Message from the Director

Warren Grant Magnuson Clinical Center, NIH

July 6, 2003 marks the 50th anniversary of the first patient admission to the NIH Clinical Center. Press clippings from that day heralded a a state-of-the-art medical facility with unique research capabilities and a commitment to improving the nation's health. Oveta Culp Hobby, the Secretary of Welfare, remarked, "We are now carrying on in the United States the most intensive and widespread research attack on human disease that the world has ever seen." Fifty years later, the Warren Grant Magnuson Clinical Center remains a national focal point for clinical research.

Today we celebrate the patients and staff who have helped to make the Clinical Center a place of compassionate care and extraordinary scientific achievement. The Clinical Center is more than a large brick building. Throughout the years, dedicated scientists partnering with remarkable patients and devoted staff have created the perfect environment for long-term clinical research studies. As we pause to look at the past, our many accomplishments remind us of the potential for the future.

Thank you for making the Clinical Center a special place.

John I. Gallin, M.D.

CLINICAL CENTER 50th ANNIVERSARY CELEBRATION

CELEBRATING 50 YEARS OF CLINICAL RESEARCH

JULY 9, 2003 • 1–2 PM • MASUR AUDITORIUM

Master of Ceremonies	John I. Gallin, M.D. Director, Clinical Center
Presentation of the Colors	Armed Forces Color Guard United States Army Military District of Washington
Musical Invocation	Chaplain Karen M. Morrow Department of Spiritual Ministry, Clinical Center
Opening Remarks	Elias A. Zerhouni, M.D. Director, NIH
	The Honorable Claude A. Allen Deputy Secretary, HHS
	Michael M. Gottesman, M.D. Deputy Director for Intramural Research, NIH
Recollections of Senator Magnuson	Terry L. Lierman Former Staff Director, U.S. Senate Committee on Appropriations
Patients as Partners	Jerry Sachs Patient Advisory Group, Clinical Center
Volunteer Support	Howard P. Drew Blood Donor
Staff Reflections	Julie Kohn, R.N., M.S.N. Nursing and Patient Care Services, Clinical Center
	Stephen I. Katz, M.D., Ph.D. Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases
	Harvey J. Alter, M.D. Clinical Center, Department of Transfusion Medicine
"Bench to Bedside and Back"	A 50th Anniversary Video Presentation

(Left) The Ambulatory Care Research Facility (ACRF), dedicated in 1981, greatly increased the Clinical Center's capacity for outpatient care.

All guests, patients, and staff are invited to attend a reception on the south grounds of the Clinical Center. Reception music featuring David Rubinow's Bad Business Blues Band and Clenton Winford II.

Thank you to the R&W Association for the donation of anniversary balloons.

ON THE 50TH ANNIVERSARY OF THE NIH CLINICAL CENTER'S OPENING

"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

In building a 14-story research hospital with 500 research beds surrounded by twice that number of scientific laboratories, the idea 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. In 1953, 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 three clear-sighted Public Health Service officials—to strike a careful balance between basic and clinical research—prevailed, and the intramural program that centered on the patient base in the Clinical Center flourished. The NIH mandate was to produce not new knowledge for the sake of new knowledge but new knowledge that led to prevention, treatments, and, where possible, cures. At the end of World War II, "the NIH was an agency largely devoted to biology and chemistry, and mice were the major experimental subjects," writes Alan Schechter. 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."

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 importantly, 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 in Building 10 would remind them of the urgency of that mission.

(Left) In February 1999, the front entrance moved to the south side of Building 10 to allow for the construction of the Mark O. Hatfield Clinical Research Center.

[1]JAMA *180*: 1440, 1998.

The excitement of the new venture drew bright young investigators from all over the world, who came to learn, make their mark, and (usually) return to their home institutions. Given full support, they made discoveries at an amazingly rapid rate. The Center got off to a strong start partly because of a brilliant recruiting device: during the Korean and Vietnam wars, the doctor draft brought many bright young physicians to Bethesda for what they thought was a two-year stint, an alternative to military service. Many of the great names in medical science—physicians like Tom Waldmann, Vince DeVita, and Tony Fauci—got hooked on research and stayed.

