

The NIH Clinical Center and the future of clinical research

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In 1947, the US Congress gave the American public a special gift—the Clinical Center at the National Institutes of Health (NIH). This gift aligned with the vision of Albert and Mary Lasker, who had successfully advocated for the US government to support clinical research. President Harry Truman laid the cornerstone of the NIH Clinical Center on January 22, 1951, saying, “Modern medicine must find ways of detecting . . . diseases in their early stages and of stopping their destructive force. That will be the major work of this clinical research center”¹ (Fig. 1).

At its opening on July 2, 1953, the Clinical Center was the largest hospital ever built specifically for clinical research, and it remains so today. It was truly a hospital within a community of laboratories. The criteria for patient admission were “how their presence will aid scientists and clinicians in basic laboratory investigations and clinical studies of the problems of cancer, mental health, heart disease and other longer term illnesses”².

For nearly six decades, the Clinical Center has admitted patients with untreatable or undiagnosed conditions, rare diseases or complex manifestations of more common ailments. Major discoveries from studies conducted at the center have had profound impacts on medicine and have provided hope for many patients. An extraordinary team of dedicated people—administrators, scientists, nurses, patient partners and myriad public servants—has made this work possible. As such, the Clinical Center’s mission has involved three core elements: patient partnership, clinical research and investigator training.

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Figure 1 President Harry S. Truman applying the first trowel of mortar to the NIH Clinical Center cornerstone, June 22, 1951.

Promises fulfilled

Patients as partners. Since the Clinical Center opened, more than 450,000 human subjects, including 56,000 healthy volunteers serving as controls, have participated in research projects. These partners in research are essential to the success of the Clinical Center. The late Susan Lowell Butler, a Clinical Center patient, described the Clinical Center as “this house of hope...the magical place where science and compassion come together to save our lives.” Providing help and hope is central to work at the Clinical Center.

Clinical research is risky business, and protecting human research subjects is the most crucial part. Indeed, patient protection has been important since the first meeting of the Clinical Center’s Medical Board in March of 1952. That meeting resulted in the development of the “Guiding Principles in Medical Research

Involving Humans,” one of which required that all potential research projects should undergo prior peer review by a special medical committee³. In 1966, the US Surgeon General drew from these principles when he requested in a memorandum that the heads of all Public Health Service–funded research institutions establish institutional review boards⁴. Today, the Clinical Center continues to work both within NIH and with the broader biomedical research community to ensure that the best interests of individual patients and of society are well-served by the clinical research process.

Clinical research: discovery of new diseases and new treatments. As an organization dedicated to medical discovery, the NIH Clinical Center provided a venue for groundbreaking ‘translational research’ well before the term became commonplace. The return to taxpayers for their investment in the Clinical Center has



Figure 2 The Clinical Center in 1954.

more than fulfilled the dreams of its founders who hoped the Clinical Center would transform medicine in many areas (Fig. 2).

In the 1940s, cancer was generally considered a fatal disease. During the following two decades, work at the Clinical Center led to three milestones that made treatment of cancer a reality. In the 1950s, a team led by Min Chiu Li developed the first cure for a metastatic cancer (choriocarcinoma): a prolonged course of methotrexate⁵. They were also the first to use a biomarker of cancer, human chorionic gonadotropin, to determine duration of treatment, and the method proved a more reliable predictor of treatment outcome than monitoring disappearance of symptoms. Shortly thereafter, Emil Frei and Emil Freireich were able to cure acute childhood leukemia with combination chemotherapy⁶, and, in the 1960s, Vincent DeVita and his colleagues showed that combination chemotherapy could cure Hodgkin's disease⁷. These monumental accomplishments, all by National Cancer Institute investigators working at the Clinical Center established that cancer can be cured, providing hope for patients and galvanizing the nation to increase support for cancer research.

Similarly, when the Clinical Center first opened, treatments for mental illness were largely ineffective or nonexistent. Highlighting the need for behavioral health research, 96 of the center's 500 beds were allotted to the National Institute of Mental Health. A major breakthrough occurred about a decade later, when Frederick Goodwin and his team at the Clinical Center showed in a double-blind trial that lithium carbonate was an effective treatment for depression and mania⁸. This early study gave hope to millions suffering from

mental illnesses and was an important forerunner in the development of new drugs for treating these diseases. Today, the Clinical Center is the world's largest resource for studying behavioral disorders, with groundbreaking studies in areas such as attention deficit disorder⁹ and schizophrenia¹⁰.

The 1960s was also when Donald Frederickson and his colleagues at the National Heart Institute discovered in patients a rare disease characterized by large, orange tonsils, hepatosplenomegaly and, often, premature atherosclerosis. They named the condition Tangier disease, after the island off the coast of Virginia where the patients lived¹¹. The study of these individuals, together with other patients with familial hypercholesterolemia, provided the link between blood levels of cholesterol and other lipids and atherosclerotic cardiovascular disease¹² and led to the use of blood lipid levels as an important biomarker of heart disease risk. Michael Brown and Joseph Goldstein, two young NIH investigators who were stimulated by Frederickson's patients with familial hypercholesterolemia in the 1960s, received the Nobel Prize in Physiology or Medicine in 1985 for "their discoveries concerning the regulation of cholesterol metabolism." Reflecting on their past work, Brown has remarked, "If we hadn't seen those patients at NIH, we would have never known about this illness, and we would never have worked on it"¹. Importantly, their work also highlighted that the investigation of the etiology of rare diseases can lead to therapies for more common ailments.

