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Creating the Science of Medicine: A Centennial Essay

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THE ROCKEFELLER UNIVERSITY HOSPITAL

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CREATING THE SCIENCE OF MEDICINE

A CENTENNIAL ESSAY

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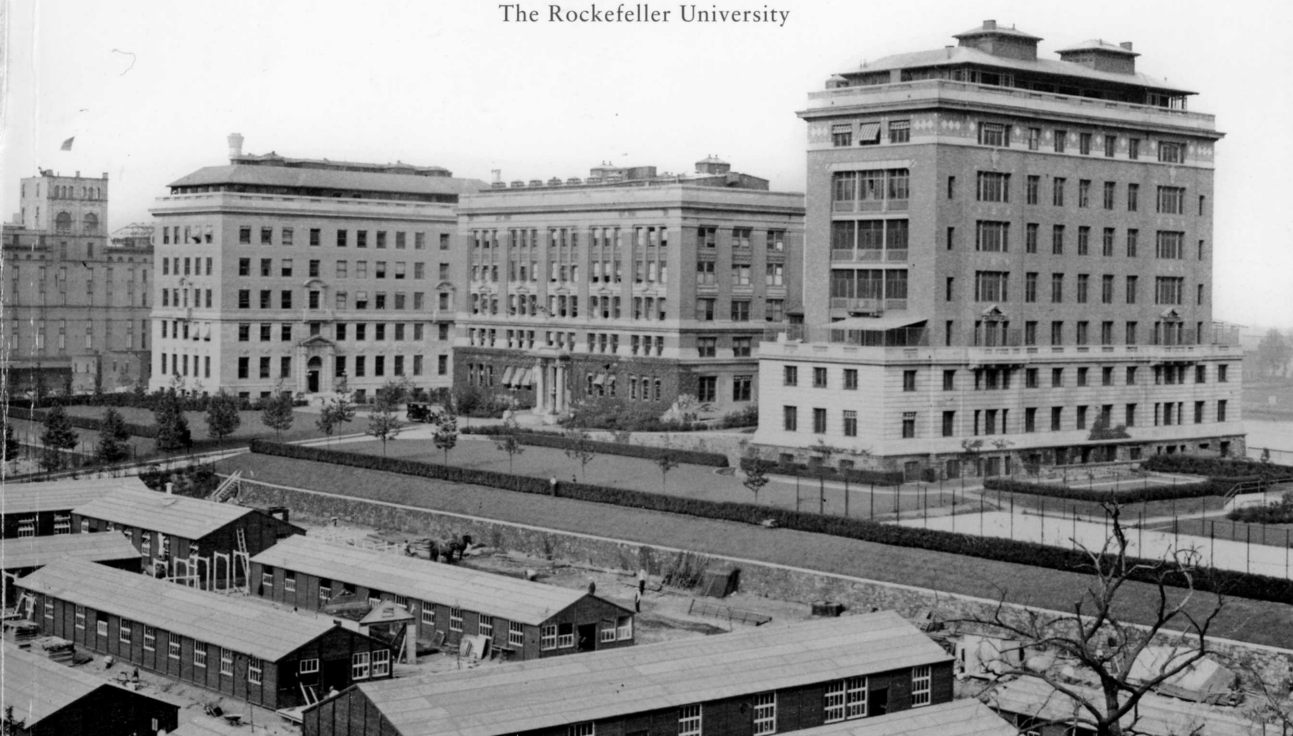
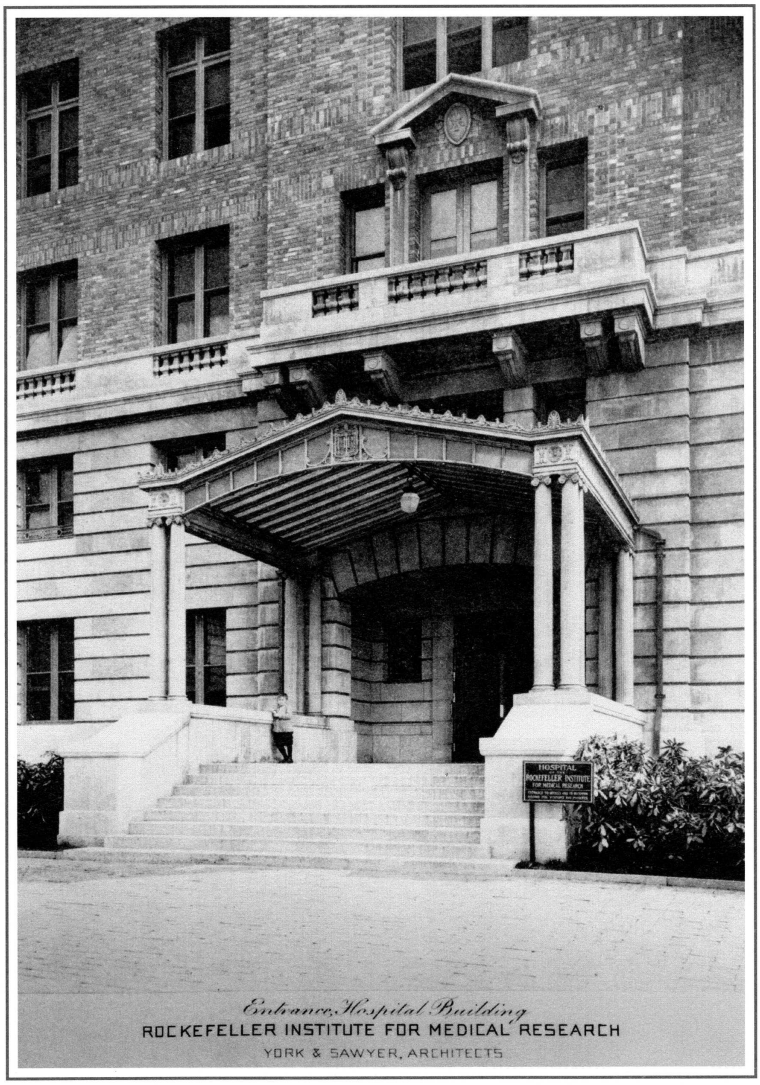




Entrance, Hospital Building

ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

YORK & SAWYER, ARCHITECTS

DEDICATION

This essay is dedicated to David Rockefeller, outstanding leader, visionary philanthropist and longtime friend. Since 1940, when he joined the Board of Trustees of what was then The Rockefeller Institute for Medical Research, David has served this community with great devotion and generosity, continuing a family tradition that began in 1901 when his grandfather, John D. Rockefeller, founded the Institute and then, in 1910, created its Hospital as the first center for clinical research in the United States. Succeeding his father, John D. Rockefeller Jr., as president of the Board in 1950, David guided this institution through an era of historic growth and change, including its transformation from Institute to University. Now, as we celebrate another milestone—the Centennial of The Rockefeller University Hospital—my colleagues and I offer our deepest gratitude to David for his seven extraordinary decades of service and commitment to the University and its Hospital.

PREFACE

The year 2010 marks the Centennial of The Rockefeller University Hospital, one of the great philanthropic achievements of the 20th century. For ten decades, the Hospital has played a central role in the development and growth of medical science by enabling physician-scientists to make intensive study of human biology and disease. With ingenuity and devotion, they have greatly enriched medical and basic biological science.

This account emphasizes the founding and first half century of the Hospital as it became a germinal center for clinical science. The second half of the century saw rapid change in medicine and health care with vexing problems, many yet unsolved.

I believe this presentation of historical details will be found accurate. The interpretation and search for relevance in this history may be questioned. Yet by focusing on the past, I offer this essay as a call to arms for maintaining science in medicine and in its basic discipline: patient-oriented research.