The spectacular launching of clinical research in 1953 also spawned a generation of research scientists in the 1950s and 1960s who left and established new centers of scientific creativity throughout the United States. In what for decades was known (in classic government jargon) as Building 10, the Clinical Center became a center for studying and training in clinical research as much as it was a place to do clinical research. "For the past 50 years the Clinical Center has provided a place where the most creative, brightest doctors in the country could come, train, and become leaders," observes Elias Zerhouni, director of the National Institutes of Health. "When I go around the country, I'm amazed at the number of people who have trained here, who had their experience as clinician scientists at the Clinical Center here at NIH."

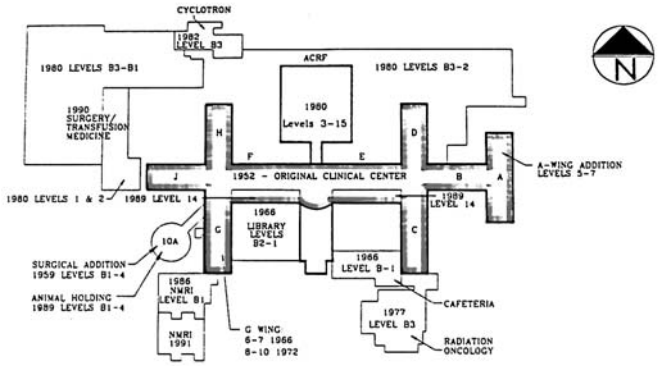
Roy Hertz admitted the Clinical Center's first patient—Charles Meredith, a Maryland farmer with prostate cancer—on July 6, 1953. Since then, NIH investigators have seen more than a quarter million patients. In the early years, there were far fewer institutes than there are today. The bed activation schedule 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 20 institutes and centers see patients. With 6,000 scientists on campus, the Bethesda campus contains the most powerful concentration of biomedical scientists in the world.

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 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.

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, for safety and efficacy—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 and usually involve patients from all over the nation and sometimes the world. Many of them probably would not have been done if they had not been done in the Clinical Center.

Clinical Center's Changing Footprint



Building Elements – Gross Square Feet x 1000

1952	Original Clinical Center	1,302
1959/89	Surgical Addition (Bldg 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 I	11
1989	Solarium	6
1990	Surgery/Transfusion Medicine	37
		2,887
Recent Additions		
1992	A – Wing Addition	56
1991	NMRI Research Center – Phase II	10
		2,953

Building 10, which opened 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 one corridor and in the wings of the huge red brick building were laboratories; along the south corridor were patient rooms and a 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 concept 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 remains in a constant state of growth and renovation. Renamed the Warren G. Magnuson Clinical Center in 1979, 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 day hospital stations), the need for patient beds in the hospital declined to the current steady-state level of about 240 beds.

The newest addition to Building 10 is the Mark O. Hatfield Clinical Research Center (the CRC), also named to honor a senator, opening in 2004. The CRC will allow rapid changes in hospital settings—for example, to accommodate patients with special needs or disease conditions that require isolation. The Magnuson and Hatfield Centers combined will be the NIH Clinical Center—all still part of Building 10. Aiding in the renewal promised by the Hatfield Center are two buildings that support patients and families in the Clinical Center, the Children's Inn and the new Safra Family Lodge (also opening in 2004).

