. He was a docile kid."

Next Max was moved to a different facility, where the psychiatrist said Max had pervasive developmental disorder. PDD is a spectrum disorder, and along that spectrum lie autism and Asperger's syndrome. Asperger's children are more social; they can talk but they obsess about a topic. Autistic children don't socialize. Schizophrenia and autism share certain features. When people have schizophrenia, they also have social problems; what is going on in their head is so distracting that they become disconnected from external stimuli. Max was at his worst at this facility. The disorder was still progressing, he had changed meds and was on a high dose, and the facility was

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very restrictive. He was disoriented, anxious, less communicative, and more bizarre.

### Respite in a boys' home

"For eight months, I was a mess," says Diane. "When the Max I knew disappeared, he was gone and I was grieving. I couldn't take joy in anything."

After being in a hospital setting from May through mid-August, Max was placed in a pleasant boys' home that housed eight boys roughly Max's age who had behavioral problems, most of them also associated with psychiatric disorders. "The staff there was so nice to him," says Diane, "I started feeling better. It was like my kid had died for eight months, and now he was in a place where he was comfortable. It was a supportive but relatively normal environment, I could visit him there as much as I wanted, and we were able to have him home on weekends. Because I was more relaxed, I was able to enjoy Max and adapt to the changes in him. When I wasn't with him I could be distracted by things I had once enjoyed, and could go for hours at a time without thinking of him.

"In the hospitals," says Diane, "where they were security-crazy, Max would become angry and out of control when he couldn't get out of the unit. In the boys' home he became more passive. He would still head for the door, but you could distract him. I thought there was a 1 percent chance that Max would go missing or something bad would happen to him, but I would rather take that chance than have him locked up, which makes him agitated, so that they end up restraining him and things snowball downward. Max was comfortable in the boys' home, and I liked seeing him with seven other boys his age, coming in and out the front door, walking to school and back for lunch." The young staff was enthusiastic, taking the boys camping every other week during the summer and once during the winter. Everybody loved Max and the boys looked out for him.

### Family denial

Luckily, most of the people in their life, including the staff in John's firm, have been totally supportive, asking repeatedly if they could do anything to help. Unexpectedly, there was a painful lack of support from John's family, adding to their problems. Several weeks into Max's hospitalization, John's sister had telephoned and told Diane, "You have to get him out of there. He's your son." She and John's mother couldn't understand why Max was hospitalized. They had not been around during his decline, and when Diane described it, they still couldn't understand. John's mother seemed to feel the problem had to be someone's fault. "Diane used to treat him like a jewel," she would say, or "Maybe it's fetal alcohol syndrome" (even though Diane didn't drink during pregnancy). She thought they must "be hiding something."

The family had planned to go to a cottage with John's mother in June, and when she visited their home one weekend when Max was home, she proposed taking Max to the cottage by herself, clearly thinking she would "fix" him. Worried not only about Max's safety but about his mother's, John said, "Why don't you just spend the night tonight, so you know what you're getting yourself into," and his mother walked out the door. Their relationship deteriorated.

Finally, in early autumn, the boys' home was going to give a diagnosis, and the whole family was invited to come, including the grandparents. They said, "He has this symptom and this symptom and this symptom, and it looks like he has childhood schizophrenia." The social worker asked John's mother if she had anything to say and she responded, "Max doesn't have schizophrenia, but if he stays at the boys' home for a year he will have." She firmly believed it was something you could cause. The psychiatrist put both elbows on his knees, looked at her intently, and said, "Maybe you didn't understand me. I said Max does have schizophrenia." She didn't budge, and Diane and John are no longer in touch with her, except for a message she left on their answering machine: "Give Max to me. I can't believe you are abandoning your son." To them, it felt as if she were abandoning her own son, John.

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"MAX NOW LIVES IN A TOTALLY DIFFERENT WORLD, UNABLE TO SEPARATE FANTASY AND REALITY. FOR THE MOST PART HE SEEMS CONTENT IN HIS WORLD, BUT OCCASIONALLY HE FEELS TERRIFIED OR ANGRY. I FEEL WORST WHEN HE'S TERRIFIED."

## Finding the NIH

None of the psychiatrists who had seen Max specialized in schizophrenia, and even before the diagnosis at the boys' home Diane began to feel strongly that's what Max had. That's the diagnosis that came up when she punched the symptoms into the computer. On the Web she had learned that experts don't always agree on when to classify someone as schizophrenic, but that certain symptoms are associated with schizophrenic psychosis, especially hallucinations (auditory or visual), delusions (strange beliefs), and disordered thinking. Schizophrenics may suffer one or all of them. They have trouble drawing the line between reality and fantasy; they are taking information in but perceiving it differently, arriving at different conclusions. Watching a bus go by, its passengers staring out the window, a schizophrenic might think the passengers are staring at him. Voices in his head might tell him he is being persecuted. The television might be sending him different messages than it's sending to the average viewer. That seemed to fit with Max. He sometimes walks past another child watching a movie and says, "I was a star in that movie."

What was happening to Max reminded Diane of what she had heard years earlier in her Psych 100 course: "Neurotics build castles in the sky. Psychotics live in them. Psychiatrists collect the rent." Neurotics have worries they shouldn't have, but they are still on this planet with us, building the castles and worrying about them. The psychotics are living in that castle and think it's real. "Max now lives in a totally different world, unable to separate fantasy and reality," says Diane. "For the most part he seems content in his world, but occasionally he feels terrified or angry. I feel worst when he's terrified."

Diane read, on the Web, that of all the mental illnesses studied, schizophrenia is the most chronic and disabling. Adult schizophrenia typically begins as a psychotic episode in young adulthood, with devastating hallucinations, delusions, social withdrawal, blunted emotions, and the loss of social and personal care skills. Schizophrenic people hear voices all the time, have strange delusions, and their lives deteriorate. Unlike adult schizophrenia, schizophrenia in children usually emerges gradually and is often preceded by developmental

disturbances, such as lags in motor and speech development. Childhood-onset schizophrenia also tends to be harder to treat and to have a worse prognosis than the adult-onset form. A new generation of antipsychotic medications has helped many patients manage their symptoms with fewer side effects, but because childhood schizophrenia is so rare, few clinicians have experience medicating children.

One day Diane found herself at the website of the National Institute of Mental Health (NIMH), with an application in front of her. She and John filled it out, John called the institute, and they asked for all Max's reports. Two weeks later, says Diane, "They asked us to come down. We learned later that they turn down 50 percent of the patients who apply, based on reports. Then, after a three-week diagnostic period, they turn down another 20 percent who fail to meet the criteria for the protocol."

They went to the interview in Building 10 and Max was accepted. The NIMH researchers wanted him the next week. They wanted him on his medication three weeks, then off for three weeks—to establish the baseline they needed for research.

"That the NIH responded so quickly was wonderful," says Diane. "It gave us something to hope for. Max would finally be diagnosed and treated by professionals who had experience with childhood-onset schizophrenia—who believed it existed!"

### A period of adjustment

When Max came to the NIH he decompensated. "He was into Dungeons and Dragons and in his fantasy world he seems to be working out a system that makes him safe and strong," says Diane. "At first, he stood peeing on the floor, like he was marking his territory. He also stopped wearing clothes. He spent a good five weeks naked in his room. Twice when he struggled to get his clothes off, and I kept him from removing his shorts, he said, 'You made me lose.' So I think he's playing a video game—I interfered with it so he's lost the battle—but this is all speculation on my part because he doesn't communicate clearly enough for us to know exactly what's going on." Max had always been picky about his clothes,

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"IF HE'S IN MOTION, HE'S COMFORTABLE. SO MAX AND I WALK A LOT."

pulling at the collar of his tee shirt, disliking clothes that were tight, preferring a loose waistband. He still has some clothing issues and takes clothes off when he's in bed, but he now seems to feel safer in the hospital.

Max not being able to communicate at all is rather unusual. Max had been a talker before, and funny—and then, when he began to perseverate, he kept talking about the same thing over and over. Now he doesn't talk enough to perseverate. What most frequently comes out of his mouth is a jumble of words, or what they call "word salad." Now he has no enthusiasm; they can see the withdrawal and flatness.

Max takes frequent showers, which was an issue even before he got to the NIH, says Diane. "I got an inkling of why when he plugged the tub one day and said 'I am making a lake.' Adam, his older brother, told me later that Max said he was going to fight Adam at the water level and then at the fire level. His behavior seems to reflect that video game in his head. It was helpful, I thought, for the nurses, who like showers to happen at a certain time (routine being part of behavior modification), that Dr. Tossell, Max's doctor at the Clinical Center, called Max's showers 'hydrotherapy,' which probably made it easier for them to handle."

With adult schizophrenia there is a sudden change: there was a normal child and suddenly that adolescent or adult is schizophrenic. With childhood schizophrenia there are lots of premorbid symptoms. "The psychiatrist at the NIMH says Max had few premorbid signs," says Diane. "They looked at a video of his ninth birthday party and thought he was unusually normal for a child who was so close to becoming psychotic. Usually schizophrenics are clumsy and tend to be sedentary. Max's coordination is still unusually good and he has always been extremely active." Premorbid symptoms, along with early onset, maleness, or a genetic link in the family, predict a poor prognosis.

Before Max became psychotic, he was unusually disciplined and concerned about his physical health. He exercised an abnormal amount and ate the right things. If he ate a chocolate bar he would have a piece of fruit, too. "He would play

hockey as if he were trying to drive something away," says Diane. "Maybe he was trying to keep himself grounded—trying to manage the internal stimuli even before we were aware a problem existed." He once said to Diane, after he went outside and did a little workout, "Sometimes when I sit down I feel like I fall asleep." Looking back, she can see why he felt he had to keep himself in motion, wonders if he was trying to manage his disorder, and hopes, if so, that that bodes well for a better outcome—once a drug treatment is found that gets him to the point where he has more control over his internal stimuli. "If he's in motion he's comfortable," says Diane. "So Max and I walk a lot, since he's had his clothes on."

### **Finding the right drug for Max**

The NIMH was doing two drug studies. "We had a choice," says Diane. "Dr. Tossell was wonderful. She said, 'It depends on what you want to do. We can treat him as best we can and send him home, or he can participate in a protocol.' There was no pressure to choose one or the other."

On one protocol some patients would be given Risperdal (generic name, risperidone) and others would be given Abilify (aripiprazole). Risperidone, which Max had taken at the boys' home, had little or no effect on him. Aripiprazole was known to have fewer side effects.

The other protocol was comparing the effects of clozapine and olanzapine. Clozapine works best with most schizophrenics, but has severe side effects, including weight gain and a drop in the white blood cell count. Patients' families must pick up the medicine once a week after a weekly blood test; the FDA rules about its use are cautious, but because it works so well it is considered worth the risk. "Clozapine wasn't even suggested at our local hospital," says Diane. "Because it is so heavy-duty it's a scary drug. They would have been nervous giving it to him and they wouldn't have had any experience giving it to a child. We wanted to save those big guns for the last." Knowing they would probably eventually have to try clozapine, for now they decided to try the risperidone/aripiprazole protocol.

It was a double blind study: Neither the patient nor the person administering the drug knew which one was being administered, to avoid any unconscious bias being conveyed about a particular drug's probable effectiveness. Because he was not responding, Diane and John suspected Max was on risperidone, and it turned out that he was. Now they have moved from research to treatment and they are trying the aripiprazole, but he seems to be getting worse. The plan was for Max to be on aripiprazole for three to four weeks and if it doesn't work to do an eight-week trial on clozapine. There is still hope that Max will improve.

"I don't know that there is any therapy other than drugs for a child like Max," says Diane. "I've done a lot of reading. I had hoped the NIH would have research therapies other than drugs, but that doesn't seem to be the case. There are recreational or occupational therapists to keep him active. From one to three he's in school (a big component of research) on the same floor where he sleeps. There are two teachers (both with masters' degrees) in a small classroom, where three bipolar kids go in the morning and three childhood schizophrenia kids go in the afternoon."

While Max stays in the Clinical Center, the family has a room in the Children's Inn, a guest lodge on the NIH's Bethesda campus for young patients and their families. Diane stays at the Children's Inn; John and their other two children come for weekend visits. One benefit of staying at the Children's Inn is that parents meet and often become close to other parents whose children have health problems. "We don't always talk about our children, but it's comfortable to be distracted by people who are in a similar position. If I were only in touch with Max, I'd be very sad. The chance to socialize makes life seem more normal. You feel part of a community in the Inn."

### Max's prognosis

Max is relatively stable now. "He goes in cycles, from agitated, to stable, whether on or off medication," says Diane. "He's calmed down because he is used to being here. His internal stimuli peak and then quiet down. Max's restlessness,

which is a 24-hour thing, is one of the main problems in managing him."