A REVOLUTIONARY IDEA

"The Rockefeller Hospital was established on the hypothesis that direct contact with illness is a strong force in igniting the curiosity and energy that can, from time to time, lead to great leaps in our understanding of human biology and disease."

An Observation Post Among the Sick

On October 17, 1910, the Hospital of The Rockefeller Institute for Medical Research in New York City was officially inaugurated and the next day opened for public viewing. The event of greatest relevance to physicians and clinical investigators took place the following week, with the admission of patient number one on October 26.

The Hospital in 1910. The small building to the left was the isolation unit, for studies of patients with infectious diseases.

Doctors George Draper and Alphonse Dochez were on duty that day to sign into the Hospital a severely ill, 40-year-old tailor. For some six years he had suffered from repeated bouts of "inflammatory rheumatism." Ten months prior to admission he had developed palpitations and shortness of breath, and five weeks before admission he took to bed with rapidly increasing disability. Dr. Draper found the patient to be severely ill, with a 102° F temperature, pulmonary edema and cardiac enlargement with loud mitral and aortic valve murmurs. In spite of treatment with codeine, digitalis, ice caps and mouth washes, by evening of the first day the patient's "pulse rate

On page 6: Walter Jacobs in the chemistry laboratory of Phoebus Levene.

increased, heart action became more and more tumultuous and suddenly ceased."[1] The postmortem analysis performed by Dr. Dochez uncovered aortic valve disease with acute and subacute myocarditis. A spherical, or coccal, bacterium in pairs and chains was grown in broth medium; thus, streptococcal disease, rheumatic fever and finally subacute bacterial endocarditis, common occurrences in those days, had claimed another victim.

Were this patient to enter a hospital today, he most likely would be saved or, better yet, the disease would not occur. Many of the advances in medical science that would assure this happier outcome were developed in the very same building on the East Side of Manhattan where the patient had succumbed. This progress can be attributed to the birth and development of an entirely new type of hospital, existing not only for the treatment of disease, but as an observation post among the sick. This remarkable resource allows physician-scientists to learn more about the nature of human illness and develop sciences for prevention and cure.

During the first century of the Rockefeller Hospital, streptococcal disease became treatable because of these events at the Hospital:

- A detailed classification and analysis of streptococcal types, developed by Rebecca Lancefield. One type inaugurated our patient's disease and another led to heart valve destruction and his demise.

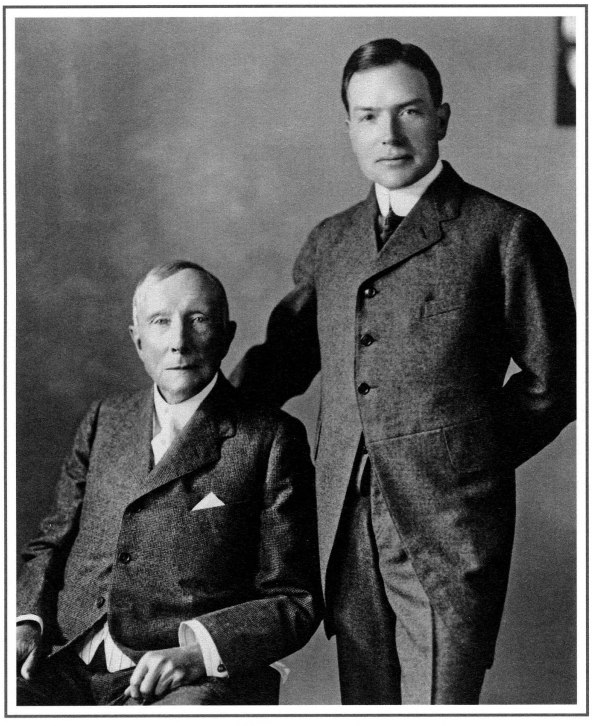
- A half century of work by physicians from Homer Swift to Maclyn McCarty, analyzing the immune reaction to the streptococci responsible for rheumatic fever.

- Pioneering use of sulfonamides and penicillin to eradicate streptococcal disease.

Over the years, other diseases were observed and studied in the Hospital, and many Rockefeller physician-investigators were trained to become the vanguard of scientific medicine in America.

One of them, Dr. Martin Henry Dawson, who worked in the Rockefeller laboratory of Oswald Avery from 1926 to 1929, made major contributions on the interconvertability of pneumococci[2] and then moved to the College of Physicians and Surgeons of Columbia University. While at Columbia, he obtained a sample of a penicillin-producing mold, sent from Oxford, England. With Gladys Hobby, he set up many large incubators, and with the assistance of Karl Meyer, extracted penicillin. On October 16 and 17, 1940, this penicillin was administered to two patients with subacute bacterial endocarditis—the first administration of penicillin to human subjects.[3] One of the two patients was believed to have received only 4,000 units of penicillin, yet may have improved.

Dawson and his group continued their work on two patients with subacute bacterical endocarditis and eight others with chronic streptococcal blepharitis, obtaining dramatic results that were presented at the American Society for Clinical Investigation meeting in Atlantic City on May 5, 1941.[4] The first page of the May 7 *New York Times* announced: "New Non-Toxic Drug Said to Be the Most Powerful Germ Killer Ever Discovered." Soon thereafter, penicillin in much larger amounts became a widely used, successful means of treating subacute bacterial endocarditis, thereby defeating the disease that Draper and Dochez could describe so well but had little power to treat. Dawson's clinical investigative talent begun at Rockefeller flowered in his work at Columbia. His co-worker Gladys Hobby described him as "a clinician with drive, purpose, dedication and vision."[5] Also in 1941, Dawson was diagnosed as suffering from myasthenia gravis. The enthusiasm and ingenuity of this remarkable physician-scientist, kindled at the Rockefeller Hospital, were



The Institute was founded through the philanthropy of John D. Rockefeller and the leadership of his son, John D. Rockefeller Jr.

extinguished by his death in 1945.

The Rockefeller Hospital was founded on the hypothesis that direct contact with illness is a strong force in igniting the curiosity and energy that can, from time to time, lead to great leaps in our understanding of human biology and disease. This was repeatedly proven at the Hospital, a special locale where the "prepared minds" of physicians uncovered new facts that often led to effective treatments. It is neither a hospital nor a laboratory, but a hospital-laboratory, which is celebrating its 100th birthday this year.

Although this was a first for America, the idea had been in the minds of European and British physician-investigators from the late 19th century onward. Sir Thomas Lewis, a British pioneer of clinical investigation, had this to say about his discipline:

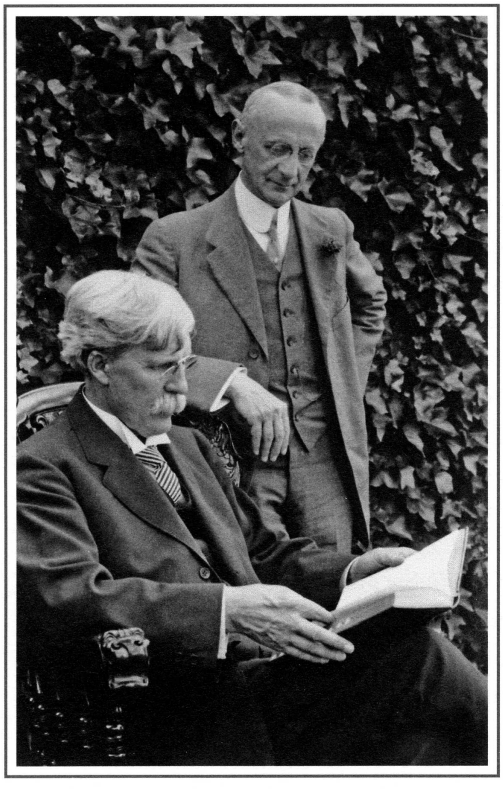
> It is essential that those who have held charge of patients and have studied phenomena in the living should themselves, and not through skilled deputies, explore the tissue changes that may underlie disturbed function.... To divide or attempt to divide medical research into ward research and laboratory research is narrow and harmful; it is a profound error to believe that there is any essential

> difference in general method, however different may be the technique. The close union of the two maintains throughout the work both the full perspective of the central problem in its practical bearings, and the inspiration that should drive to its solution. It is just this integration that is of so much consequence to the vitality of medical research; and this integration is, and always must remain, chiefly within the province of clinical science. He who can see the source of the problem, who can appreciate the fittingness of its final solution, is uniquely fitted to guide the whole train of thought and of enquiry.[6]

Sir Thomas Lewis's belief in the vital role of clinical investigation was put to the test by the creation of a hospital-laboratory at The Rockefeller Institute for Medical Research in October 1910.