A short list of research advances that have taken place in the Clinical Center would include the following:

- First cure of a solid tumor with chemotherapy
- First chemotherapeutic cures for childhood leukemia and Hodgkin's disease
- First use of immunotherapy to treat cancer
- Evidence of a genetic component in schizophrenia
- First successful replacement of a mitral valve
- Use of nitroglycerin for acute myocardial infarction
- First controlled trials of lithium's effect on depression
- Analysis of the disorders of lipid metabolism and the pathogenesis of arteriosclerosis
- Immunosuppressive therapy for nonmalignant diseases (lupus, Wegener's granulomatosis, midline granuloma)
- Use of interferon gamma to reduce bacterial infections in chronic granulomatous disease
- Enzyme replacement to treat Gaucher's disease
- Use of hydroxyurea to treat sickle cell anemia
- First computerized hospital information system designed to facilitate clinical research
- Description of the pathogenesis of AIDS
- Blood tests for AIDS, hepatitis
- Use of AZT as the first treatment for AIDS
- Reduction of transfusion-transmitted hepatitis from 30 percent to near zero
- First gene therapy (for adenosine deaminase deficiency)
- Use of magnetic resonance imaging to rapidly diagnose coronary artery disease in emergency room settings
- Immunosuppressive therapy for aplastic anemia

And that just skims the surface of clinical research achievements in Building 10. The mini-history in this program is a sampler of stories of research and patient care being gathered for a brief history of the Clinical Center, currently in preparation.

Pioneering in 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 bright 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 advances in cancer research came early in Building 10, for example, but 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 to Roy Hertz administering large doses of a new folic acid antagonist, known now as methotrexate, and was allowed 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.

In the 1960s, against strong external resistance from a cancer community that felt the science wasn't ready for it, the National Cancer Institute's Emil ("Tom") Frei and Emil ("Jay") Freireich introduced intensive combination chemotherapy for the treatment of acute lymphocytic leukemia of childhood. They were aware of preclinical studies of combination chemotherapy by Howard Skipper and Abe Goldin. They had seen Lloyd Law, one of the first NIH "mouse doctors," have some success administering combination chemo to leukemic mice. At a time when a diagnosis of leukemia was a death sentence, the two Emils decided to try combination chemotherapy in leukemic children. They 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. It had been shown that combinations of drugs had a synergistic, not just an additive, effect, so there was some reason to think combination chemotherapy would work, and they had strong support from their boss, NCI's Gordon Zubrod, who proposed dividing clinical trials with new cancer drugs into three phases.

In those days, mainstream cancer researchers considered surgery and radiotherapy to be the only appropriate treatments and strongly denounced Frei and Freireich's approach as "toxin of the month." But Frei and Freireich produced the first cure by chemotherapy of a childhood cancer and helped establish the intramural cancer institute as willing to take high risks for high rewards—based on evidence of a good chance an experiment will 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 NCI is testing the long-term effects of radiation therapy given long ago 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 Vince 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."

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 the 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).

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 importantly, 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.

Immunology: another frontier

Paralleling 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 and Bill Paul 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-like substances developed from a single line of B cells, targeted to a specific disease.

NIH became phenomenally strong in immunology. Some researchers began studying genetic immunodeficiency diseases, not because they're 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 NIAID have been developing immunosuppressive therapy for non-malignant diseases such as lupus. Shelly Wolff and Tony Fauci in the National Institute of Allergy and Infectious Diseases (NIAID) had produced the first "cure" of a formerly lethal non-neoplastic disease, Wegener's granulomatosis, by using low doses of cytotoxic agents. John Gallin and colleagues applied immunotherapy to boost host defenses to prevent infections in patients with chronic granulomatous disease of childhood, using interferon gamma, and Harry Malech has made important advances toward gene therapy for the same disease.

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. So would work done in the Clinical Center's Blood Bank.

Cleaning up the blood supply

The Blood Bank 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 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 precipitant 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, which led to the isolation of this medically important virus.

In the '50s and '60s, the technology for open-heart bypasses was in its infancy, and several units of blood were 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. "This all evolved at a time when such a repository was quite expensive and simply wasn't done, and this turned out to be a gold mine," says Harvey Klein, who became department director in 1984, the year the Blood Bank was renamed Transfusion Medicine.

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 because there were so many cases to prevent." 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 tests 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 it had developed a test it wanted him to run against his panel. The test worked; it broke the panel.

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.

"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 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.

Addressing the AIDS crisis

On 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 immune disorder 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 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—son of the Clinical Center's first director, Jack 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 at 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.