What does the future hold for Max? Diane and John have been told that two-thirds of schizophrenics can function relatively well. "There is no such thing as a cure," says Diane. "I've read that a third of patients on medication are considered to be in remission (have no symptoms), a third have improved significantly, and a third haven't improved significantly. But as a rule children with schizophrenia have the worst prognosis, so all we can do is treat him so he is the best he can be. Hopefully he'll be well enough that he can be home with us. As long as we are moving on, we have hope. As long as we're in motion we feel good. It is a relief to have him in a special facility—we also have to think of our other kids—but we do want him home, too."

Their caseworker is looking for accommodations for Max in case he doesn't improve significantly when he leaves the Clinical Center. They would like to find a residential facility rather than a hospital. "Max will probably end up in a place with autistic children. I don't know how I feel about that. In a home with autistic kids he'd be the highest common denominator. I would prefer he was the lowest, so activities were geared somewhat beyond his abilities so he would be working up instead of down." The NIMH staff, which wants Max to come back every two years, has said it will always be available for consultation with whatever doctors John and Diane find at home.

"I think a lot about what Max was like before he got ill and what made him different," says Diane. "I adored Max, and I think it's partly because Max didn't complain. He didn't say he was bored, he didn't say his brother and sister had more than he had. Everything that was a little odd about Max felt positive. Emotionally, Max has always been sound—like a rock. Adam and Rebecca were more difficult. Max was an angel from birth. I now wonder if that was a symptom."

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## WATCHING BRAIN DEVELOPMENT

NIMH investigators like Judith Rapoport are also studying how a disease such as schizophrenia affects the developing brain, because there are many changes in the brain in adolescence—and because the biology of mental illness at any age has come to be linked increasingly with the biology of neurodevelopment. "One benefit of the Clinical Center is that MRI time is available for research," says Rapoport. "So since 1989 we have collected literally thousands of MRIs on the same machine on both healthy and psychiatrically disturbed children and adolescents who've come back every two years for ten years. We can now literally watch normal brain growth by viewing movies of brain development that we have made with the help of collaborators at UCLA. And by

getting that huge amount of normative data for ourselves, we could then coordinate the clinical program so that patients matched for age, sex, handedness, and so forth, would come back at the same time, in the same time period. So in a project that's been going for the last 12 years, we've been able to look at how schizophrenia in childhood and adolescence affects brain development, and compare that with brain development in hundreds of boys and girls with a milder problem called attention deficit hyperactivity disorder (another study), and, of course, compare both with controls."

# ALZHEIMER'S: AN UNCERTAIN INHERITANCE\*

by Barbara Geehan

The thick metal door at the Clinical Center at the National Institutes of Health (NIH) buzzed shut, locking me in, just it had my dad several years ago. Once a year for the last three years of his life, he registered this sound with dread. Now, it is my turn—with one difference. For me, the buzz represents my best hope.

When my father was diagnosed with Alzheimer's disease in the early 1990s, he decided to volunteer for a research program at NIH aimed at finding possible causes of the disease. If he didn't find a cure for himself, he figured, at least he might help others. "I don't just want to sit here turning into a vegetable," he said. "I know what is going to happen."

The knowledge came firsthand. He'd watched his grandmother die of the disease in 1944, his mother 40 years later. He would die of it himself in 1999. His sister, who also volunteers in the NIH program, was recently diagnosed at age 77.

I have no symptoms of Alzheimer's, but I am 52. The doctors at the Alzheimer's Family Study have invited me to participate in a longitudinal study; the volunteers—250 are now enrolled, recruited from across the country—return annually for retesting. They include people with memory disorders, people like me with a family history of the disease and some who have neither symptoms nor a family history.

Why spend three days in this Bethesda high rise? For one thing, there are the personal benefits: an amazingly thorough

physical for free and the chance to put yourself in line for experimental therapies. There's also the idea that you might help find a cure to an ailment that's replacing cancer and heart disease as the old-age illness many families fear most.

Alzheimer's, the most common form of dementia, affects at least 2 million people in the United States. The disease proceeds over years to gradually snuff out the brain's operations. You begin to forget words, lose the ability to reason—and eventually to carry out even the most simple tasks.

"Most volunteer because they have been personally impacted by . . . Alzheimer's," said my nurse practitioner, Irene Dustin.

"How do you put a price on that?"

I have been in denial about my chances of getting this disease. NIH asked me to participate several years ago, but I thought I was too young to worry. Doctors say they cannot calculate who will get it and who will not, although they agree a family history of it certainly increases the risk. All my life, my mother would joke, "You think just like your father!" The teasing comment I used to be so proud of now rattles me a bit.

I remember when Grammy, that proper lady from Cornwall, England, began in the 1970s to change her clothes 12 times a day, to talk to refrigerators and look at me with stark, helpless fear. And as I look back at my wedding pictures from

\* Barbara Geehan's story was originally published in the Health Section of the *Washington Post*, December 17, 2002. It is reprinted here by permission of the author.

ENROLLED IN THE SAME ALZHEIMER'S STUDY AS HER LATE FATHER, SHE HOPES FOR A BETTER OUTCOME.

1990, I see Dad staring into space with an odd slack downturn of his usual smile. Mom said he was just emotional about the wedding. I know better now.

### Ham and eggs

Doctors told me that for the Alzheimer's study, I would undergo cognitive tests and physical tests, such as an MRI of my head and a lumbar puncture, more commonly known as a spinal tap. I would also conduct a household task while an occupational therapist took notes. This exercise is done to track the participants' motor and mental skills.

My father's task every year was to make a ham sandwich in a stocked kitchen. We always joked that he never made anything in the kitchen at home; how the heck would he do there? Actually, he made quite a fine sandwich the first year. By his last year, though, he would open and close cupboards again and again, sure he was supposed to find the answer behind them—somewhere.

"It is very sad for me to watch the changes," said Fran Oakley, the occupational therapist in charge of the kitchen. "But it is nothing like it must be for the family."

This fall, I decided it was time for me to find some answers, so I agreed to sign up for the study. The night before I was to check in, I anguished over how many novels to bring. Would there be shampoo? Could I jam that terry-cloth bathrobe into the suitcase? Was I perhaps focusing on these details as a form of diversion?

The center was an easy walk from the Metro's Red Line. Once through security, I signed consent forms and had a plastic ID bracelet snapped on my wrist. Then I approached the locked door of the Alzheimer's ward. Dad had hated that door. The whole family hated it. Alzheimer's patients often wander, so locking them in is necessary. But Dad never understood that. As the disease progressed, he'd bang the door to leave with us when our visits were over, peering through the small glass window with increasingly clouded eyes.

I was buzzed in and shown my room. As I sat on the edge of a thin mattress, a nurse and a nurse practitioner explained what

would happen over the next three days. Then the tests began. I gave numerous tubes of blood. They will be tested and analyzed, and some frozen for future use. There was also the spinal tap. While you hunch over a chair, the doctor uses a needle to withdraw about a tablespoon of spinal fluid. That fluid, I am told, offers a chance to find markers for what is happening in the brain. The procedure is not as gory as it sounds; the siphoned fluid is replaced by the body within two hours.

Doctors study both the blood and the spinal fluid to rule out any abnormalities. Because there is no way yet to diagnose Alzheimer's definitively while a patient is alive, the clinical diagnosis is referred to as a diagnosis by exclusion: Rule out other disorders first. They also look for disease markers—among them proteins called beta-amyloids that build up in the brains of Alzheimer's disease patients—and other common patterns in study patients.

For my household task, I was assigned to make scrambled eggs spiced with diced onions and cheese. I cook every day, but now a therapist was watching my every move, constantly scratching in her notebook. Was I doing okay?

Then, there were numerous cognitive tests, some relatively simple: Who is the president? Tell me the three words I mentioned 10 minutes ago. Where are you now? Then, more complicated ones: Count backward from 100 by sixes. If the red dot flashes in the same spot as the black dot did a moment ago, press "same." Read the math problems out loud, then say if the answer is correct or not, and say the word after the problem. After four to eight of these, we will ask you to write down the words in the correct order. Argggghh.

### Brain games

I sat at the edge of my seat, determined to get an "A," to show my mind was not only smoothly running but maybe bordering on genius. These tests were challenging. How, I asked psychologist Ginny Rosen, could a person with Alzheimer's possibly take these tests? They do not get all the same tests, and they do get frustrated, she said, "but you would be touched at how hard they try." The best cognitive testers are college-

"YOU THINK JUST LIKE YOUR FATHER!" THE TEASING COMMENT I USED TO BE SO PROUD OF NOW RATTLES ME A BIT.

aged. Their brains are agile, and they are used to absorbing and memorizing many diverse facts. “I want to tell them to enjoy it now,” said Rosen, “because this is as good as it gets.”

The staff was comforting and professional. Some remembered my father. Even though he threw his pills on occasion, and even popped a nurse once, they remember the true Dad, a gentleman with a fine dry wit. As a former CEO, Dad was most comfortable making decisions—okay, giving orders. As he spiraled deeper into the miasma of Alzheimer’s, the staff let him sit in on their daily meetings. He was sure he was running them; they accepted that.

There is a special knack to working with Alzheimer’s patients: Treat them with respect and dignity. They may be confused, but they recognize fear or patronizing behavior. The staff also helped my mother learn how to help Dad through the stages of the disease.

There were some mishaps during my visit to NIH: The lumbar puncture proved difficult because of a previous injury to my back. Also, some kind of electrical surge caused dust to burst from the vents at 1:30 a.m. the first night. As a precaution, we were evacuated to the floor for patients with bipolar disorders. My new roommate was very nice, but she talked much of the night. How am I going to remember more red dot tests and math problems on three hours of sleep, I wearily wondered. Between tests, in the living room and dining area, I met several volunteers who were in the early stages of Alzheimer’s. Some were attached much of the day to rolling racks of fluids. Others were there to be assessed.

One man, from the Virgin Islands, brought reggae music and picture books of the islands. A second, a 65-year-old from Colorado, relayed what he called his Greek tragedy: He had been his mother’s caretaker as she struggled with Alzheimer’s. More recently, a week before he was to marry for the second time, he and his bride called off the wedding because they began to suspect he also had Alzheimer’s. “I don’t wish [the caretaker role] on anyone,” he told me.

## What they won’t say

A certain gene, ApoE or apolipoprotein E, may play a role in determining who gets Alzheimer’s and who doesn’t. But because doctors are not sure of that role, I would not be told whether I had the gene or not. “You can have the gene and not get Alzheimer’s,” Trey Sunderland, the doctor in charge of the family study, told me. “You can not have the gene and get it.”

I pushed a bit. If I do get Alzheimer’s, it will be for genetic reasons, I said. I’m here for information-gathering purposes. Tell me.

What would you do differently if you knew? asked Sunderland. You are indeed at a higher risk because of your family history, he said. If I were you, he continued, I would take 1,000 milligrams of vitamin E daily, take estrogen. Sign a living will, think about long-term care insurance. This probably was the lowest moment of my visit. Long-term care insurance? These people really think I might get this disease!

I must have done adequately on the tests. Staff members do not relay scores, but they do tell you if you are “normal,” or if you are showing early signs of Alzheimer’s. I’m still normal. But I will be back next year. I also have signed up for an auxiliary study, where I take a medication—a cholesterol-lowering statin drug or anti-inflammatory ibuprofen, I won’t know which—for three months, then have that lumbar puncture again to see if any of the disease markers have changed. Research suggests one of these might help delay the progress of Alzheimer’s.

I wish I did not have to worry about this. My mother had left me a note earlier, expressing admiration for how brave I was to volunteer. I’m not brave, I’m scared. It’s all the more real now, after my three-day visit. But I thank my father for setting the example of not taking this disease lying down.

My last day, I packed the bathrobe, which I used a lot, and the novels, which I did not. For a final time during this visit, I was buzzed through the door and returned to the outside world.

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WHAT WOULD YOU DO DIFFERENTLY IF YOU KNEW? I WOULD TAKE 1,000 MILLIGRAMS OF VITAMIN E DAILY, TAKE ESTROGEN, SIGN A LIVING WILL, THINK ABOUT LONG-TERM CARE INSURANCE.



South Entrance to the Clinical Center. The new entrance and lobby were built as the first stage of construction of the new Hatfield Clinical Research Center.

**B**udgeting in the Clinical Center is peculiar. The chief currency is space (of which nobody has enough) and full-time equivalents, or FTEs—that is, full-time staff positions. The size of the salary is not the point with an FTE so much as the number of full-time positions a particular unit is allotted—although departments have to come up with the money they need to cover their FTEs.

The Clinical Center's funding comes from the institutes, who essentially contribute money to a big slush fund for that purpose. The Clinical Center does not have its own appropriation from Congress, and from the day it opened there have been arguments about how much the institutes should pay for its support and on what basis. "In the years that I was executive officer and hospital administrator, I developed a routine that I referred to as the 'tin cup' approach," says Earl Laurence, former hospital administrator, referring to the tin cup of gentlemanly beggary. "The Clinical Center would get a certain amount through the usual budgetary formula from the institutes. You used the tin cup when you needed additional money, and the institutes would happily adjust the formula. Tin cupping worked for the Clinical Center fairly well in years when the institutes' budgets were increasing, but when they were not, you couldn't count on it."