The Founders

Who were the thinkers and philanthropists who built this first hospital-laboratory on our shores? The story begins with the Reverend Frederick Taylor Gates, a Baptist minister and secretary of the American Baptist Education Society, who met John D. Rockefeller Sr. when Rockefeller made gifts to various Baptist undertakings. Gates became such a close adviser to Rockefeller on educational, philanthropic and business matters that he was provided with a permanent office in the Rockefeller headquarters in New York. At a memorial service in 1929, lamenting Gates's death, John D. Rockefeller Jr. noted that "the enterprise in the educational and scientific field that lay nearest [Gates's] heart was the Rockefeller Institute, and this was not strange, for the Institute was conceived in his own mind; it was a child of his own brain. For



Frederick T. Gates (left) was John D. Rockefeller's chief adviser on philanthropy; Simon Flexner served as the Institute's first director.

years he had felt that the study of the cause and prevention of disease offers the greatest possible field for science to mankind and to his earnest advocacy of that belief, the founding of the Institute was due."

Simon Flexner, the first director of The Rockefeller Institute, speaking at the same memorial service for Gates, stated that "the project of an Institute of Medical Research grew out of a personal experience. He had a very dangerous illness when he was in the prime of life. Escaping with his life, he decided to acquaint himself with the state of medical knowledge existing at the time."[7]

To this end Gates, who was living in Montclair, New Jersey, turned to Elon Huntington, a medical student at the College of Physicians and Surgeons, in New York City. According to Gates:

> [Elon] was a lonely student without a friend and almost without an acquaintance in New York, and he used to come out to visit us in Montclair, often spending the night or the Sunday with us to relieve his loneliness. In this way he spent many hours with me. We used to take long walks together, and the subject of our conversation was quite naturally medicine, the subject in which he was most interested and in which he was then most intelligent. Thus, in simply entertaining Elon I found myself intensely interested in medicine.

My interest reached a point in which I determined to know something more definite about medicine, and in the spring of 1897, when Elon, if I recall it, was about to graduate, I told him that I would like to read medicine, and I asked him if he could suggest to me a book which a layman like me might be able to understand and to read with profit. I remember telling him that I did not want any ordinary medical books for the family. I wanted to know what the best doctors are reading; I wanted the literature that was being taught currently in the best schools to medical students. Was there any such book preeminently good? He replied that there was one such book; it was Osler's *Principles and Practice of Medicine* and said that this book was being taught to students in the College of Physicians and Surgeons and that it was written in a style so clear that with very slight knowledge of medicine I could read it with understanding and interest.

The book came into my hands at a fortunate moment. I spent a considerable part of the months of July and August following with my family in the Catskill Highlands, at Lake Liberty, in Sullivan County, New York, where I had leisure to give my undivided attention to Osler's book. I read the whole book without skipping any of it. I speak of it not to commemorate my industry but to illustrate Osler's charm. Osler's *Principles and Practice of Medicine* is one of the few scientific books possessed of literary attraction. There was a fascination about the style itself that led me on and, having once started, I found a hook in my nose that pulled me from page to page, and chapter to chapter, until the whole of about a thousand closely printed pages brought me to the end.

> When I laid down this book, I had begun to realize how woefully neglected had been the scientific study of medicine in the United States. Why this was so seemed clear. While other departments of science such as astronomy, chemistry, physics, geology, etc. had been endowed very generously in colleges and universities, medicine, owing to the commercial organization of medical colleges, had rarely been endowed, and research had been left to shift for itself, dependent altogether on such chance time as a rare spirit, without facilities, might steal from his practice. It became clear to me that medicine could hardly hope to become a science until medicine was endowed, and qualified men were enabled to give themselves to uninterrupted study and investigation, on ample salary, entirely independent of practice. To this end, it seemed to me an institute of medical research ought to be established in the United States. And here was an opportunity for Mr. Rockefeller to do an immense service to his country and perhaps the world. The idea took possession of me. The more I thought of it, the more interested I became.[8]

Gates also noted:

> Being preoccupied with other things, I introduced to Mr. Rockefeller a legal friend of mine, Mr. Starr J. Murphy, of Montclair, as qualified, though personally unacquainted with medicine, to make extensive inquiries of medical men in New York, Baltimore, Philadelphia, and Boston respecting the feasibility of the proposed Institute. The conclusions of the medical men were disappointing.

> Instead of the Institute I advocated, they suggested that Mr. Rockefeller give a small sum—I think it was twenty thousand dollars per year for ten years—to selected individual laboratory workers in various parts of the country. The plan proved utterly futile.[9]

During the last years of the 19th century, the Rockefellers kept Gates's plan in mind. Rockefeller Jr. remained interested and used every opportunity to become informed about medical research. In November 1900, he happened to meet Dr. L. Emmett Holt, a distinguished pediatrician and fellow member of the Fifth Avenue Baptist Church in New York City. Holt told him of an extraordinary recent event, the demonstration that an antitoxin had become available to treat diphtheria, a scourge of childhood. Holt emphasized that this was not a chance discovery, but the result of years of clinical and laboratory work. Very soon thereafter illness struck again, not to a Rockefeller adviser, but to the family itself.

John D. Rockefeller Sr.'s daughter Edith had married Harold F. McCormick in 1895 and produced the first Rockefeller grandchild, John Rockefeller McCormick. The darling of his grandfather, little Jack was stricken by scarlet fever in December 1900. Unfortunately, there was no treatment. When Jack died on January 2, 1901, Rockefeller grieved profoundly and promptly made known his decision to go ahead with plans for a medical research institute.[10]

The Board Convenes and the Institute Is Born

Rockefeller Jr., Holt and Christian A. Herter, a friend of Holt's, met in early March 1901, in Holt's home. Over dinner they reviewed various ideas as to how a medical institute might be formed. Holt

was a successful academic physician, soon to be appointed professor of pediatrics at the Columbia University College of Physicians and Surgeons. Herter, also a physician, had a deep interest in scientific investigation and, with personal wealth, had built a laboratory in his New York home. He was also well known to Rockefeller Sr. because both vacationed at Mount Desert Island, in Maine, where Herter had built another private laboratory for his investigations. Thus Holt and Herter became the central planners and began to identify others who might join them on a board for the Institute. On March 15, 1901,

The original Board of Scientific Directors, in 1909. From left: T. Mitchell Prudden, Christian A. Herter, L. Emmett Holt, Simon Flexner, William H. Welch, Hermann M. Biggs and Theobald Smith.