Scientists describe as "elegant" the work Fauci, H. Ciff 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 bone marrow and 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 were working together, routinely sharing observations. That AIDS was so complex made it both difficult and fascinating to study. Researchers in NIDR, 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 Clinical Center 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 thirty 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 NCI had discovered the first human retrovirus, human T-cell lymphotrophic 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 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.

"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 A. Rosenberg,** NCI, pioneer in cancer immunotherapy

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 the scientists the funds they sought. An important spinoff 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 Clinical Center decision-making. Gallin, when he later became Clinical Center director, strengthened that emphasis.

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 anticancer 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 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 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 NIH, like Baby Bear's porridge, was just right. An AIDS researcher at 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.'"

Studying genetic diseases

After 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. One of the first such studies was closely linked to earlier studies in the National Heart, Lung, and Blood Institute of the disorders of lipid metabolism and the pathogenesis of arteriosclerosis.

Among the most beloved of NIH researchers (and for a period NIH director), Donald Fredrickson 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 our 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 only places in the world that conducts 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 in 1968-70, 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 NHLBI) were intrigued by two young patients of Donald Fredrickson's.

As clinical associates, the two men spent one year taking care of NIH patients and a second year doing research. One of their patients 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). 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 ten 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 children 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 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."

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 Fredrickson and his colleagues studied, these were lipid storage diseases. Much of this work 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. Brady went on to describe the enzyme deficiencies in Nemann-Pick disease (1966) and Fabry's disease (1967) and with colleagues the specific defect in Tay-Sachs disease (in 1969). In 1991, he developed effective enzyme replacement therapy for patients with Gaucher's disease, and more recently, has been instrumental in getting approval for enzyme replacement therapy for patients with Fabry disease. Many researchers have followed his 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.

"I cannot say enough about the NIH Clinical Center. 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."

—**Marybeth Krummenacker,** mother of a cystinosis patient

Approaches to treatment being developed for these storage disorders include enzyme therapy, protein therapy, and gene therapy. Bill Gahl (formerly with Child Health and Human Development and now clinical director of the National Human Genome Research Institute) has saved many children from early death through his work on a rare disorder called cystinosis, a lysosomal storage disorder that destroys the kidneys and other organs—for which he has developed effective small-molecule therapy.

Biological approaches to cancer treatment

It was more difficult achieving cures with solid tumors than with liquid tumors. Biological approaches using the body's immune system are now being applied in 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. In working on a fourth therapeutic approach, Rosenberg's team in 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 that infiltrated the tumors 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 fighting 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 each specific patient along with 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.

Patient perspectives

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, and pharmaceuticals, 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 the Clinical Center history expressed appreciation that an intelligent, skilled, and knowledgeable staff provides an intensity of care they had not experienced before: no test was unimportant, every result mattered, and yet patients were not just the subjects of research. The staff also showed compassion and a sense of dedication. Patients and staff alike value the fact that what's going on in the Clinical Center is important 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 really are considered partners in the research enterprise.

"Here at the Clinical Center we're all kind of learning things together," says Clenton Winford II, a patient with von Hippel-Lindau syndrome who has been coming to the Clinical Center since 1988, when the National Cancer Institute began studying the hereditary condition. "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 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.'"

Patients are also struck by the building-wide sense of teamwork. "From day one, the treatment I got at NIH was superior and still remains that way," says patient Ellen Berty, who underwent an islet cell transplant when her diabetes became life-threatening. "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."

THE NIH CLINICAL CENTER

"There is no other hospital like it."

This mini-history of the Clinical Center is a sampler from a brief history of the Clinical Center being researched and written by Pat McNees. Yes, many stories and accomplishments have been left out and Pat is at work learning and writing about them. If you have a story or accomplishment to share, please contact the Clinical Center Office of Communications at 301-496-2563 or send an e-mail note to Pat McNees at pmcnees@compuserve.com, providing details about how to get in touch with you.