The complex relations between the Clinical Center director and the various institutes bear a certain resemblance to marriage—a marriage with many wives, who control the purse

strings but don't necessarily agree about how to do so. The Clinical Center director has the difficult—one might say thankless—job of trying to keep all the institutes happy enough to give him enough money to keep the household running. Over the years, the formula for how they contribute has varied, depending partly on how much the institutes have and how much they value or use the Clinical Center. Typically, for example, the Cancer Institute and the Heart, Lung, and Blood Institute get sizeable funding and make substantial use of the Clinical Center, so their contributions have been larger than those of other institutes.

The Clinical Center is probably the most expensive hospital in the world—because it is organized not just to provide patient care but to support clinical research and provide patient care. At a retreat in Easton, Maryland, in the mid-1980s (the first of several Easton retreats), the institutes complained strongly that Clinical Center costs were rising too high, too fast. In fiscal year 1985 a new "fee-for-service" cost-allocation system was instituted, under which institutes were assessed a portion of the Clinical Center's costs based mainly on their patient activity in the immediate past quarter.

This system worked for a while, until funding got scarcer and the institutes began tightening their belts. The less they did in the Clinical Center, the less they paid, so the budget for the Clinical Center slimmed down dramatically. Patients stopped flowing in because institutes realized that the fewer the patients they brought in, the more they saved. Molecular and

THE CHIEF CURRENCY IN CLINICAL CENTER BUDGETING IS SPACE AND FULL-TIME EQUIVALENTS, OR FTES—THAT IS, FULL-TIME STAFF POSITIONS.

genetic science were hot and the institutes retreated increasingly into basic research, which costs less and is less heavily regulated. In about 1988, the number of patients admitted to the Clinical Center started declining, the average daily occupancy dropped, the outpatient numbers fell—and the fewer patients there were, the higher became the cost per patient. Everyone agreed on the need for the Clinical Center, clinical programs, and clinical research. But institute after institute began redirecting their intramural funds to nonclinical programs. Things would begin to turn around only when the formula changed.

In early 1995, Health and Human Services Secretary Donna Shalala asked her deputy administrator, Helen Smits, to review Clinical Center operations. Dr. Smits was to consider, among other options, privatizing the Clinical Center—reinventing it by contracting out all or some services to nongovernment firms—to save money and improve efficiency. Clearly something had to be done, because of poor building conditions, under-use of the facilities, high patient costs, and reduced funding for patient travel by the institutes. The patient census, at about 55-percent occupancy, was far too low.

The Smits report (*Opportunity: Revitalizing the NIH Clinical Center for Tomorrow's Challenges*), issued in January 1996, recommended, among other things, that the NIH actively seek funding for a new Center facility; explore contracting out more Clinical Center services as part of more flexible operations; find new ways to recruit patients to protocols; and provide a stable budget for the Clinical Center. Out of concern

for the declining patient census, the NIH, advised by a new Board of Governors, agreed to abandon the fee-for-service model of funding and replace it with a *school-tax model*, under which the institutes would pay because the Clinical Center was there, whether they used it or not. The same considerations led to the decision to build the Mark O. Hatfield Clinical Research Center, to replace the aging hospital. And many patients are finding their own way to the Clinical Center through information on the Internet; they are referring themselves.

Neither science nor medicine is organized the way the NIH categorical institutes are organized, says Laurence, and there is constantly talk of reorganizing the NIH into a more efficient organization. But on balance, it has been a successful organizational structure—not for the practice of medicine, not for science, not from a management school perspective—but for fundraising. It allows Congress and the public to express their support by identifying what's important to them. It takes a lot of basic science to make breakthroughs in cancer and heart disease and Alzheimer's disease. Congress and the public are prepared to accept that there is a lot of serendipity in basic science if basic science represents the underpinnings of something they are willing to support with tax dollars.

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MANY PATIENTS ARE FINDING THEIR WAY TO THE CLINICAL CENTER THROUGH INFORMATION ON THE INTERNET.

## SEARCHING FOR A DIAGNOSIS

As Dan Magrino's Pontiac approached the NIH Clinical Center, a security guard poked his head in the window. "I'll need the driver's license of everyone in the car," he said. It was December 8, 2002, and federal buildings were on high alert. A second guard banged his fist on the car's hood, yelling for Dan to open it, the trunk, and the glove box.

Already on edge, Dan fumbled to find the right lever, mistakenly trying the gas tank and the emergency brake as he grabbed for the licenses his wife and parents were thrusting at him.

Dan looked more like a deliveryman than a patient. At 37, he was a vigorous 5 foot 10, now weighing 220 pounds. "Where's your letter of admission?" the first guard demanded.

Dan's stress level was rising fast. The drive from his home in West Paterson, New Jersey, to Bethesda, Maryland, had taken less time than the search for a door in Building 10 that was open on Sunday, and he couldn't believe this research hospital was worth the bother, even if it held half the research beds in the nation. "The best place in the world?" he'd cracked on the ride down. "What are they going to tell you? We're sending you to the crappiest place in the world? It's a government institution. They're going to lock me in a cell, and I'll never be seen again."

Now he snapped, and a flood of profanity poured from his mouth. "Shut up! Shut up!" he screamed. "Do you think I'm here to blow up this place? I'm a sick man."

Sharon, his wife of seven years, rushed to intervene. "It's the Cushing's," she shouted over the din. "That's what's wrong with him. It makes him lose control."

Once the security guards backed off, Dan began to unwind, and he and his family entered the special world of NIH's Clinical Center.

Quickness to anger is one of the many symptoms of Cushing's disease and syndrome, a fairly rare glandular disorder. People who suffer from Cushing's usually travel a long, hard road to diagnosis and treatment—5 to 20 years is common. Dan's journey of just under a year hadn't been long, but it had been rough. He had earned the right to be suspicious, cynical, and frightened.

A scuba diver and an officer in the merchant marine, Dan had spent three years at sea, laying undersea fiber-optic cable. But in February 2002 he was laid off, an event he viewed as a godsend because he hadn't been feeling well. He was also worried about his recently acquired "pregnancy" belly—straight out, like a basketball. For many years he'd maintained a 34-inch waist and a weight of 175 pounds. Lately, no matter how much he dieted or exercised, he kept adding pounds. Clothes that fit one week were too tight the next. Now he would have time to go to the doctor.

Unconcerned, his primary physician told him to give up beer and blamed creeping middle age, an explanation Dan couldn't



Overnight, the previously fit Dan Magrino developed a pot belly and other symptoms of a condition known to occur mostly in children and post-menopausal women. And he had a heck of a time getting diagnosed. What do you do when your doctor says you're normal for your age and your body tells you something's gone haywire?

accept. But she didn't like his blood pressure, which had been well controlled but was now spiking as high as 173 over 110, even after she adjusted his medication. She ran tests to find the cause of the trouble. The results that came in over the next weeks raised the possibility of prostate cancer, diabetes, kidney problems, or liver disease.

The lack of progress frustrated Sharon. An aesthetician in a upscale beauty salon (in a Nieman Marcus department store), she chatted daily with a clientele of well-educated men and women. "It sounds like an endocrine problem," said one of them. Sharon reported this opinion, and Dan decided to ask for a referral.

Like her colleague, the endocrinologist he saw regarded middle age as the culprit, but she ordered more tests to rule out prostate cancer and diabetes. In June, she sent him to a nephrologist.

Throughout July Dan—now 200 pounds, despite running, lifting weights, and eating next to nothing—shuttled from one laboratory to another, his moods swinging rapidly from anxiety to depression to anger and back. Your kidneys, said the nephrologist, are fine, "but your blood pressure is still uncontrollable, and you're still gaining weight. I think you might have Cushing's disease."

Dan nearly fell off his chair. A month earlier Sharon had uttered exactly the same words. Rolling his eyes, Dan had asked where she'd earned her medical diploma. When she produced a printout from Web MD, he admitted that many of the symptoms fit—the weight gain around his middle, four stretch marks down his side that looked almost like cat scratches, the hypertension, the joint aches and pains, the muscle weakness, the increased irritability, the difficulty concentrating. He had lost his firm musculature and had a doughy look—the weight gain was showing in the face and neck. But he certainly didn't have the round chipmunk face, the ruddy complexion, or the Buffalo hump on his back. In the end he had dismissed the idea. Now he realized Sharon was right.

"This is not my field," the nephrologist said. "Go back to your endocrinologist."

The endocrinologist still didn't see Dan as a candidate for Cushing's. He didn't look like the Michelin tire man, and he was the wrong age and sex. (Cushing's is more prevalent among young children and postmenopausal women.) Reluctantly she sent him for a dexamethasone test.

In Cushing's disease and syndrome, the body produces too much cortisol, one of the "fight or flight" hormones secreted by the adrenal glands (located above the kidneys) to enable us to respond to threats and stresses. Usually blood levels of cortisol are highest in the daytime and low at night, but in Cushing's the complex regulating mechanism goes awry, and the cortisol level never goes down. The drug dexamethasone, a synthetic cortisol, ordinarily suppresses the body's regular cortisol production; if it doesn't, Cushing's might be the reason. Even with dexamethasone, Dan's cortisol levels were high, and the endocrinologist ordered another round of tests. The results again suggested Cushing's syndrome.

By now—September—Dan weighed 210 pounds. Determined to find a solution to his problem, he refused to buy new clothes and wore nothing but sweat pants. "I'm going to get my body back," he said. "I'm going to fit into size 34 pants."

Cushing's is a complicated glandular disorder, with several possible causes. Often it is medically induced: People can get it when they're taking high doses of steroids. When it occurs naturally, a tumor in the pituitary gland is responsible about 65 percent of the time, an abnormality in the adrenal gland about 15 percent of the time. In the remaining cases there is an "ectopic" tumor (from the Greek *ec*, "out of," and *topis*, "place") with the odd capacity to secrete ACTH (adrenocorticotropic hormone), which stimulates the adrenal glands to produce cortisol. Because ectopic tumors can grow anywhere, finding one can involve a search of the entire body.

Dan didn't understand what a gland in the brain had to do with a gland near the kidney, and he never thought he would be praying for a tumor, but that's what he did now, because if they found a tumor they could remove it and stop the Cushing's.

### You can't tell the players without a scorecard

Too much cortisol over too long a time causes the many symptoms of Cushing's. Cortisol—a hormone that allows us to react quickly to threatening or frightening situations—relies on a cast of characters and a delicate feedback loop for its production and regulation.

- The hypothalamus at the base of the brain makes corticotropin-releasing hormone or CRH.

- CRH stimulates the pituitary gland (which sits just beneath the hypothalamus) to produce adrenocorticotropin hormone or ACTH.

- ACTH goes to the adrenal glands (situated above the kidneys) and stimulates them to make cortisol.

The hypothalamus and pituitary contain a thermostat for regulating ACTH. When there is too much cortisol in the blood,

CRH and ACTH levels drop, which in turn lowers the amount of cortisol made by the adrenal gland.

When a tumor or abnormality arises in the pituitary or adrenal glands—or when an ectopic tumor makes extra ACTH—the feedback loop can't function properly and Cushing's develops.

A CT scan of his abdominal region revealed a mass the size of a large grape near his adrenal gland. When Dan asked the endocrinologist for a second opinion, she sent him to her mentor, the head of endocrinology at a large university teaching hospital. He looked at the CT scan and said, "We have to operate. This thing belongs in a jar of formaldehyde." The adrenal surgeon concurred. They ordered one last test: an MRI of the pituitary gland. It came back negative.

When Dan learned his insurance company might not cover the costs of an operation at the hospital he'd selected, the physicians and hospital agreed to waive all fees. Dan felt that luck was at last on his side.

On October 17, he awoke from surgery to find that the so-called tumor was actually a hemangioma (a benign vascular tumor like a cluster of varicose veins) on the outside of his liver. Harmless, the hemangioma was also unrelated to his symptoms, so there was no reason to touch it or the adrenal glands. But the surgeon had gone ahead and removed Dan's right adrenal gland, explaining later that that would lower production of cortisol. Since he found no tumor, Dan wondered why the specialist removed the right adrenal gland and not the left, and why he didn't just close Dan up and pursue a diagnosis. His body told him he still had Cushing's, and new tests confirmed that his cortisol was as high as ever.

While recuperating at home Dan gave his local endocrinologist a full report and asked her help getting a follow-up appointment with her mentor, who wasn't returning his calls. When he finally saw the expert again, he took his wife and his parents, "the FBI and the CIA."

The doctor said Dan's ACTH was high and recommended more testing. "Let's start by scanning your lungs."

Sharon exploded. "Why are you piece-mealing my husband?" she cried. "Look at him. He weighs 220 pounds, he looks like a bum, and he's driving everyone crazy. We're all nervous and concerned. Why don't you scan him all over at once? We've got to get this taken care of."