Herter asked William Welch of Johns Hopkins, with whom he had studied, to suggest members for the Board. They decided to invite Simon Flexner of the University of Pennsylvania, Hermann Biggs of the New York City Department of Health, T. Mitchell Prudden of Columbia University, and Theobald Smith, a student of animal diseases who had recently been appointed to a Harvard professorship. (Further details on the founding and early history of the Hospital are available in excellent publications.[11, 12, 13, 14])

All appointees to the Board were "Old Turks," the appellation for members of the Association of American Physicians, a small, select group of scholars of disease that was founded in 1885. "The heart of medical learning was what the membership was seeking."[15] In 1908, a much larger group of "Young Turks" founded the American Society of Clinical Investigation, under the leadership of Samuel Meltzer at Rockefeller. (In those days, many youthful surges of vitality took the name "Turk" from contemporaneous efforts to modernize the Ottoman Empire.) The Rockefeller Hospital at its start and in its first century was well represented in the membership and leadership of the Turks. The linking of science and medicine was very much in the air, and the new Rockefeller Institute was poised to lead the way.

The Rockefeller Board began working together closely. In late April 1901, Holt, Herter, Biggs, Prudden and Welch met during the annual gathering of the Old Turks in Washington, D.C. At their meeting in the Arlington Hotel, Welch, then president of the Old Turks, was appointed chairman of the new Rockefeller Board. They approached Theobald Smith to become the first director of the Rockefeller Institute laboratories, but Smith felt he could not leave his post at Harvard, and the Board turned to Simon Flexner.

On June 14, 1901, The Rockefeller Institute for Medical Research was formally incorporated. The *New York Times* reported: "The new institution is to be wisely and conservatively managed." Commenting

on the Board, the *Times* noted, "they are scientific men working in the scientific spirit and that spirit is not concerned with impressing the multitude."[16] Initially, the Board worked slowly, carefully and deliberately outside of public view. Welch wrote to research leaders advising them of the new Institute and the availability of a fund to assist them or special students. Twenty-three grants of $250 to $1,500 each were given during the program's first year of operation. The number of grants was slowly decreased over the years and, by 1917, they were discontinued.

Offers were made by several universities and by the New York Department of Health to house the Institute and link it to an existing organization. The Board elected, however, to create a totally independent, free-standing research center. This decision reflected a strong wish to preserve the freedom of the Institute's investigators, who might be of various temperaments and eccentric dispositions, perhaps not suitable for university life, but nevertheless possessed of great creativity and ingenuity.

In the fall of 1903, the newly appointed director, Simon Flexner, left New York to spend a year abroad studying the structure of European research laboratories. He also wanted to acquaint himself with the developing science of biochemistry, which he believed would be fundamental to research at The Rockefeller Institute. When he returned in the fall of 1904, space for temporary laboratories had been acquired in brownstone buildings at 127 East 50th Street in Manhattan.

A choice group of investigators was appointed: Eugene Opie, Samuel Meltzer, Hideyo Noguchi, Phoebus Levene and their young associates, all destined to become luminaries in the investigation of human disease. The charge given to them by the director was that they be free to work on whatever they wished. Flexner himself continued his interests in bacillary dysentery and cerebrospinal meningitis. In order to enlarge the new Institute, a 13-acre tract of land was

The Schermerhorn farm, before it became the site of The Rockefeller Institute.

purchased. It had been the Schermerhorn farm since the 18th century and was one of the few remaining large sites available in Manhattan, situated on a bluff from East 64th to East 68th Street, overlooking the East River, with an expansive view of Long Island.

A Pioneering Hospital-Laboratory Is Established

From the beginning, the creation of a hospital was integral to the building plans for the new Institute. The 1901 founding charter of The Rockefeller Institute states: "The objects of said corporation shall be to conduct, assist and encourage investigation in the sciences and arts of hygiene, medicine and surgery, and allied subjects, in the nature and causes of disease and the methods of its prevention and treatment."[17] As early as 1902, Flexner and Herter had conversations

in which it was assumed that Herter would become the first physician-in-chief or director of the Hospital. Herter had followed Flexner abroad. When they both returned, plans for the Hospital evolved, becoming finalized in 1908 when Mr. Rockefeller made a special gift for the construction of a 60-bed facility. It was thought that the Hospital would be staffed by physicians from the New York area, caring for selected patients who would provide blood samples or be the recipients of new treatments developed in the Institute's laboratories. Thus the Hospital was envisioned as an important core resource, very useful, but not the central locus for scientific work, which would be in the laboratories.

Then, illness struck again, this time affecting Christian Herter, who suffered from myasthenia gravis.[18] Today, there is a reminder of his illness in the main corridor of the Rockefeller Hospital: a portrait of Herter, done by his daughter Christine Herter Kendall. It shows his sad, but handsome face with left hand placed behind the head—not so much in a thoughtful manner, but rather to hold his head from drooping. Herter died in 1910, unable to participate in the final planning for the Hospital, and another director had to be found.

Rufus Cole: A Visionary Director

The search for Hospital leadership narrowed to Theodore Janeway, later to become the first full-time professor of medicine at Johns Hopkins, and Rufus Cole, also at Johns Hopkins. Janeway came highly recommended as a classical physician of the Oslerian type. Osler—whose medical text had inspired Frederick Gates—was a superb physician and teacher, but he was neither a laboratory researcher nor an exemplar of the unique blend of hospital and laboratory that was to become a major invention of the Rockefeller Hospital.

Cole was highly skilled in clinical medicine, and, unlike Osler, he was deeply devoted to laboratory science as well. In 1905, Osler left Johns Hopkins to become the Regius Professor at Oxford University. His successor, Lewellys Barker (who had been greatly influenced by Franklin Paine Mall, a pioneering advocate of scientific investigation in medicine), recognized Cole's special talents and promoted him as a new type of physician-investigator who could bring great distinction to any medical enterprise.

At Hopkins, Cole became a prime example of the inseparability of clinical medicine and laboratory science as joint building blocks for academic departments of medicine. Cole was profoundly influenced by a personal illness, as seems to have been the case for many of the heroes of our Rockefeller Hospital story. As a medical student, typhoid fever brought him to a sick bed under the care of Osler, an event that shaped his career as a clinician; but he was also greatly influenced by the new plans of Barker and Mall for academic medicine. In an Osler memorial issue of the *Archives of Internal Medicine*, published in 1949, Cole told of his gratitude to and great admiration for Osler, and of his own view that laboratory skills had to be added to clinical and diagnostic abilities to provide new leadership in medicine.[19] Cole's research was generated by clinical observation, but made use of the laboratory to study the typhoid bacillus in blood samples. His work marked the beginning of sound methodology for blood culture, a fundamental tool for the diagnosis and scientific study of infectious diseases. When the offer came, Cole accepted the challenge to lead the Rockefeller Hospital as director and physician to the Hospital.

Five diseases were the initial priorities for study: poliomyelitis, lobar pneumonia, syphilis, heart disease and intestinal infantilism, or celiac disease (perhaps what we would now know as gluten enteropathy).

Cole immediately set about identifying young associates to share his vision and work with him to create the new hospital-laboratory. At the

Rufus Cole, seen here with a patient, served as the first director of The Rockefeller Institute Hospital.

beginning and throughout his 28-year tenure as director, he showed an extraordinary ability to select promising candidates for success in his endeavor. George Canby Robinson, a clinician with experience in a pathological laboratory, was designated senior resident. George Draper, a graduate of the Columbia University College of Physicians and Surgeons, Henry Marx of Harvard and the Massachusetts General Hospital, Alphonse Dochez, already at The Rockefeller Institute, Francis McCrudden of Harvard and the Massachusetts Institute of Technology and Francis Peabody of Harvard were appointed to the Hospital staff. Senior appointments were given to Alfred Cohn, a student from Columbia University who had already done clinical investigation with Sir Thomas Lewis, and to Homer Swift, a teacher of pathology and dermatology at New York University. From abroad came Arthur Ellis, later an Oxford Regius Professor, and Florentin Medigreceanu, a Romanian visitor who soon after leaving the Rockefeller Hospital lost his life in World War I.