When AIDS emerged in the 1980s, a number of investigators at the Clinical Center quickly redirected their work to begin investigating what would become a devastating public health

emergency. Their research resulted in the first treatment of AIDS using zidovudine (AZT)¹³, the development of a screening test for AIDS¹⁴ that helped make the blood supply safe, and the observation that HIV can lie latent in individuals infected with the virus, which had important therapeutic implications¹⁵.

Today, the center continues leading the way in clinical research, supporting well-established programs in areas such as infectious diseases and cancer, as well as newer ones in areas such as obesity and undiagnosed diseases. The Undiagnosed Diseases Program admits patients with a wide range of phenotypes and uses genomics and other advanced technologies to identify the etiology of their illnesses. Studies in this program have already led to discovery of a new molecular pathway for the formation of vascular calcium deposits¹⁶. Capitalizing on extraordinary advances in genomics, imaging and other areas, Clinical Center researchers have developed new treatment strategies for kidney cancers based on genetic characteristics¹⁷, applied new imaging approaches to the diagnosis of prostate cancer¹⁸, used leptin to treat lipodystrophy¹⁹ and described autoinflammatory diseases and treated them by inhibiting interleukin-1 β ²⁰.

Training: sustaining the pipeline of excellence. Because clinical research requires a cadre of highly trained investigators, the Clinical Center works to sustain a 'pipeline of excellence' by training leaders in clinical and translational research. This legacy is evident in the broad national presence of more than 7,300 NIH intramural scientists who came to the NIH directly after their residency training, often with little or no experience in research. These young investigators were placed in an unparalleled community of mentors at the Clinical Center, including 27 future Lasker awardees and seven future Nobel laureates. Many young trainees have become leaders in academia and industry, and some remained to lead major NIH programs. As members of top medical societies, NIH alumni have a prestigious awards track record, including six Physiology or Medicine Nobel Prizes. Today, the Clinical Center, with over 460 principal investigators writing protocols, continues to serve as an important talent incubator and to feed the national clinical research enterprise.

Fifteen years ago, the NIH Clinical Center recognized that, with the international attention on protection of human research subjects resulting in increasing regulatory requirements, formal training in clinical research was necessary to complement trainees' hands-on laboratory- and patient care experiences. Responding to this need, the Clinical Center developed and globally disseminated a robust clinical research



Figure 3 The NIH Clinical Center in 2005.

curriculum. Notably, the Clinical Center has trained, using long-distance learning tools, more than 22,000 students on five continents, and its clinical research curriculum has served as a model for many training programs throughout the world.

A new vision

Recently, the NIH Scientific Management Review Board, a committee appointed by Congress, recommended a new vision for the Clinical Center: “The role of the NIH Clinical Center should be to serve as a state-of-the-art national resource, with resources optimally managed to enable both internal and external investigator use”²¹. The NIH embraces this recommendation and plans to make the Clinical Center’s resources accessible through new partnerships between intramural and outside investigators (Fig. 3). Examples of these resources are the Pharmacy Department’s Good Manufacturing Practices facility for formulating drugs; the Department of Transfusion Medicine’s cell products; and the center’s clinical research curriculum, its information-technology tools for authoring and managing clinical protocols²² and its access to special patient populations. The intent is that the Clinical Center will be positioned to enable clinical research on a broader scale than previously possible.

Without ready access to patients, carrying out a comprehensive clinical research agenda is impossible. Therefore, the Clinical Center will also participate in an aggressive campaign to engage the public in the clinical research process. A campaign of public education should start in early education and extend through higher education, especially medical, dental, nursing and other health-related curricula. Such a strategy is crucial for the future vital-

ity of clinical research: at some point, every citizen will become a patient, and recruiting sufficient numbers of patients to volunteer as human subjects is an increasingly serious bottleneck²³.

Moving forward

This new direction for the Clinical Center aligns with a key component of Francis Collins’s agenda as NIH director—to strengthen the continuum of translational research. The center will actively collaborate with the proposed National Center for Advancing Translational Sciences (NCATS) to help catalyze innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of diseases and conditions²⁴. The Clinical Center will continue to interact closely with the NIH network of Clinical Translational Science Awardees, an important component of NCATS. In addition, the Clinical Center will work with the new NIH Intramural Center for Regenerative Medicine. This initiative aims to create a world-class center of excellence for clinical applications of stem-cell technology (including induced pluripotent stem cells), and a major motivation for its founding is the potential for a powerful relationship with the Clinical Center. While pursuing these new directions, the Clinical Center will remain steadfast to its core mission and to the guiding principles that have fueled success in clinical investigation for so many years. Experience shows that a strong and viable infrastructure for clinical research relies on excellence in patient care to attract and fully support patient partners in clinical research, on specialized services and modern technology to enable investigators to pursue unique opportunities, and on a robust and

accessible curriculum to train the next generation of clinical investigators.

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