Dan struggled to maintain his composure. He knew these tumors were hard to find, but what the doctor was proposing would take forever. And would he trust him if a tumor turned up? At last he spoke. "I'm too nervous about this."

The doctor suggested they try the National Institutes of Health. "They're the definitive experts on Cushing's."

Again Dan fought for control. What was he doing here if the experts were in Bethesda? But he held his tongue and asked the doctor to make the arrangements.

The endocrinologist explained that he had to be accepted into a research protocol at the NIH; they would hear in about a week. But it was already November, and after a week had passed Dan decided to take matters into his own hands. The worst NIH could tell him was no, he reasoned. He had the name of the Cushing's doctor, and he found an 800 number for NIH on the Internet.

The employee who answered the phone found two Cushing's protocols and took Dan's information. Dan asked, "Are both protocols run by Dr. Lynnette Nieman?"

"Yes," she said. "Would you like to speak to her?"

He did. "I'm calling the Pope, Jesus, and Mary," recalls Dan, "and this wonderful, wonderful woman came on the line. No pompous attitude, no prima donna syndrome."

Nieman looked at his file, asked some questions, and suggested a screening visit. Dan was so grateful and astonished that he made her swear she was actually Dr. Nieman. Laughing, she told him, "Relax. We'll be in touch," and a few days later he had a date: December 8, just a week away.

Now December 8 had arrived, and Dan was finally inside Building 10. Nieman started her investigation from scratch: She was going to prove that he had Cushing's and pinpoint its origin once and for all. He would have an answer by Christmas. The staff of 8-West gave him literature to read, explained the tests and physiology, and answered all his questions.



Lynnette Nieman  
and her patient,  
Dan Magrino

THE DOCTOR SUGGESTED THEY TRY THE NATIONAL INSTITUTES OF HEALTH. "THEY'RE THE DEFINITIVE EXPERTS ON CUSHING'S."

Nieman, who has seen nearly a thousand Cushing's patients—as many as anyone in the world—joined the team at the Clinical Center in 1982. The Cushing's program, started a year earlier by endocrinologist Lynn Loriaux, neurosurgeon Ed Oldfield, and the gifted radiologist John Doppman, was focusing on diagnosis, which (as Dan could attest) is often extremely difficult. They had developed the tests that Dan would undergo, tests that were far more accurate than those he'd taken already (which often produce a false positive and falsely abnormal results).

They began with an improved version of the screening dexamethasone test, which gives a higher dose of the drug for two days to distinguish between true Cushing's sufferers and others with high cortisol levels, such as psychiatric patients. They also gave him synthetic CRH—corticotropin-releasing hormone—which stimulates the production of ACTH and cortisol in healthy people. In combination with dexamethasone, the CRH stimulates a positive test result in Cushing's patients, but the people with pseudo Cushing's do not respond. The results pointed straight to Cushing's.

It's not enough to confirm a diagnosis of Cushing's; a surgeon also needs to know where it originated. The NIH team had figured out an ingenious way to detect a tiny tumor in the pituitary—one that an MRI could miss. They could measure the level of ACTH in the blood flowing from the pituitary. The IPSS—inferior petrosal sinus sampling—test is an intrusive and somewhat risky procedure, but it is the gold standard for the differential diagnosis of Cushing's.

Radiologist Richard Chang put catheters into veins in Dan's groin and threaded them all the way up his torso and neck into the petrosal sinuses, which collect venous blood on either side of the pituitary. Simultaneously, he injected Dan with CRH to increase his ACTH production. When the catheters were in place, the team took several blood samples to measure Dan's ACTH. Awake throughout the two-hour procedure, he kept quiet only when the team asked him to hold his breath.

Again the findings were clear: He had “blazingly” high ACTH levels in the right petrosal sinus, indicating a tumor in the pituitary.

The next day Nieman and Oldfield visited Dan together. The neurosurgeon, whose success rate with Cushing's disease is 95 percent, explained the nuts and bolts of the operation to his wary patient. “I wouldn't be going into your head if I weren't sure,” Oldfield said as Dan fired questions at him. “Don't ‘what if’ me. I'm telling you, I'll get the tumor. Merry Christmas.”

Before the surgery on Friday, January 17, the anaesthesiologist, William Kammerer, came to explain his role, then visited Dan twice afterwards. “He didn't have to,” Dan said. “I was awake, and his job was done, but he's typical of everyone in this place. I haven't met one doctor, one nurse, one janitor, one food service provider who hasn't been an absolute pleasure and an absolute help.”

The surgery was over in two and a half hours. Normally Oldfield would have entered Dan's skull through the nose, carefully avoiding the overlying brain, and approached the pituitary from the bottom, cutting it in very thin slices, like a loaf of bread, excising the tumor, replacing the bottom piece of the pituitary, and leaving it to heal itself. But Dan's tumor had started externally, in the bone in front of the pituitary, had penetrated the dura (the thick outer membrane protecting the brain), and was just nicking the pituitary—enough to cause all his symptoms. Removing it required drilling out the bone and cutting through the dura and into the area of the pituitary that was affected. Dan was spitting out pieces of bone for months.

For Dan, the hardest part was still to come. Ever since the MRI that preceded his adrenal surgery, he had experienced claustrophobia. For years he had gone scuba diving and ridden a motorcycle in a full-face helmet, but suddenly “you put a hat on my head and I want to kill you.” Cushing's again.

What was worse, he felt he couldn't breathe. “I was afraid that if I didn't think about my breathing I would forget to breathe and die.” He'd had medication (Ativan) for anxiety during his MRIs at the Clinical Center, but after the pituitary surgery they would pack his nose with cotton tampons that would have to stay in place for three days. In anticipation he'd

### Improving diagnostic techniques

In exploring a complex syndrome like Cushing's, researchers in NIH's Clinical Center have the advantage of stable, long-term funding, which promotes interdisciplinary collaboration (in this case, among endocrinologists, neurosurgeons, interventional radiologists, and nurses skilled in caring for Cushing's patients) and draws patients from all over, who are willing to participate in research and follow-up over long periods in exchange for excellent medical care. Doctors all over the country are encouraged to refer patients who meet the criteria for research

protocols. But part of the NIH mandate is to make its discoveries available—and useable—in communities everywhere.

Created at NIH, the petrosal sinus sampling (IPSS) test is the best there is for diagnosing Cushing's, but it is expensive and hard to do. To translate their work into a more practical form, endocrinologist Lynnette Nieman and the late radiologist John Doppman decided to try sampling blood and measuring ACTH in a more accessible spot: the jugular vein.

They chose the jugular because it is just downstream from the petrosal sinus that drains the pituitary, and is technically easier to reach—all physicians learn to catheterize it during their training. It's also a safer place to work, well away from the brain.

Trials over the last few years have shown that this technique picks up about 80 percent of patients with Cushing's disease and pituitary tumors. It isn't quite as sensitive as IPSS, but it means more people can be easily tested and far fewer need the riskier procedure.

practiced holding his nose and breathing through his mouth, and his wife and parents had taken time off from work to help him cope.

As soon as he arrived on the neurology floor he started to scream: "I'm going to pull this packing out."

"Absolutely not," said an attending neurologist. "I'm telling you now: It comes out on Monday. Don't touch that packing, and don't ask me again."

For three nights Dan did not sleep. During the day, his nurse Jose, a big man, acted as the enforcer, doing everything in his power to make Dan comfortable. At night Dan begged his nurse Susie for painkillers and offered her \$1,000—then \$5,000—to remove the packing. When it came out on Monday, he finally calmed down.

Nieman can't guarantee that he's cured (about 12 percent of patients have a recurrence), Dan's adrenal and pituitary glands haven't started working again (that could take up to 18 months), and his joints still ache. But he has lost 35 pounds and once the cortisol was out of his system he began feeling and behaving more like himself again. His persistence and his determination to get to the root of his problem paid off. "I'm proud that I didn't listen when the doctors said there was nothing wrong with me," says Dan, "that, knowing my own body, I pursued an answer and called the NIH myself when the specialist said I might not get in."

He has to wear a medic alert bracelet to warn people about his condition. "I have to take things in stride," he says. "I get hyper very quickly, and I have to learn to control that tendency and put things in better perspective."

What does he think of the NIH? "There is no place like it," he says. "This is the best of America. I'm proud of this place, proud to see my tax dollars at work in this way. When Dr. Nieman told me as far as she was concerned I am her patient and Dr. Oldfield's patient for life, that's like a big kiss right on the lips."



John Doppman on left reviewing x-ray images.

## JOHN DOPPMAN, A GENIUS IN RADIOLOGY

The late John Doppman was a genius at invasive radiology and at endocrine radiology—the latter a field he started and defined, says investigator Lynnette Nieman. "There was nobody like him for coming up with ideas about how and where to put catheters and inject dye or chemicals that would make cells respond, then re-measure their response with a catheter in another place. And he implemented those ideas himself."

His career spanned the development of angiography and the growth of cross-sectional imaging techniques (ultrasound, CT scans, and MRI)—techniques he was quick to adopt. But use of imaging technologies was secondary to the challenge of radiologic diagnosis: He was first and foremost a clinician, trying to improve patient care and the efficiency of diagnosis.

He was a pioneer in developing spinal angiography (using injections of radio-opaque dye to visualize blood vessels and tumors) and endovascular treatment of spinal arteriovenous malformations. His research on the blood supply to the spinal cord led to the first textbook on the subject in 1969. "At 72 years of age, despite serious medical problems, he would don a lead apron to teach the 'new guy on the block' how to ablate an ectopic parathyroid adenoma or thread, with a steady hand, a barely visible microwire," wrote Andy Dwyer and Catherine Chow, in *Radiology*, after his death in 2000. Through "such dogged efforts and technical virtuosity" he invented and refined such techniques as petrosal venous sampling of pituitary tumors and techniques for localizing and treating small, elusive endocrine tumors of the pancreas, parathyroids, and adrenal glands.

He was also a superb radiologist. Giftedness in radiology is partly giftedness in pattern recognition. "Dr. Doppman could read any film," says Nieman. "On ectopic tumors you really need someone who understands what he is seeing and who can do the sampling. He would pull the files for the chest, the abdomen, and other areas, put everything together, and see things that didn't seem quite right. He was as concerned as I was about finding where that tumor was."

As ward chief of patient care in the early 1980s, Nieman asked Doppman if he would be willing, on Fridays—not every Friday, but whenever he could—to pull the films of their patients and review the radiology with the staff so they could see and understand the results. Endocrinologists order so many imaging tests that she thought the staff would benefit from learning more about radiology. He agreed and from 1984 through 1999, until shortly before he died, "every single Friday all year long—and he was rarely out of town—John got films pulled, read them ahead of time, put up the best ones, and told us about radiology."

"John's cheerful whistling could be heard wherever he went," wrote Dwyer and Chow. "Countless clinical associates at the Clinical Center benefited from John's expertise, as he was unstinting with his time and knowledge, guiding the training of many neuroendocrinologists and surgeons during his career. He would think nothing of spending many hours going over patient studies with clinicians, teaching while solving the diagnostic puzzles. The highlight of his week was endocrine rounds, where his imaging studies and wisdom held center stage. He was a consummate academic, insightful and articulate, with a contagious curiosity that found in every case a point of interest, a question to be pursued."



The organ transplant team, shown, left to right: Terri Wakefield, research coordinator; Kristina Rother, head, endocrinology group, transplant and autoimmunity branch; Christine Chamberlain, transplant clinical pharmacist; Allan Kirk, senior investigator, transplant section chief; Lori Purdie, nurse manager, 11-E; Boaz Hirshberg, staff clinician; Douglas Hale, investigator, head, bone marrow group; David Harlan, branch chief, transplant and autoimmunity branch.

# IMPROVING TOLERANCE IN TRANSPLANTS

One day in July 1998, Allen M. Spiegel, then scientific director of the National Institute of Diabetes and Digestive and Kidney Diseases (now its head), came to see John Gallin. “We need an organ transplant unit at the Clinical Center,” he said to the Center’s director. “There are terrific scientific opportunities in transplantation immunity and tolerance that we want to study, and we want to do it fast.” Research was beginning to make important breakthroughs that might improve patient care. Somebody had to develop and test them, and where better than the Clinical Center, the foremost practitioner of “bench to bedside” medicine?

Gallin and Spiegel walked across the hall to the office of David Henderson, the Clinical Center’s deputy director for clinical care. “How fast can we create a transplant unit?” Gallin asked.

Henderson quickly listed the necessities. In addition to space, infrastructure, and the national certification required to receive donor organs, they would need surgeons, nurses, and coordinators, all highly trained in transplantation. At the moment they had none. “When do you want to begin?” he asked.