AMBULANCE
HOSPITAL
OF THE
ROCKEFELLER
INSTITUTE

MEDICINE AND SCIENCE UNITED AGAINST DISEASE

"With Cole's plan in place, the Hospital flourished and the Rockefeller clinical research approach was carried across the country by those who had trained and worked there. By 1940, half of the chairmen of departments of medicine in the United States were Rockefeller Hospital alumni."

A ward in one of the temporary War Demonstration Hospital buildings.

A Tradition of Service and the Challenge of an Epidemic

Response to national emergency was prominent in the life of the Hospital, most evident during World Wars I and II, when not only staff were given to the national effort but the entire Hospital became a military unit. In June 1917, a War Demonstration Hospital covered a large area of the new Rockefeller Institute site. The treatment of infected wounds by the Carrel-Dakin method was demonstrated to medical officers in two-week courses held regularly from August 1917 through March 1919, and the Hospital was officially commissioned as U.S. Auxiliary Hospital Number 1. Staff members who were qualified were made officers in the army, but the top rank of lieutenant colonel was reserved for Simon Flexner.

On page 24: A Hospital ambulance.

During World War II, U.S. Naval Research Unit Number 2 was commissioned in January 1944, under the command of Captain Thomas Rivers, Cole's successor as director of the Hospital. The entire

unit was moved to active duty on Guam, where various parasitic and tropical diseases, as well as viral encephalitis, were studied until June 1946, when the unit was decommissioned.

It is not surprising that when a severe epidemic of poliomyelitis struck New York City in 1911, during the Hospital's first summer, the staff mounted a major effort to serve by studying the disease. At the time, the Rockefeller Hospital was staffed by a small group of enthusiastic young investigators. As remembered by George Canby Robinson, the chief resident physician: "Life in the Hospital was full of joy—a few patients in whom we had special and intensive interest; laboratories such as none of us had ever before seen in any clinic; varied interests both within and without the realm of medicine; the East River with its great span of light at night, and its lapping waters; a blazing hearth about which we gathered after dinner."[20] Into this peaceful, joyous scene came the cruel poliomyelitis epidemic.

Peabody, Draper and Dochez were designated as the primary physician-investigators to care for the poliomyelitis victims. More than 160 cases were studied, as well as the records of 22 patients ill in previous years. Seventy-one of the victims were admitted to the Hospital, usually for several weeks; the others were seen as outpatients. In July, Flexner wrote to his wife, Helen:

> The poliomyelitis situation at the Hospital is entering its tragic stage. The isolation pavilion is full and other quarters will probably have to be found. But the tragedy is the severe and fatal cases. One child (an infant) died this morning and I've just come from the side of a lovely boy of 5 who is dying. My heart has been torn into shreds. The little fellow has extensive paralysis that has affected the nerves of the diaphragm. He is a little pale-haired, almost red-haired fellow, obviously the idol of his grief-stricken

> parents—two simple, dear American people. The Hospital staff has suddenly wakened up to the importance and seriousness of the disease—it is a tragedy.[21]

The Rockefeller physicians made detailed observations of their patients, documented in "A Clinical Study of Acute Poliomyelitis," published on June 24, 1912, in Monograph Number 4 of a new series of Rockefeller publications.[22] On page four, they stated their purpose, "to emphasize the fact that poliomyelitis is an acute disease, in which the often insignificant febrile stage is of highly epidemiologic and therapeutic importance," recognizing the special significance of a form of poliomyelitis in which paralysis does not occur but other symptoms are the same as in paralytic cases. They noted that serum from individuals who very likely had non-paralytic polio in childhood could neutralize the virus of poliomyelitis. The Rockefeller patients with the non-paralytic form of polio also developed such neutralizing factors. This was determined by incubating patients' sera with virus for several hours and then injecting it into monkey brain. It became clear that sera obtained both from those with paralytic and with non-paralytic polio developed substances that could disarm the virus.

Important original work on polio was done by Karl Landsteiner in 1908, prior to his leaving Europe and joining The Rockefeller Institute at the East 50th Street laboratories. He showed that a "filterable" virus isolated from the spinal cord of a victim of poliomyelitis produced a paralytic disorder when injected into the brain of a monkey. Simon Flexner, the director of the Institute, had followed Landsteiner's work with great interest. During a previous epidemic in New York, in 1907, Flexner obtained cerebrospinal fluid from affected individuals and injected it into the spinal canal of animals, with no effect. But after Landsteiner's publication, Flexner replicated Landsteiner's findings and showed that the virus spread from monkey to monkey

Nobel laureate Karl Landsteiner, whose studies of the chemistry of immunological reactions led to many discoveries, including blood types and the Rh factor.

via the nasal passages. On the basis of this work, Flexner was confident that a cure would soon be at hand when the epidemic of 1911 began. The *New York Times* of March 9, 1911, some months before the full fury of the epidemic struck, noted the following:

> The Rockefeller Institute in this city believes that its search for a cure for infantile paralysis is about to be rewarded. Within six months, according to Dr. Simon Flexner, definite announcement of a specific remedy may be expected. We have already discovered how to prevent the disease, says Dr. Flexner, in a statement published here today and the achievement of a cure, I may conservatively say, is not now far distant.

Flexner thought that the answer to the problem of poliomyelitis would come from laboratories rather than clinics and would be arrived at very swiftly on the basis of data obtained in his laboratory.

Simon Flexner, a physician who had attended a "pre-Flexner medical school," recalled: "I did not learn to practice medicine, indeed I cannot say that I was particularly helped by the school. What it did for me was give me the M.D. degree."[23] He and his younger brother Abraham, the author of the famous 1910 Flexner report that transformed medical education in the U.S., felt that medical science in their day required revolutionary changes to become an academic discipline and that answers to the problems of human diseases such as

poliomyelitis were more likely to come from laboratory researchers than from clinicians. Such strong feelings about the inadequacy of physicians and their training had important consequences.

According to John Paul, a distinguished virologist and student of the history of poliomyelitis, Alphonse Dochez, one of the Rockefeller clinicians working with patients during the summer of 1911, had on numerous occasions made efforts to obtain the virus from patients for further study. Flexner, however, felt that this was a matter for the Institute's laboratories and not for the Hospital workers.[24] Flexner believed that the virus entered humans through the nose and went directly into the central nervous system, without passage through the bloodstream; thus there would be no use in developing antisera or vaccinations to prevent or ameliorate poliomyelitis. He was certain that the matter would soon be clarified in the laboratory, but it took 40 years before the surmises of the Hospital clinicians would be proven more useful than Flexner's approach to the illness.

A Hospital Designed for Physician-Scientists

Rufus Cole objected to the use of his Hospital staff as medical attendants rather than primary investigators. In a 1911 letter to Flexner he wrote: "Men who were studying disease clinically had the right to go as deeply into its fundamental nature as their training allowed, and in the Rockefeller Institute's Hospital, every man who was caring for patients should also be engaged in more fundamental study."[25] This was a decisive moment in the history of the Hospital, and in the history of clinical investigation in America. The mold for casting physician-scientists as described by Rufus Cole was put to work.

No further research on poliomyelitis was to occur at the Rockefeller Hospital at that time, although the staff retained a continuing interest

in the disease. Draper became a skilled practitioner and medical teacher in New York City and was the physician for Franklin D. Roosevelt during his attack of poliomyelitis and its later effects. Thomas Rivers, the Hospital director following Cole, was an important figure in virology research and in the final success combating poliomyelitis. Support for research, which came about as a result of Roosevelt's illness, was backed enthusiastically by Rivers, a founder of the March of Dimes. Ultimately these efforts led to the application of the work of Enders, Sabin and Salk in the preparation of a vaccine that vanquished the disease throughout much of the world.