This is a participatory history, with an emphasis on interviews and oral histories and a de-emphasis on documents, especially about official meetings. In connection with this sampler, we thank Harvey Alter, Ellen Berty, Vincent DeVita Jr., Tony Fauci, Emil Frei, John Gallin, David Henderson, Harvey Klein, Ann Plunkett, Cokie Roberts, Alan Schechter, Thomas Waldmann, and Clenton Winford II, although many others were interviewed for it. The account of Clinical Center involvement in the AIDS crisis was drawn both from interviews with the people involved and from material on the NIH History Office's invaluable website http://aidshistory.nih.gov where, among other things, you can read oral history interviews and hear the voices of researchers recalling the early years of AIDS "in their own words."

Beacon of Hope: The NIH Clinical Center Through 40 Years of Growth and Change, by Richard Mandel, published for the Clinical Center's 40th anniversary, is available online at http://history.nih.gov/history/index.html, along with other valuable resources.

An online videocast of a symposium on the first ten years of intramural research in NIMH and NINDS can be found at <http://videocast.nih.gov/PastEvents.asp?c=4> for April 11, 2003. Let us know of any similarly rich sources of material about life and work in the Clinical Center that we might have missed.

COMING IN OCTOBER

CLINICAL CENTER 50TH ANNIVERSARY SCIENTIFIC SYMPOSIUM

THE PAST, PRESENT, AND FUTURE OF CLINICAL RESEARCH

TUESDAY, OCTOBER 14, 2003

8:30 AM	Introductory Remarks Roadmap for Clinical Research		**Elias A. Zerhouni, M.D.** Director, National Institutes of Health
9:00 AM	**Cancer Therapeutics**		
	PAST	Proving the Point: The Cure of Advanced Cancer with Combination Chemotherapy	**Vincent T. DeVita, Jr., M.D.** Director, Yale Cancer Center
	PRESENT	Monoclonal Antibodies and Systemic Radioimmunotherapy	**Thomas A. Waldmann, M.D.** Chief, Metabolism Branch, NCI
	FUTURE	The Development of Immunotherapy for the Treatment of Patients with Cancer	**Steven A. Rosenberg, M.D., Ph.D.** Chief, Surgery Branch, NCI
10:45 AM	**Cardiovascular Disease**		
	PAST	Myocardial Ischemia	**Eugene Braunwald, M.D.** Chief Academic Officer, Partners Health System
	PRESENT AND FUTURE	Genomics, Devices, and Cardiovascular Medicine	**Elizabeth G. Nabel, M.D.** Scientific Director for Clinical Research NHLBI
11:45 AM	**Clinical Applications in Neuroscience**		
	PAST	The Modern Era of Psychopharmacology: The Role of the Clinical Center and NIMH	**Steven M. Paul, M.D.** Group Vice President Lilly Research Laboratories
	PRESENT AND FUTURE	Multiple Sclerosis: A Story of Remarkable Progress	**Henry F. McFarland, M.D.** Director, Clinical Neurosciences Program, NINDS

1:45 PM	The Molecular Basis of Disease		
	PAST	Gene Therapy: The Beginning	W. French Anderson, M.D. Director, Gene Therapy Laboratories University of Southern California
	PRESENT	Endocrine Disorders of Signal Transduction	Allen M. Spiegel, M.D. Director, NIDDK
	PAST AND PRESENT	The MPS: from Serendipity to Therapy	Elizabeth F. Neufeld, Ph.D. Dept. of Biological Chemistry David Geffen School of Medicine at UCLA
	FUTURE	Medicine in the Genome Era	Francis S. Collins, M.D., Ph.D. Director, NHGRI
4:00 PM	Infectious Diseases		
	PAST AND PRESENT	The Charge of the Yellow Berets: The Battle against Post-Transfusion Hepatitis	Harvey J. Alter, M.D. Chief, Infectious Diseases Section DTM, Clinical Center
	PAST, PRESENT, AND FUTURE	AIDS: Past, Present and Future	Anthony S. Fauci, M.D. Director, NIAID
5:00 PM	The Future of Clinical Research		John I. Gallin, M.D. Director, Clinical Center, NIH