“In May,” Spiegel replied. Ten months away. Nothing in the federal government ever happens that fast, but this was important, and speed in adapting to changing scientific protocols is one of the Clinical Center’s strong suits. Henderson

pulled together a planning team of everyone involved (especially NIDDK’s clinical director, James Balow, and administrative officer Barbara Merchant) and called in architects and the NIH’s renovation crew. They all rose to the challenge: working tirelessly, they created—on time and under budget—the first solely experimental transplant ward in the world, which in Spiegel’s words would “test the newest, most innovative ways of overcoming transplant rejection for patients with type 1 diabetes and end-stage renal failure, and ultimately other diseases.” Ten months later the transplant ward opened on 11-East. The first kidney transplant took place in June. Not bad for government work!

The NIDDK’s Transplantation and Autoimmunity Branch, under chief David Harlan, an endocrinologist and diabetologist, works mainly in two related areas. One involves Harlan’s specialty, diabetes, a so-called “autoimmune” disease in which the body develops an immunity to itself. The other is making it easier for transplant patients to accept another person’s organ, which the immune system regards as foreign and tries to reject. Transplant teams administer strong drugs—steroids, cyclosporin, and other immunosuppressive agents—to block or slow down the action of the immune system and make the environment more comfortable for the newcomer. But these drugs can have vicious side effects. As Allan Kirk, the transplant surgeon who heads this effort, explains, “An organ transplant dramatically improves a patient’s life, but it doesn’t make him disease free. He trades the disease he had for a condition of immunosuppression,” which can involve debilitating

and life-shortening medical problems. If the unit could figure out what happens immunologically, it could reduce the complications.

A 41-year-old former professional tuba player and naval officer with an MD and a doctorate in immunology, Kirk is interested in tolerance—that is, the ability of the immune system to accept something foreign. What he and other scientists would like to do is induce the immune system to adapt to the new organ—or the new organ to adapt to the immune system—so the patient could lead a normal life. This sounds as if the immunologists want the immune system to do something altogether contrary to its nature—to refrain from reacting to this particular new object while it goes on protecting the body from infection, trauma, and various other attackers and invaders. But, says Kirk, it isn't actually so strange. The immune system has the natural ability to be tolerant; it is always adapting to its surroundings. Consider pregnancy, when a foreign organism grows within a woman's body without being rejected. "I don't think there's a fundamental barrier that says we must reject foreign tissue," says Kirk. "Rather there are physiological incompatibilities between molecules from different people that we have to understand better."

The transplant team—which includes surgeons Douglas Hale and John Swanson and nephrologist Roslyn Mannon—has performed more than a hundred kidney transplants on human patients since the unit opened four years ago. Their patients come in with renal failure—end-stage renal disease brought on by diabetes, hypertension, autoimmune disease, anatomical anomalies, or other problems—and they are willing to forego the usual kidney transplant in order to try a cutting-edge procedure. Because Kirk is running several clinical trials, they can choose among more and less radical protocols, but they are always trading known risks for unknown ones. Some of his patients experience "rejection episodes," but "when you're doing a tolerance trial," Kirk says, "you're always going to walk very close to rejection. In fact some people think rejection is necessary because the immune system can't learn not to react to something it hasn't ever seen." If the experimental regimen fails, the team can fall back on conventional treatment.

## STAR PATIENT ELLEN BERTY



For 40 years, diabetes was just part of Ellen Berty's life. Diagnosed at the age of 13, she counted her carbohydrates and took the appropriate amount of insulin. She married, had a son, and went to work each day testing children for special education classes in Prince William County, Virginia. An active woman, she always found time to hike, ski, bike, and do aerobics. When she biked 50 or 60 miles in a day, she monitored her blood sugar and carried along food to eat to keep her blood sugar up. "I lived with my diabetes," she says. "I just accepted what I had to do."

But five years ago she began having disturbing episodes. Previously she had been able to sense when her blood sugar was low, but now, without warning, it dropped so quickly and drastically that she passed out—sometimes for three hours. It happened at home; on several occasions, Ellen's blood sugar dropped so quickly in the middle of the night that she was already having seizures when her husband Peter awoke and gave her a shot of sugar solution. It happened at work; her colleagues called 911 several times. And it happened when she was driving; though she checked her blood sugar before she got into the car, she would wake up at the side of the road with a glucose IV in her arm and the emergency squad beside her. (Miraculously she was never involved in an accident.) These events, called hypoglycemic unawareness, began occurring with alarming frequency.

Nothing her doctors suggested seemed to help. Then in the fall of 2000 Ellen read about the NIH and the Edmonton protocol for type 1 diabetes. She phoned immediately, started the extensive screening procedure, and was accepted into David Harlan's protocol. From the start, she was informed of the risks and told she could drop out whenever she wished. In February 2001, when she made the official

recipient list for an islet cell transplant, she purchased a cell phone so they could reach her the minute a donor with her blood type became available.

She was driving home on June 14 when the call came from nurse coordinator Lisa Viviano. "Ellen, we have a match. Can you get to NIH?"

Calmly she replied, "Yes, of course. I'll be right there." Then she let out a yelp.

She waited on 11 East while the lab team prepared the islet cells. Harlan explained the procedure's risks once more, and she signed an agreement saying she understood them. At 2 A.M. she was wheeled to a sterile room, where she nearsightedly watched the radiologist find her portal vein and Harlan inject the islet solution with a huge syringe. Her new islets produced insulin almost immediately. By 4 A.M. she was back in her room, with Boaz Hirshberg, an endocrinology fellow, monitoring her constantly. In the afternoon four people from the lab came up to visit. "We did the preparation, and we wanted to meet the person we did it for," one of them said as they wished her good luck.

At home she measured her blood sugar eight times a day, sending the results to her doctors, and stayed on insulin to spare her new islet cells as much stress as possible. As the islet cells settled into their new home, the insulin injections tapered off, and ten days later Ellen Berty was insulin free. She hasn't needed insulin since, making her the only NIH patient to reach insulin independence with just a single islet transplant. When she asked them why she alone so far has needed only a single transplant, they said, "That's why we call this experimental. We don't know yet."

Ellen has been lucky. She has avoided most of the risks that Harlan warned her about. She did endure enormous mouth ulcers the first year, some diarrhea, and infections: A tiny rash she acquired hiking in Yosemite turned into a systemic bacterial infection.

The quality of her life has improved tremendously. She no longer has to depend on other people—"I have my independence back"—and her friends and family no longer have to worry about her. "My hus-

band sleeps more soundly, and when an ambulance goes by the office everyone says, 'Not for Ellen any more.' I don't have to take 20 tons of food when I go skiing, and I don't have to adjust everything I'm doing to my diabetes."

Ellen, who sits on the NIH Patient Advisory Group, travels the country giving talks about her transplant. She's often asked if she would do it again. "Yes," she says, "in a flash, but it's not for everybody because of the side effects." She goes to NIH monthly to check the levels of her anti-rejection drugs, and whenever she has questions or the hint of a problem the transplant team wants to see her immediately.

"From day one, the treatment I got at NIH was superior and still remains that way," says Ellen. "I am part of that team, but it is an enormous team. The team includes the parking lot attendants, all the people I know in phlebotomy, all of the nurses and the wonderful doctors on my floor, all the specialists in dentistry and dermatology. I know many people because I've been involved in many procedures, and they have always given me a special sense that they really care about me personally and what's happening with me—not just as part of their experiment, but me personally. They're so caring, every single one. I think part of it is a lot of people are at NIH as a last resort. You know, they've tried their own doctors, they're willing to try something experimental because what they've been living with has not worked, and they don't know what else they can do. But I think part of the requirement to work there is that you have to really care about the people. The whole big team is another concept that is critical to their success, and it works for them. For me it's a wonderful place."

THIS UNDERTAKING IS HARDER THAN ROCKET SCIENCE,  
WHICH WAS BASED ON LAWS OF PHYSICS KNOWN FOR  
HUNDREDS OF YEARS.

Acting on a theory proposed by Polly Matzinger of NIAID, which says that the trauma and cell damage involved in transplant surgery actually stimulate the immune response, team members try to make the transplant as gentle as possible for both organ and body. They procure organs in the room next door to cut down on the time organs have to spend in the outside world; they preserve the organs in solutions that minimize cell damage from oxygen loss; they deploy drugs to support the molecules that are known to lessen trauma rather than focus on subduing T cells (which attack foreign bodies and are thought to cause rejection); and they use potent short-term drugs to inactivate the immune system while the graft is still damaged, letting it return to normal only after the graft has healed. By emphasizing the context, says Kirk, “we have been able to greatly reduce the amount of immunosuppression the patient needs.”

Because they are doing clinical research, the team monitors, tests, and follows patients much more closely than a regular transplant team. Their ongoing projects include trying to diagnose rejection early and analyzing patients’ lab results to predict who needs immunosuppression. Four years after surgery, 95 percent of their patients are at home and well, most are employed, and many are on small amounts of immunosuppression. Such good results are encouraging, but four years is still a pretty short time.

In the lab, Kirk and Harlan collaborate to produce agents that block one of the immune system’s signals for foreignness. The research group is also searching for markers and genes for tolerance. The connection between lab and clinic is extremely close. When Kirk does a biopsy, someone from the lab is in the room with him, ready to dump the sample directly into liquid nitrogen to preserve the tissue. As a result, the researchers get very fresh, high-quality samples—as well as respect for their patients, recognition of their responsibility, and motivation to continue their work.

Kirk’s boss and colleague David Harlan also has one foot in the clinic and the other in the lab, where their interest in transplant immunotherapy coincides. But instead of concentrating on the body’s reactions to outsiders, Harlan wants to

understand why and how the body decides that some of its own parts are foreign, a phenomenon seen in diseases such as lupus, multiple sclerosis, rheumatoid arthritis, and diabetes, Harlan’s passion. Inspired by the story of the discovery of insulin by Canadian researchers Banting and Best, he has been working all his professional life on type 1 diabetes, also called juvenile diabetes, an autoimmune disease that begins in childhood and affects about a million Americans. (Type 2, diagnosed more commonly in adults, affects about 15 million.) In type 1, the immune system sets about eradicating the insulin-creating cells (called beta cells) in the islet of the pancreas—and no one knows why. “We’re still figuring out the laws of the immune system,” says Harlan, “and at the same time we’re trying to manipulate them to our advantage.” As Allen Spiegel is fond of saying, this undertaking is *harder* than rocket science, which was based on laws of physics known for hundreds of years.

Type 1 diabetes is a terrible disease. To manage it, those who have it must monitor their blood sugar levels throughout the day and night, give themselves daily insulin shots, and adjust everything they eat and do, from schoolwork to sports. But even this careful attention can’t necessarily prevent its consequences: blindness, kidney failure, nerve damage, heart attacks, strokes, and a life cut short by as much as 15 years.

Harlan’s dream is to cure type 1 diabetes by coming up with a transplant therapy to replace the islet’s insulin-producing beta cells, or a treatment to prevent their loss to begin with, or both. This idea has been around for years, but getting it to work hasn’t been easy. In 1972, Paul Lacey of Washington University in St. Louis accomplished it in rodents, but success in humans was much more difficult than anyone imagined it would be. In 1999, a group headed by transplant surgeon James Shapiro at the University of Alberta in Edmonton reached a milestone by achieving insulin independence in seven consecutive islet transplant recipients. Their protocol introduced two key changes to the transplant procedure. To begin with, they replaced the steroids normally given to weaken the immune system, which they believe killed the freshly transplanted islets, and substituted a new combination of drugs tried by just one other transplant group. Next, they gave their patients more islet cells. None of their recipients achieved

insulin independence from one donor's islets; all required at least a second transplant, and some a third dose of islets.

In the fall of 1999, as Harlan and his new team were preparing to launch their own islet transplant protocol, using their own animal data, they heard about what was happening in Edmonton. They went to visit, along with Camillo Ricordi of the University of Miami, the specialist who developed modern islet isolation techniques, and Bernhard Hering of the University of Minnesota, another islet transplantation innovator. They were impressed, and they didn't let their egos stand in the way. Harlan says, "I thought since my mission here was to try to develop and perfect islet transplantation, the smartest and best thing to do was to see if we could reproduce what they'd done in Edmonton. We set up an isolation lab and wrote a protocol based 99 percent on theirs."

The only significant changes the NIH group made were concessions to safety (their protocol allowed recipients to receive islets from at most two donors, since each islet infusion is associated with some risk) and necessity (as a new center performing an unproven technique, they were allowed access only to those donor pancreases already declined by the surgeons as a transplantable organ). To date they have performed six islet transplants; three of their patients have been able to discontinue insulin for at least one year (the milestone for success), and all six displayed islet function for at least one year.

This giant leap forward captured headlines all over the world, and Harlan thinks it is worth the risks involved. But as a scientist he is committed to looking hard at the facts, and he can see that this method of doing islet transplantation is not the cure everybody wants it to be. Patients and their families, who struggle so mightily with the disease, find it especially difficult to hear that the technique has severe limitations. "It was very depressing for me and my colleagues here to start communicating that message," Harlan says, "but we had to put the moderating voice of realism back into the discussion. We began communicating the message 'Let's do this appropriately and cautiously, but let's also freely discuss the procedure's risks and the problems associated with the subsequent immunosuppression.'"