If events had been different at the Hospital in the summer of 1911, would some physician-scientists have been able to end the tragedy of poliomyelitis at an earlier time? A reading of the original publication by the Rockefeller group suggests that they might have been near the beginning of work for the prevention of poliomyelitis, but a technique for maintaining and propagating the virus in tissue culture—which was very much needed—was not yet available. Nevertheless, the experience in the Hospital with poliomyelitis and the confrontation with Flexner had the beneficial consequence of settling the debate on how research was to be conducted at the Hospital.

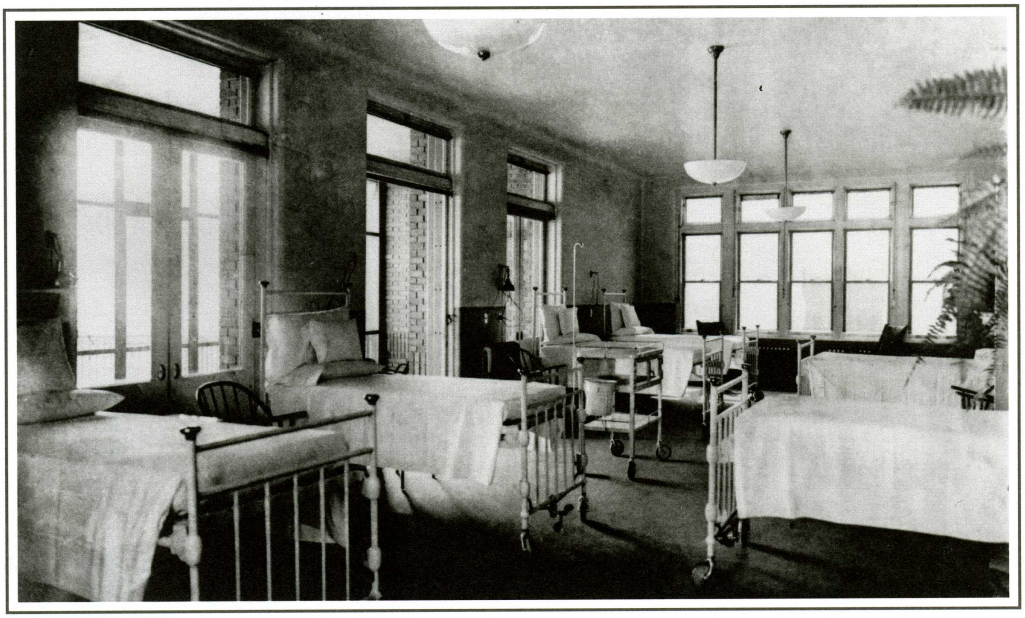
Separation of physicians on the ward and workers in the laboratory, against which Sir Thomas Lewis had so strongly spoken, was not to be the rule. Instead, those trained in this hospital were to learn how to become academic physician-scientists equally adept at the bedside and in the laboratory. There is no evidence to suggest that Flexner objected or stood in Cole's way after this episode. (From personal conversations I had with James Flexner, Simon's son, it is evident that his father had great admiration for Cole.)

With Cole's plan in place, the Hospital flourished and the Rockefeller clinical research approach was carried across the country by those who had trained and worked there.[26] By 1940, half of the

chairmen of departments of medicine in the United States were Rockefeller Hospital alumni. The achievements and training of Rockefeller physician-scientists dealt with many different areas of human disease, but the structure of the various Hospital groups was similar. An outstanding "mentor" would gather a small "house staff" of young physicians, working and living in the Hospital for a two- or three-year period, fully immersed in a particular clinical problem emanating from the bedside, but requiring laboratory inquiry. The most successful investigators were those who became committed to the belief that the understanding of clinical problems required laboratory skills.

Investigations of Pneumonia

Rufus Cole led the way in clinical investigation with his study of pneumococcal pneumonia, the disease that Osler, his clinical hero, termed "Captain of the Men of Death." One hundred years ago, pneumonia carried a mortality rate of 25 percent.[27] Patients with high fever, cough and ultimately pulmonary failure succumbed to a suffocating, agonizing death. Careful examination of the patients' sputum was the link between the bacteriological process rendering the lungs incompetent and the wish of investigators to cure the disorder. Pneumococcal bacteria were easily identified by microscopy in stained samples of sputum, showing a characteristic clear zone or capsule. When cultured in Petri dishes, most grew into smooth, round colonies with a distinctive mucoid appearance, but some colonies had a dry, rough appearance. Samples injected into mouse peritoneal cavities produced an inflammatory reaction and an abdomen filled with pneumococci. When the offending organisms from peritoneal fluid were injected into a horse, antisera developed that could clump and destroy the organisms.



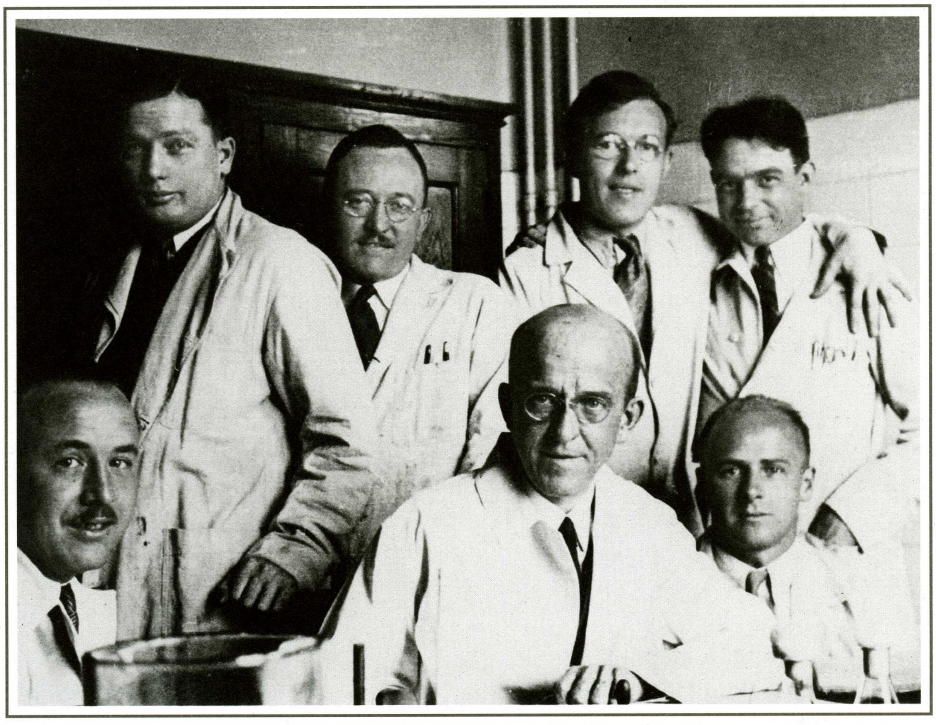
A Hospital ward in 1911. Admission was limited to patients with diseases under study.

The study of horse antisera led to the observation that there are different strains of pneumococci, and by 1912 a serum for type I pneumococcus became available for the typing of sputum samples to determine which cases might benefit from treatment with specific antisera. These new and important findings were published in 1917 in Monograph Number 7 of the Rockefeller Institute for Medical Research series. As physician and historian A. McGehee Harvey observed: "The attack on lobar pneumonia, begun by Cole and carried on by Avery and others, was one of the most elegant performances from the stand point of both theory and technique in the history of medical science."[28]

Although the definitive treatment of pneumococcal pneumonia in later years would be sulfonamides and penicillin, making sputum typing unnecessary, the Rockefeller work was the prelude to the development of pneumococcal vaccination, important to this day. But, another offshoot of these studies is of enduring relevance to the study of human disease, and perhaps the most remarkable research finding in the 100-year history of the Hospital.