What are the problems?

- There aren't nearly enough donor pancreases to supply all the people with type 1 diabetes who need islets—only about 0.1 percent could benefit. To develop a new supply, NIDDK has established the Beta Cell Biology Consortium (BCBC), a comprehensive islet cell project that will provide information, resources, technologies, expertise, and materials to researchers around the world about how beta cells in the islets are formed. BCBC scientists are working on new methods to extract beta cells from the pancreas and to create islets from adult and embryonic stem cells.
- The drugs used to suppress the immune system and prevent rejection of the new islets cause serious difficulties in a sizeable proportion of patients. Harlan, Kirk, and others at the transplantation lab (and around the world) are beginning to make some progress with this thorny problem, but there is still a long way to go. "Breakthroughs" occur rarely in biomedical research and on an unpredictable timetable.
- The procedure itself is risky. An islet transplant isn't actually an operation; doctors don't replace the whole pancreas. It's more like a blood transfusion, where the physician infuses the islet cells into a tube specially trained radiologists have placed in the portal vein, a main vein that feeds the liver. Because the portal vein lies deep within the body, there is a danger of both bleeding and clotting. Both complications have in fact occurred, and both can be most serious.
- The procedure is expensive. Harlan estimates that the price tag for treating one patient for one year is more than \$100,000, a cost not yet covered by insurance.
- So far, there is no good evidence that this technique decreases the risk for diabetes-associated complications: kidney failure, heart disease, nerve damage, blindness, amputations, and premature mortality.

"BREAKTHROUGHS" OCCUR RARELY IN BIOMEDICAL RESEARCH AND ON AN UNPREDICTABLE TIMETABLE.

## TWO PATHS TO THE TRANSPLANT TEAM

David Harlan found his way to the NIH Clinical Center through a book, a movie, and the Navy. Like his engineer father, Harlan always wanted to understand how things fit together, but instead of studying engineering in college he studied physiology, the “engineering of biology.” He had no particular inclination to join the military, but when it came time to go to medical school the Navy offered him a scholarship to put him through. The Navy also provided him with an excellent career in basic and clinical immunological research. But what inspired his medical passion—improving outcomes for diabetes—was a movie, “Glory Enough for All,” about the discovery of insulin, and then the book, *The Discovery of Insulin* by Michael Bliss. Frederick Banting and Charles Best, the two Canadian physician-scientists he read about, became his role models. Small clusters of cells in the pancreas called the islets of Langerhans, which secrete the body’s supply of insulin, became the territory he would explore.

For eight years, the Navy Medical Research Institute and the NIH—across the street from each other, on Bethesda’s Rockville Pike—collaborated on islet cell research. The institutions still cooperate on research, but Harlan now works fulltime for NIDDK. And on the 82nd anniversary of Banting’s idea that led to the discovery of insulin, Harlan went to dinner with Michael Bliss, who was in town to do grand rounds at the Clinical Center.

Allan Kirk took a more circuitous route to the transplant ward. In college he took no science or math for the first couple of years; his passion was music and that’s all he thought about. He played tuba at the Tanglewood Institute, studied with the Boston



Allan Kirk: “Practice makes perfect.”

Symphony, and was essentially making his living as a professional tuba player. He decided to become a transplant surgeon one day when he was 20 and he and his wife were in a realtor’s office, looking for an apartment. Something told him he wasn’t going to spend his life playing the tuba, and he went back to college, teaching tuba to work his way through all the science courses he’d skipped the first time through. His father had been a botanist, and Kirk himself

had always done well enough in science classes—he’d just loved music and the humanities more than he’d loved science.

Nor was his experience as a tuba player wasted, in terms of transplant surgery. “People who grow up without an understanding of some performing art—be it sport or music or horseback riding—people who have not learned some discipline, don’t understand the connection between practice and performance,” says Kirk. “A lot of people go to medical school thinking that the gene on how to sew well is on the Y chromosome and they are just going to pick it up. When I’m trying to teach new residents how to do a procedure, I ask them, ‘How many knots did you practice last night?’ They look at me, puzzled. ‘Practice knots?’ If you talk to someone who has played the piano, they understand completely that there is such a thing as muscle memory and that there are rewards to practice. They also understand the concept of delayed gratification, which is something you definitely need in science.”

On the other hand, some interesting results are emerging. Harlan and his team have discovered—or “re-discovered” 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 planning protocols to explore these issues.

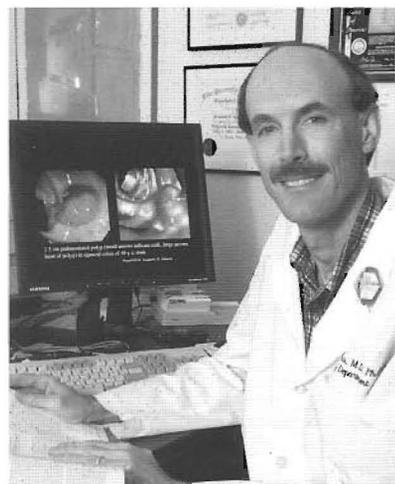
These are big questions, but Harlan believes in swinging for the fences. At the Clinical Center, he says, “we can ask important questions, big questions, that are difficult to address in other venues, and that’s what I think our mission should be. It minimizes the Clinical Center to say that it’s a national treasure; it’s an international treasure. It epitomizes all that’s best about America, because there’s no place else on earth that I’m aware of where resources are applied just to the general good.”

“This is the best place in the world to do science,” adds Kirk. “We’re trying to do it right, make sure the appropriate patient protections are in place, animal experiments are done with appropriate care, conflicts of interest are exposed. The arguments that win here are the arguments that the science is being done correctly, not the arguments based on profit or popularity. The Clinical Center is a resource that is incomparable in this country or anywhere in the world.”

### Virtual Endoscopy

Ron Summers is searching for ways to replace various forms of endoscopy (examining the interior of a body cavity) with more effective “virtual endoscopy,” using imaging techniques and computer power to produce images that look like what physicians see when they use an instrument to look inside the body. An endoscopy reveals accurate and important information (such as the presence of lesions), but it is expensive, time-consuming, and invasive. It can be uncomfortable—even painful—for the patient.

Ron Summers:  
Training computers



Summers, a clinical investigator in the Clinical Center's diagnostic radiology department, began with a study of bronchoscopy. Patients who needed a bronchoscopy to detect airway problems also got a special kind of CT scan that produced images similar to those produced by the actual bronchoscopy, except Summers never put a tube down anyone's throat. He found that virtual bronchoscopy was excellent at finding airway narrowings, especially combined with information from previous actual bronchoscopies. It was good at detecting three kinds of airway abnormalities: cancer, infection, and inflammation.

Toward the end of that research, he became interested in teaching computers how to identify abnormalities. The idea was not to replace radiologists but to help them, because the number of CT scans and images to be read is increasing faster than the number of radiologists. CT scans and MRI scans generate so much information—one study might generate 1,000 or 2,000 images—that a radiologist can never look at it all. Summers began writing mathematical programs (algorithms) to tell the computer how to identify the images the radiologist should look at—the ones most likely to reveal lesions.

It is possible to make virtual images of any part of the body in which a space is filled with air or fluid, so scientists who have been working on virtual endoscopy are now looking at virtual imaging of the bladder, sinuses, biliary and urinary tracts, and the fluid-containing spaces of the brain and inner ear. Because colon cancer is the second leading cause of cancer death in Americans, Summers set out to develop algorithms for colonography—that is, virtual colonoscopy. If radiology could do a better job of identifying the polyps thought to be precursors to colon cancer, screening could markedly reduce the incidence of that disease. In collaboration with the Mayo Clinic and the National Naval Medical Center, who both scan their patients and do colonoscopies for the protocol, Summers' team is developing software to find those growths.

"We know where the polyp is supposed to be, we find it, we mark its location, and we use that information to develop a computer technique that we think will find polyps. It generates thousands of possible polyps, so we identify the real polyps, train the computer to ignore the false ones (the false positives), and run the program again. It does much better, but still not good enough. Then we identify what radiologists see in a polyp. Well, a polyp looks like a protrusion from the wall of the colon, so we teach the computer to look for protrusions. Maybe the colon wall is thicker where the polyp is, so we teach the computer how to measure the thickness of the wall. We feed all the information in so we can teach the computer to think like a radiologist—except the computer doesn't get tired or grouchy or throw in the towel after it feels it's been given too many scans to read. A radiologist can read maybe ten scans a day—a computer can keep going.

Summers is currently running a clinical trial to see if his technology actually helps radiologists to find more polyps. Although medical imaging centers all over the United States are offering "virtual endoscopy," Summers feels the tests are still generating too many false positives—only one in five to ten possible abnormalities per patient turns out to be truly bad—to be in general use.

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## RON SUMMERS, HARNESSING TECHNOLOGY TO MEDICAL RESEARCH

Summers got hooked on computers as a high school student in the mid-1970s. Every day he spent an hour before school in a dismal book closet, hooked up to a main-frame computer he called up on a phone. "They actually had a computer in the back, but that was for the seniors; as a sophomore and junior, I wasn't allowed to touch it." Then at the University of Pennsylvania he was a physics major, doing work-study projects processing high-energy physics data on a computer. In medical school he got the radiology bug, saw how his techno-

logical interests could be brought to bear on medicine and began a PhD.

He had a practical bent and he wanted to do something that would help people. A fellowship exposed him to virtual endoscopy, which he started working on when he came to the Clinical Center. One of the Radiology Department's attractions was that radiologists at the Clinical Center had more dedicated research time than radiologists at academic centers and universities and no pressures to write grants (a huge stressor in

academic medicine). Tom Lewis, who oversaw the development of the Clinical Center's medical information system, got him the funds he needed to buy his first computer equipment. He is now on the Clinical Center's tenure track, has built a lab, and has a staff scientist, two post-doctoral fellows, and a graduate student working for him.



The new Mark O. Hatfield Clinical Research Center—named for the senator from Oregon—is connected to the Ambulatory Care Research Facility. The ACRF is the dark square building attached to the original Clinical Center, which was built in the shape of a Lorraine Cross. The whole complex—the CRC, the ACRF, and the Warren Magnuson Clinical Center—will be known as the NIH Clinical Center, or Building 10.



FOR THE PAST 50 YEARS THE CLINICAL CENTER HAS PROVIDED A PLACE WHERE THE BRIGHTEST, MOST CREATIVE DOCTORS IN THE COUNTRY COULD COME, TRAIN, AND BECOME LEADERS

# THE MARK O. HATFIELD CLINICAL RESEARCH CENTER

**F**ifty years is a long time for a hospital. It became apparent several years ago that the infrastructure in the Clinical Center was no longer adequate for cutting-edge research and patient care. Congress was persuaded that the time had come for a facility upgrade and in February 1999 the front entrance moved to the south side of Building 10 to allow for construction of the new Mark O. Hatfield Clinical Research Center. Named for the senator from Oregon and scheduled to open in 2004, the CRC will be connected to the Ambulatory Care Research Facility. The whole complex—the CRC, the ACRF, and the Warren Magnuson Clinical Center—will be known as the NIH Clinical Center, or Building 10.

The Clinical Center's traditional emphasis on flexibility will take a new form in the CRC. There are seven floors in the new building, but only four floors for patient care. Between each two patient-care floors is an infrastructure floor that accommodates huge ducts, venting, cabling, and supplies. Laboratories can become offices, or offices can become laboratories, and when patient facilities must change to meet unexpected needs, work can be done on the infrastructure

floor with minimum interference with activities on the patient floor below. The CRC's ability to change rapidly from a normal hospital setting to a high-containment facility will enable biodefense work, such as the development and testing of vaccines against agents of terrorism. Special isolation procedures will permit research on, and treatment of, patients exposed to infectious diseases such as SARS. (The hospital is also being built with "single-pass air," meaning that air comes in one end and goes out without being recirculated—a major investment to ensure good air quality and to minimize the presence of allergens or the spread of pathogens.) Spaces can also be modified to accommodate the special needs of patients with mental disorders or diseases such as Alzheimer's, for which special containment is needed.

The 870,000-square-foot complex will open with 240 inpatient beds and 90 day-hospital stations, an arrangement that can easily be adapted to allow more inpatient beds and fewer day-hospital stations—or the other way around. Instead of small, specialized patient units, there will be larger, more flexible units, equipped to facilitate both research and patient care. In the original Clinical Center, patient wards were

owned by the institutes. In the CRC, institutes will share wards—and there will be more flexibility in how patients are grouped.

At the start, there will be a pediatric unit, several oncology units, a surgical oncology unit, a hematology-oncology unit, and a bone marrow transplant unit. For some of the more specialized institutes, there will be a large medical-surgical unit, a medical unit, a surgical unit, a telemetry unit, and an infectious disease unit. Many requirements are being met in such a way that, if an institute changes its focus, the space can be quickly adapted to a new protocol requirement.

There will be 60 to 80 day stations for outpatient procedures and testing. There nurses will be able to administer chemotherapy, do blood transfusions, do serial sampling (giving or drawing blood every so often), monitor various kinds of daily rhythms, or do kinetic studies (studying the metabolism of a drug).

That the CRC was built after a period when the future of clinical research itself was in doubt can be credited partly to

former NIH director Harold Varmus, who, as one long-time Clinical Center researcher puts it, “could have put his chips into something else. He wouldn’t have minded the NIH being a degree-granting institution. He decided not to fight that battle, but fought the battle for a new Clinical Center, which says to the nation, ‘Finding a new suppressor oncogene is not really enough. You have to realistically translate that into something that affects people’s health and welfare.’” It’s much easier to do basic science than it is to do clinical research because of regulation and all the time involved in developing and documenting new treatments. The CRC is a powerful symbol of the revitalization of clinical research at the NIH.

“For the past 50 years the Clinical Center has provided a place where the brightest, most creative doctors in the country could come, train, and become leaders,” says NIH’s current director, Elias Zerhouni, another strong supporter of clinical research. “The Mark O. Hatfield Center represents the future of the Clinical Center. The challenge is to be equal to or better than our past—finding different ways to advance our knowledge of applied sciences and providing discoveries that will change the paradigm of how we treat diseases.”

### The Edmund J. Safra Family Lodge

At about the time the new CRC opens, the new Edmund J. Safra Family Lodge should be ready to open, to serve patients a long way from home. The family lodge will provide a comfortable retreat—a home away from home, patterned after the highly successful Children’s Inn—for patients participating in investigational and clinical trials and their families and caregivers. The lodge will contain 34 guest rooms, plus family gathering areas, including living and dining rooms, kitchens, playrooms, a library, exercise room, patio, and garden—

and telecommuting facilities to help families manage their lives while they are at the NIH. Construction of the lodge was made possible by a public-private partnership, with donations from the pharmaceutical industry and from Lily Safra, widow of the businessman for whom the lodge is named.

The Clinical Center tested the concept of a family lodge for adult patients with a six-unit pilot guest house in the old staff apartment house (Building 20). When that was



demolished to make way for the new CRC, a temporary guest house was opened in an apartment building on Battery Lane in Bethesda.

# PATIENTS: THE HEART OF THE RESEARCH TEAM

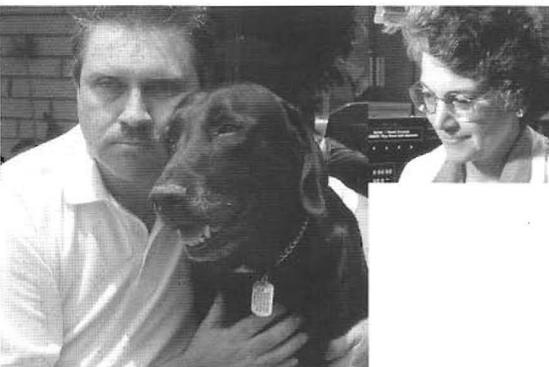
Needless to say, research in the Clinical Center requires the teamwork and support not only of scientists, physicians, and roughly 650 highly trained nurses, but also of specialists in social work, nutrition, rehabilitation, laboratory medicine, transfusion medicine, imaging sciences, pharmaceuticals, and palliative care, among other fields. With so many immune-suppressed patients in the building, and so many potentially toxic chemicals, even the people who clean patients' rooms and who work on the loading docks play critical roles in research and health care.

Patient after patient interviewed for this history expressed appreciation that an intelligent, skilled, and knowledgeable staff provides an intensity of care they had not experienced before: No test is unimportant, every result matters, and yet patients are not just the subjects of research. The staff shows both compassion and a sense of dedication. Patients and staff alike value the fact that what's going on in the Clinical Center is impor-

tant and will make a difference—and not just in the lives of current patients. Invariably they remark on staff teamwork and on one of the most unusual features of life in Building 10: that patients truly are considered partners in the research enterprise.

Clenton Winford II, a patient from Grand Prairie, Texas, came here for the first time in 1988 when the Clinical Center was just beginning to look at a hereditary condition called von Hippel-Lindau syndrome. VHL can affect the brain, the spine, the eyes, kidneys, and the pancreas. Clenton, whose father also had VHL, has had numerous operations in the Clinical Center, to remove tumors from his brain, spinal cord, pancreas, adrenal gland, and endolymphatic sac.

“Here at the Clinical Center we're all kind of learning things together,” says Clenton. “There is this sense of community and solidarity. You've got this confluence of all these people—both patients and health workers—who are trying to look for answers that we as a society have never known. The physicians are always willing to say, ‘This is what we know and this



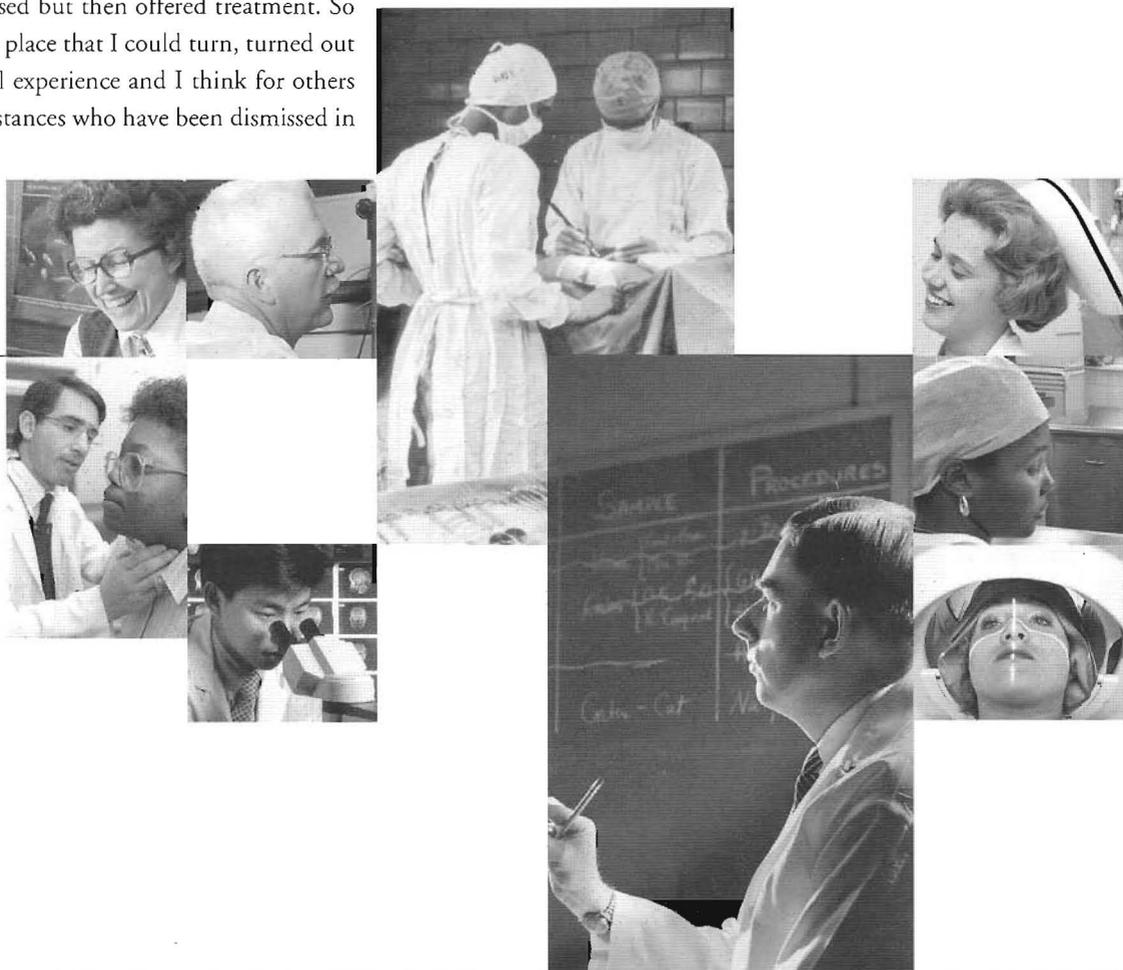
Clenton Winford II, with Herman

is what we don't know' and to admit that we're all kind of on this trek together. It's much more of a team environment, you might say, and we are part of the team. Here we are not only consumers but we are also producers. Some of us have been told, 'I'm sorry. There's nothing else we can do. Get your affairs in order.' At least coming here, quite often, we're given hope. 'We'll try this one more thing. We're looking at this, we'll try to develop this, and if you're willing, we'll do this together, and we'll all find out what happens.'"

"If I remember the story of Pandora's box correctly, the only thing left in the box was hope. And when I think about the Clinical Center, if I consider it to be a place of last resort for patients just like me, that's a wonderful thing. In my case, when I came here, my doctor had dismissed me. I didn't have anywhere else to turn. I was dreadfully ill, had no idea what I should do. I came here purely for research, to be diagnosed, and I was diagnosed but then offered treatment. So this being the last place that I could turn, turned out to be a wonderful experience and I think for others in similar circumstances who have been dismissed in

other locations and have been told there is nothing else we can do, 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. And in many, many instances, that one last chance proves to be a wonderful chance."

On July 9, 2003, Clenton played his guitar and sang for Clinical Center employees who gathered to celebrate the fiftieth anniversary of that very first patient being admitted to the Clinical Center. In August, not long after approval of his dissertation on special education and the awarding of his Ph.D. in political economy from the University of Texas at Dallas, Clenton got married and acquired a full new family.



# DIRECTORS OF THE CLINICAL CENTER

JACK MASUR	1948-51, 1956-69
JOHN A. TRAUTMAN	1951-54
DONALD W. PATRICK	1954-56
THOMAS C. CHALMERS	1970-73
ROBERT S. GORDON, JR.	1974-75
MORTIMER B. LIPSETT	1976-82
JOHN L. DECKER	1983-90
JOHN I. GALLIN	1994 TO PRESENT



## JACK MASUR

Clinical Center Director  
1948-51, 1956-69

Jack Masur was a large, strong-looking man who physically dominated a room. A physician and medical administrator, he was one of the few Clinical Center directors who was not also a working scientist. He prided himself on being a hospital administrator. During his time at the Clinical Center he became president of the American Hospital Association. He was also an honorary member of the Council of Teaching Hospitals (originally eight medical schools and their teaching hospitals, mainly on the East Coast, all engaged in biomedical research: Harvard, Yale, Cornell, Columbia, Johns Hopkins, the University of Rochester, Case Western Reserve, and the University of Chicago). Masur was an outstanding public speaker and politically well connected. When Medicare was being considered but hadn't become a reality, he was instrumental in convincing the nation's hospitals that it was a good idea that they should support.

That he had a strong—even autocratic—management style was probably critical to his role in the Center's history: He had pushed for creation of the Clinical Center, had seen that it got built, and considered it to be his hospital. After his first term as its director, he left to run the Bureau of Medical Services of the Public Health Service. He was almost appointed Surgeon General, and when he failed to win that appointment, the man who did moved him back to the Clinical Center, the place he loved. Between his two terms as director, John A. Trautman served as the first operating director (1951-54) and Donald W. Patrick (1954-56) as the next.

Part of his strength in running the Center was his closeness to Jim Shannon, NIH's director from 1955 to 1968, and to Shannon's deputy director, Bo Mider. His death in 1969 was sudden and unexpected. In the year after he died, before another director was appointed, Robert Ferrier served as acting director and, briefly, Jerry Block.



## THOMAS C. CHALMERS

Clinical Center Director  
1970-73

The physician-scientist Tom Chalmers was more scientist than hospital administrator, which was appropriate for reaching and building bridges to the institutes, engaging them in the joint effort of making the Clinical Center work effectively. Chalmers, who was credited with developing the statistical method called “metaanalysis” to merge data from different publications, took a leadership role in changing the procedures for clinical research. He enjoyed bringing medical students in and working closely with institute scientists. He left to become president and dean of the Mt. Sinai School of Medicine in New York.



### ROBERT S. GORDON JR.

Clinical Center Director  
1974-75

By his own choice, Bob Gordon had so brief a tenure as director that some old-timers forget he once filled that role. Indeed, he began to talk of leaving soon after taking the position and was better known for his role as clinical director of the National Institute of Arthritis and Metabolic Diseases. After his departure, Roger Black (also of the Arthritis Institute) filled in as the Center's associate director from 1975 to 1976.



### MORTIMER B. LIPSETT

Clinical Center Director  
1976-82

An outstanding laboratory scientist and clinical investigator, Mort Lipsett was undoubtedly better known for his work in reproductive endocrinology and as a physician-scientist than as a hospital administrator—but he provided strong, sound, effective leadership of the Clinical Center. An endocrinologist in the National Cancer Institute and then in the National Institute of Child Health and Human Development (NICHD), he made important contributions in reproductive, adrenal, and cancer endocrinology, especially in defining where the steroid hormones—especially the androgens and estrogens—were secreted and produced and in modeling their metabolic pathways. He had left the NIH for a position elsewhere when Don Fredrickson, NIH director from 1975 to 1981, recruited him back to fill the Clinical Center directorship.