CLINICAL RESEARCH CREATES SCIENCE

"After 30 years of work, Avery and his colleagues demonstrated to a surprised and even incredulous readership that deoxyribonucleic acid is the chemical agent...that confers the remarkable property of transformation. DNA flashed across the horizon of biological research, and 1944 marked the beginning of molecular genetics and a revolution in biology."



Oswald Avery (center, front) with members of his lab in the early 1930s. René Dubos (back, second from right), was a leading microbiologist who also became a noted author and environmentalist.

Discovering the Significance of DNA

Cole was devoted to the idea that knowledge of the chemical composition of the pneumococcus would be central to understanding pneumonia. The large, clear capsule surrounding the organism was shed into the blood and could be isolated as the soluble-specific substance (SSS). SSS appeared to be related to the virulence of the organism, because strains with a dry, rough appearance, when cultured, do not produce SSS and are avirulent. Thus the attempt to uncover the nature of SSS in chemical terms became a major preoccupation of the Cole group.

On page 34: An early oxygen chamber, devised by William C. Stadie.

The leading participant in this research was Oswald Avery, a pathologist recruited to the Hospital in 1913 to serve as medical bacteriologist for the pneumonia studies. Cole had made a strong

effort to recruit Avery on the basis of their shared commitment to the idea that chemical analysis of microorganisms would shed light on the basic events occurring in bacterial disease. Avery had described this approach in a paper he co-wrote with Benjamin White in 1912,[29] which was very likely known by Cole. According to René Dubos, "It was the beginning of a pattern that can be recognized throughout [Avery's] subsequent career at The Rockefeller Institute—the systematic effort to understand the biological activities of pathogenic bacteria through a knowledge of their chemical composition."[30] Dubos also noted that working on pneumonia might have been of special significance to Avery, who had lost his mother to lobar pneumonia in 1910. Rollin Hotchkiss, a colleague, commenting on Avery's commitment to the study of the pneumococcus, noted that he called the organism "that little gram positive coccus." According to Hotchkiss, Avery felt that the pneumococcus "presented in small compass most of the basic questions of biology."[31] For a 30-year period, Avery concentrated his laboratory work on the search for a chemical agent that might be responsible for pneumococcal transformation.

Avery's studies of the most common cause of pneumonia, the pneumococcus, culminated in the discovery that genes are made of DNA.

It was known that when different strains of pneumococcus were placed together in experimental animals, one strain could transform another; in this way, a virulent strain might become less virulent or a nonvirulent strain become a killer. These changes were accompanied by alterations in the roughness or smoothness of the colonies. Most remarkably, once these changes occurred they were permanent for all subsequent generations of

the transformed pneumococcus. Martin Dawson, in Avery's laboratory, showed that these transformations could also occur *in vitro*, in a test tube.

Avery was certain that some chemically definable substance in the pneumococcus would be found responsible for the transformation. He had developed a reputation for wonderful, impromptu lectures on his work and his research ideas. Colleagues often referred to his lectures as Red Seal recordings, reminiscent of the phonograph records popular at that time. His very beautifully expressed ideas about research so fascinated listeners that he was given the nickname of Professor, truncated over time to "Fess." The excitement and enthusiasm of his teaching was much in evidence in the World War I Rockefeller demonstration unit where Fess lectured to Army physicians and sanitarians.

After 30 years of laboratory work, Avery and his young colleagues Colin MacLeod and Maclyn McCarty summarized their findings in a classic publication in the *Journal of Experimental Medicine*, demonstrating to a surprised and even incredulous readership that deoxyribonucleic acid is the chemical agent in the bacteria that confers the remarkable property of transformation.[32] This observation indicated that a chemical basis for genetics had been uncovered; DNA flashed across the horizon of biological research and 1944 marked the beginning of molecular genetics and a revolution in biology.

Maclyn McCarty later noted: "All of the researchers were medical bacteriologists primarily interested in the cause and control of human pneumonia."[33] Thus a pathway had been established from the bedside to the laboratory that led to a profound enrichment of scientific knowledge. One must marvel at the patience and trust of the leaders of the Hospital who permitted Avery and his fellow physician-scientists a 30-year span of time to pursue what might have seemed to be a rather obscure problem of questionable relevance. The

principle of freedom for investigators to exercise their own curiosities and pursue their interests without interference, a guiding principle of the Hospital, had been amply vindicated.

The Success of the Cole Plan

The discovery of the role of DNA in biology could be considered full justification for the founding of the Rockefeller Hospital, but the Cole plan was repeatedly crowned with success in other areas of research. Outstanding leaders of investigative medicine were

During World War I, Nobel laureate Alexis Carrel (in white cap) trained military doctors in surgical techniques at the Institute's War Demonstration Hospital.

selected to be mentors of three or four young M.D.s who, living in Hospital quarters, took care of patients and learned laboratory techniques appropriate for the disease under study. The entire group of physicians in training numbered about 20, living in some respects like a monastic order, taking breakfast and dinner together at the Hospital each day, but having lunch with the senior members of the Institute and Hospital in the Institute's legendary dining room.

One of the physician-scientists in training was given the title of chief resident physician and charged with assuring that medical duties were promptly and properly performed. On the first Monday of each month, the chief resident hosted a special evening for the "monks" and their mentors. A splendid meal was followed by a "journal club." Two or three randomly selected participants, young or old, were called on for impromptu presentations of findings in any new publication they had recently read. An active discussion followed, often criticizing the new data and sometimes the presenter as well. Being suddenly called to speak before the group was most anxiety-provoking and never to be forgotten, yet very rewarding. The physician-scientists in training were learning to be always prepared, skilled spokespeople for their special discipline, medical science.

During the first 25 years of the Hospital, the professional staff of five to seven groups totaled 40 to 50 individuals at a time, including the "monks" and more senior assistant or associate members. Each year, 10 to 15 would "graduate" from the Hospital, to join in the development of clinical research in medical schools and other hospitals.

A description of the work in the Rockefeller Hospital over the first half century is available in many hundreds of publications, and is well summarized by George Corner in his monograph *A History of The Rockefeller Institute*, as well as by A. McGehee Harvey in his thoughtful work *Science at the Bedside*. When Cole retired in 1937, he received a gift of 35 bound volumes of 1,216 publications from

the Hospital. By giving only a few illustrations, this account does not do full justice to this remarkable body of work, but hopefully it conjures up the general atmosphere and special qualities of the Hospital in its first half century.

Donald Van Slyke: A Chemist Links Physicians and Laboratory Scientists

Alongside the Cole group, a highly productive team worked under Donald D. Van Slyke. Van Slyke was not a physician, but a trained chemist devoted to understanding human disease, which he studied in the Hospital for more than 40 years. He had joined the Institute in 1907 as a member of the laboratory of Phoebus Levene at the East 50th Street site.

The laboratories at the new Institute were staffed by Eugene Opie, Samuel Meltzer and Phoebus Levene. Opie, a distinguished pathologist, was responsible for the first demonstration of the histologic lesion of diabetes in pancreatic beta-cells. Meltzer, a practicing gastroenterologist, worked with experimental animals on a variety of issues of clinical relevance, for example, the development of techniques for endotracheal anesthesia. Levene, who had studied abroad with Emil Fischer, one of the founders of organic chemistry, recruited a group of young chemists to work in protein chemistry. Their chemical analyses of nucleoproteins uncovered four different substances to which they gave the name "nucleotides," providing a structural chemical basis for the great DNA story to come.