The Ambulatory Care Research Facility, the concept for which had emerged under Tom Chalmers' directorship, was designed and constructed during Lipsett's term as director. MIS, the Clinical Center's pioneering computerized medical information system, which came online during his tenure, was probably years ahead of its time. It met great resistance, and many credit Lipsett with pushing the system through, credibly insisting that it become a reality. He had a gift for spotting scientific talent and a forceful personality. People knew where they stood with Lipsett. If you made an appointment to get approval for an \$800 summer lab assistant, he might announce that you had two minutes, listen, and, if it made scientific sense, say yes. He was decisive in large matters and small, doing *The New York Times* crossword puzzle with a pen, for example.

Having decided that he wanted to be director of an institute rather than of the Clinical Center, he resigned as Center director to assume directorship of the NICHD, later moving from there to the position he most wanted, being director of the NIDDK, in the January before his death in 1984. One day while he was playing tennis, he noticed that a lack of coordination made him unable to make a certain passing shot that he could always make before. He had a head CT scan done the same morning, which revealed a cerebellar lymphoma—a brain tumor that would take his life fairly quickly. The Lipsett Amphitheater, built as part of the Ambulatory Care Research Facility in 1981, was named in his honor.



### JOHN L. DECKER

Clinical Center Director  
1983-90

Like Jack Masur, John Decker was a notably large man, with the additional physical trademark of bushy eyebrows. Decker had been chief of the Arthritis Institute's rheumatology branch, a "clinician's clinician." His studies in rheumatic diseases earned him international recognition. He was a kind, friendly, sweet man, who found it hard to say "no." During his time in office, there was prolonged, intense conflict with the institutes about rising Clinical Center costs and how to pay for them. Many believe he was probably too nice a person to be director, at a time when being tough might have helped him take the pounding he was getting from the institutes. After a massive heart attack in his office and significant recovery time, he was never as physically able as he had been.

After Decker's term, his deputy, Saul Rosen, served as acting director from 1990 till 1994 under difficult circumstances—including two Easton (Maryland) retreats of institute and Clinical Center representatives to discuss the problems of Clinical Center costs and financing. A jovial person, Rosen was a wonderful storyteller and an avid fan of the opera, celebrating Verdi's birthday every year by ordering food from the deli for his staff. As a senior investigator in NIDDK's Clinical Endocrinology Branch, Rosen studied patients with hypogonadotropic hypogonadism, especially the hereditary syndrome associated with anosmia (the Kallmann syndrome). He and his colleagues were the first to demonstrate ectopic production of certain placental proteins (chorionic gonadotropin and its subunits, placental lactogen, placental alkaline phosphatase, SP-1) by nontrophoblastic tumors *in vivo* and *in vitro*.



### JOHN I. GALLIN

Clinical Center Director  
1994 to present

John Gallin has provided strong leadership both for the clinical staff and for the institutes' clinical programs, steering the Center through a period of crisis in clinical research into a period of revitalization. Backed in his efforts by strong support for clinical research by NIH directors Harold Varmus and Elias Zerhouni, he has helped renew the atmosphere of teamwork and collegiality that has long characterized the work done in the Clinical Center. The strength of his own work as a physician-scientist has added to his credibility as director. He had been an outstanding scientific director in the National Institute of Allergy and Infectious Disease and chief of its Laboratory of Host Defenses. Having come to the job from a strong background in research, Gallin has been able to represent both basic science and clinical research in his leadership of the Clinical Center. He took clinical research conducted by Clinical Center staff "out of the closet" and brought it to the outstanding level seen in NIH institutes and other NIH centers. He established annual strategic planning for the Clinical Center and strengthened patient representation in Clinical Center decision-making. He instituted a curriculum for training clinical investigators, oversaw the development of a new clinical research information system (CRIS), and strengthened the procedure for writing and reviewing clinical protocols with the development of a new informatics tool (ProtoType) to help clinical investigators. He also led the Medical Executive Committee to write "Standards for Clinical Research" for intramural programs. He instituted a curriculum for training clinical investigators and introduced distance learning tools to give NIH investigators an opportunity to receive a master's degree in clinical research and to bring NIH faculty to institutions (such as Duke University) in the United States and abroad. He has overseen the design, construction, and activation of both the Mark O. Hatfield Clinical Research Center and the Edmund J. Safra Family Lodge—the physical symbols of a period of renewal in clinical research.

# ACKNOWLEDGMENTS

This brief and incomplete history is a mere sampler of what has gone on in the Clinical Center. It is a participatory history, with an emphasis on interviews and oral histories and a de-emphasis on documents, especially about official meetings.

I am grateful to the very busy people who found time for me to interview them over the course of a year: James S. Alexander, Harvey Alter, Bruce Baum Jr, Ann Berger, Ellen Berry, Dale Boggs, Roscoe Brady, Eugene Braunwald, Michael Brown, Floride Canter, Dennis Charney, Al Cohen, Vince DeVita, Andy Dwyer, Bill Eckelman, Steve Epstein, Adrienne Farrar, Tony Fauci, Leonard D. Fenninger, Howard Fine, Ray Fitzgerald, Emil (Tom) Frei III, Bill Gahl, Joe Gallelli, John Gallin, Lynn Gerber, Marc Gladwin, Joseph Goldstein, Fred Goodwin, Phil Gorden, Richard Gregg, Shirley Gregg, David Harlan, Clare Hastings, Lee J. Helman, David Henderson, Jean Herdt, Andrew Himelfarb, Carol Hughes, Heidi Hughes, Daniel Kastner, Stephen Katz, Allan Kirk, Ruth Kirschstein, Harvey Klein, Laura Krummenacker, Marybeth Krummenacker, Carl Kupfer, Earl Laurence, Claude Lenfant, Tom Lewis, King Li, Jake Liang, Daniel Magrino, Harry Maléč, Thomas Macnamara (by e-mail), Saul Malozowski, Joan Marini, Henry Masur, Lynnerte K. Nieman, Ron Neumann, Bob Nussenblatt, Elaine Offutt, Marian Yoder Payne, Ann Plunkett, Alan Rabson, Joseph (Ed) Rall, Andrea Rander, Judith L. Rapoport, Barbara Rehermann, Jacob Robbins, Kimberly and Leslie Roe, Carol A. Romano, Steven A. Rosenberg, Stephen Rosenfeld, Alan Schechter, Steve Straus, Adrian Strong, Ron Summers, Larry Tabak, Tom Waldmann, Daniel Weinberger, Storm Whaley, Trish Whitcomb, Clenton Winford II, Bradford Wood, Lyman Wynne, and a handful of people whose names I am not listing at their request. No patients' stories have been told, or photos displayed, without their (and, for minors, their parents') express permission.

Several people were especially helpful in giving me overviews of the Clinical Center's history: Vince DeVita, Earl Laurence, Alan

Rabson, John Gallin, Phil Gorden, Dick Gregg, David Henderson, Harvey Klein, Carl Kupfer, Jacob Robbins, Carol Romano, Lewis (Bud) Rowland, Alan Schechter, Tom Lewis, and Tom Waldmann.

Special thanks to former Clinical Center nurse Ann Plunkett, who arranged for several mostly retired Clinical Center nurses to meet in her home for two group interviews, from which collective reminiscence I got a wonderful sense of the Clinical Center's earlier years. Participating in those sessions were Pauline Barnes, Joanne Beman, Shirley Butters, Regina Dowling, Alice Duncan, Maureen Estrin, Bernice Crossley Felix, Pat McIntyre Griffith, Joyce Harris, Pat Kelly Kirk, Alice Macynski, Connie Pavlides, Ann Plunkett, Martha Quayle, and Joan VanderMolen. I also learned about work in the Clinical Center at memorial services for Donald Frederickson and Roy Hertz, two major figures in Building 10's history. My apologies that time ran out and I was unable to interview many more people important to the Clinical Center or to include everyone's stories in this brief version of its history. My hope is that there will eventually be time to do more interviews and a fuller history.

Midway through working on this history, I agreed to "executive produce" a video for the celebration of the Clinical Center's fiftieth anniversary, once I learned that my friend Michael Dolan was available to *actually* produce it. Naturally I drew on Mike's interviews, too. Mike interviewed many of the people listed above, plus a few others: Allison Adams-Mclean, Donna (mother of Ashley) Appell, Alberta Bourn, Michael Gottesman, Ralph Horton, Ann Marie Matlock, Mary McCarthy, Tye Mullikin, Cokie Roberts, Griffin Rodgers, Jerry Sachs, Brianne Schwantes, Melissa Teasley, Lauren Wood, and Elias Zerhouni.

Victoria A. Harden, director of the Office of NIH History, was enormously helpful, as were her colleagues, Brooke Fox, Sarah A. Leavitt, Michele Lyons, Richard Meyers, and three Stetten fellows: Jessie E. Saul (for her research on blood safety), Melissa Klein (for her paper on the "Yellow Berets"), and Buhm Soon Park, for his

paper on the NIH intramural research program after World War II. The account of Clinical Center involvement in the AIDS crisis was drawn both from interviews with the people involved and from material on the Office of NIH History's invaluable website, where, among other things, I found wonderful oral history interviews and could hear the voices of researchers recalling the early years of AIDS "in their own words." The National Conference on Rare Disorders provided useful literature about rare diseases and a conference (held annually) that shed light on the partnership between patients with rare diseases and investigators at the Clinical Center.

Among others in Building 10 and elsewhere who provided help on this project were Joan Abell, Andrew Himelfarb, Robin Bell, Dianne R. Black, Margaret Brodtkin, Trish Brooks, Tanya Brown, Lolita Butler, Sara Byars, Richard Cannon, Floride Canter (and the other volunteers), Laura Cearnal, Thomas Chase, Usha Chaudry, George Chrousos, Holly Cintas, Debbie Cohen, Don Compton, Karen Diggs, Eileen Dominick, Amelia Douglas, Sylvia Douglas, Debbie Fatula, Susan Flowers, Maureen Gormley, Mark Haines, Mary Hestand, Celia Hooper, Stephanie Hudson, John Iler, Betsy Jett, Susan Johnson, Milly Kemp, Roberta Knox, Edward Korn, Sue LaRoche, Susan Leitman, Lynn Loriaux, Peter Lyster, Stacy Mason, Tara Mason, Donna Mayo, Helen Mays, Phyllis Morrow, Alba Murphy, Dianne Needham, Cindy Nye, John Parascandola (Public Health Service), Ellen Perella, Michael Rasminsky, Diane Rioux, Barbara Robinson, Ann Roth, Patty Runyon, Susan Rynders, Emily Salmon, Bob Shamburek, Betty Shory, Karen Sniezek, Maggi Stakem, Lucius Stewart, Lynn Warwick Susulske, Stephanie Kadel Taras, Julia Tossell, Diane Walsh, John Ward, Sarah Wernick, Jan Weymouth, and Frank Witebsky. Thanks also to the wonderful staff of the Children's Inn.

I am deeply grateful to John Gallin, the Clinical Center's director, who approved the project, adapted to a stranger's ways (including informal language), and responded quickly to a couple hundred e-mails with attachments; Colleen Henrichsen, who asked me to write this history, oversaw the project, tracked down photos, and appeared calm and reassuring as we raced to meet an impossible deadline; Elaine Ayres, who caught the spirit of capturing the past, energized the anniversary planning committee, and helped mother this project; Linda Brown, who did not shoot us when we missed innumerable deadlines for getting material to the infinitely patient and thoughtful designer, Lynne Komai (of Watermark Design); Bill and Ernie Branson, for taking umpteen photos for this project, often at the drop of a hat; Julie Cowell and Ruth Elkin, who between them transcribed more than 100 interviews, with help from Joy Rabb and Karen Plunkett; Steve McNees, who did research and helped with computer technology; Margarita Dinora Hernandez, Sue McNees, and Marc Renard, who helped in countless essential ways; Linda Long, who copyedited the manuscript (and is not responsible for errors that crept in afterward); Robin Marantz Henig, who suggested me for this project and provided moral support and astute editorial comments in an early draft; Barbara Geehan, who granted permission to include the story of her experience at the Clinical Center, Marian Yoder Payne, for selections from her *Lancet* article; and Judy Sklar Rasminsky, a dear friend and wonderful writer, who in the mad rush to get the manuscript ready for an October research symposium literally drafted several parts of the manuscript, using my research and interviews—including the pieces on Roscoe Brady, cystinosis ("A desperate mother finds hope"), Osteogenesis imperfecta, Cushing's disease ("Searching for a diagnosis"), and NIDDK's transplant program—and then spent a week helping me edit and stitch the manuscript together.

But thanks, most of all, to all of the people—past and present, staff and patients—who make the Clinical Center such a fascinating and worthwhile place to write about.

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