Cole, while waiting for the Hospital to be built, spent time in the Levene laboratory and made the acquaintance of Donald Van Slyke. When the opportunity arose, Cole offered Van Slyke a position as biochemist to the Hospital. Although the separation of the laboratory

The dining room on the first floor of Welch Hall was an important gathering place for Rockefeller scientists.

groups from the Hospital groups was an organizational reality, the interests of the two were bridged in many ways.

The Institute's remarkable dining room became an inspirational agora. Lunch was served to groups at small tables in an elegant wood-paneled room with large windows facing the East River on the ground floor of the central building. Young investigators were joined by senior members without regard to age, training or interest. Laboratory workers were always curious to learn what clinical problems were under study in the Hospital, sometimes talking about their own illnesses or the illnesses of friends, and delighted to have interchange with physicians. In return, aspiring physician-scientists were eager to receive the insights of basic scientists.

Every Friday afternoon, all laboratory and Hospital groups joined to hear a presentation by a staff member summing up recent work. At a similar, but smaller Wednesday morning session, the chief resident physician arranged for Hospital physician-scientists to present their

work in progress. At both sessions, distinguished visitors occasionally spoke, but the more usual activity was a report of work at the Institute and Hospital. On Saturday, the main subject of discussion at lunch would often be the lecture delivered the day before. A senior member might ask a young colleague, "Do you understand what he was driving at?" or "What did you think of the talk?" Such exchanges enlarged the horizons of young and old and bridged the laboratory and the Hospital.

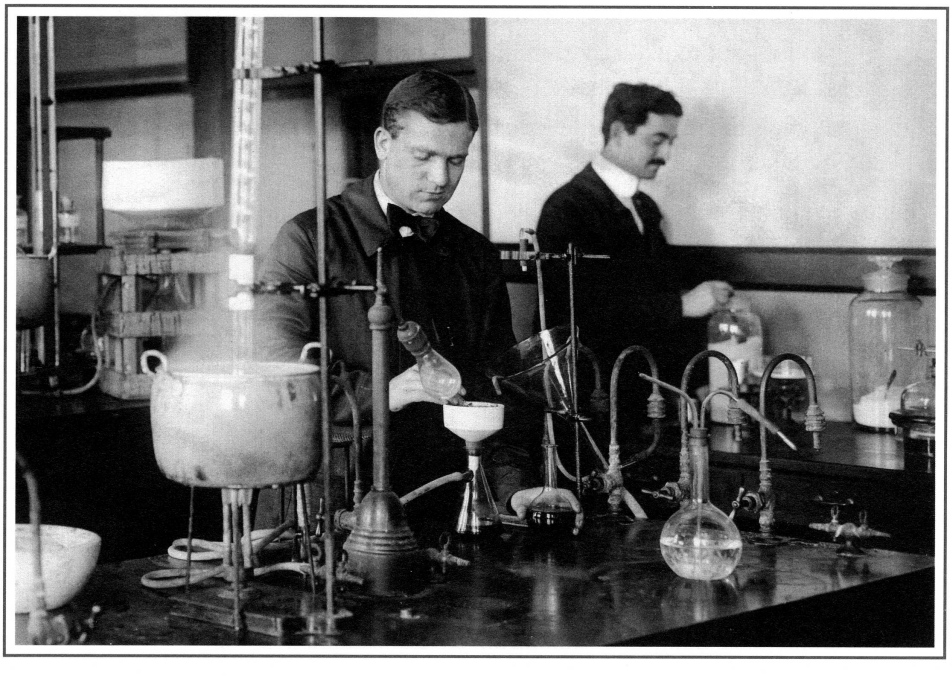
When Van Slyke and his associate Glen Cullen began work in the Hospital in 1914, they wondered how their chemical talents might be helpful to sick patients. Their uncertainties did not last very long. They readily put their abilities to work on the chemical study of diabetes, pulmonary disease and nephritis, and in so doing, gave birth to modern clinical chemistry. Twenty-eight years later, Van Slyke, no longer an ordinary chemist, but now a clinical chemist, was given the Kober Medal of the Association of American Physicians, an award specifically for achievements in *clinical* medicine.

The Flourishing of Clinical Chemistry

Van Slyke studied the acidosis of diabetic patients at the Hospital, whom Frederick Allen and Edgar Stillman were treating with carbohydrate and calorie restriction, which led to profound biochemical changes, often extending the lives of the patients. Some of these "survivors" were among those given the revolutionary new pancreatic extracts containing insulin, prepared in 1922 by Frederick Banting in Canada.

For detailed analysis of serum ketoacidosis occurring with the Allen diet, Van Slyke designed a special instrument of glassware and mercury manometers, to make exact measure of blood carbon dioxide. This Van Slyke device became a widely used tool, essential in the study of

blood gases in Cole's pneumococcal pneumonia patients who were receiving oxygen therapy. A special oxygen chamber was designed by William C. Stadie for maintenance of high oxygen tension.[34] With Van Slyke's methods for blood gas analysis, it became possible to make precise chemical measures of the efficacy of oxygen therapy. Stadie revolutionized the study of pulmonary physiology by being the first to perform arterial punctures on humans, using himself as the initial test subject. Venesection was a time honored procedure for sampling blood, but arteries were avoided for fear of uncontrollable hemorrhage or gangrene distal to the puncture. It took someone with courage, dexterity and determination to overcome these fears and develop the technique that was soon widely used for physiologic studies of the circulation.



Donald Van Slyke (left) and Gustave Meyer, in the laboratory of Phoebus Levene. Van Slyke invented instruments for analyzing blood chemistry.

During the early years of study in the oxygen chamber, the influenza pandemic of 1918 struck. The virus attacked healthy, young army inductees, who often succumbed after a brief illness characterized by intense cyanosis and dyspnea—blue skin coloration and shortness of breath. A visiting Danish scientist, Christen Lundsgaard, joined with Van Slyke to make definitive studies of the nature of cyanosis. Rather than being the result of sluggish venous blood flow, as was then thought to be the case, Lundsgaard and Van Slyke showed that cyanosis was a direct expression of low oxygen tension in arterial blood.

As Van Slyke continued his studies of acidosis, he set the stage for a chemical understanding of acidosis and alkalosis, and the role of bicarbonate, to maintain normal pH and chemical homeostasis in blood and tissues. His studies were extended to patients with nephritis, or inflammation of the kidneys, who were admitted to the Hospital for prolonged study. The changes in blood chemical constituents characteristic of uremia were described, leading to an understanding of renal function in chemical terms. From these observations, Van Slyke developed the concept of urea clearance for quantitative analysis of renal function, cleansing the system of nitrogenous waste yet maintaining pH in the presence of acidic byproducts of metabolism.

Van Slyke's productive laboratory became a major training ground for leaders of biochemistry, physiology and clinical investigation. Cole saw the need for a new *Journal of Clinical Investigation* to publish these important results. The recently formed American Society for Clinical Investigation sponsored the journal. Meltzer, an early member of The Rockefeller Institute, was influential in the founding of both the society and the journal, as well as the Society for Experimental Biology and Medicine, fondly known in those days as the "Meltzer Verein."

A MODEL FOR CLINICAL RESEARCH

"The Hospital had grown from an idea into a productive research venture, and also a training ground that was transforming American medicine from a craft into a scientific discipline. Individuals who wished to investigate disease no longer needed to turn to the great laboratories of Europe for training."

Research Subjects as Partners in Medical Science

The Van Slyke studies often required prolonged hospitalization of research subjects. Appropriate treatment was always provided, but the opportunity to undertake detailed study of the disease was a central feature of the endeavor. This was achieved in humane fashion by an excellent nursing staff, paying close attention to the day-to-day needs of patients: for youngsters, regular school sessions, for adults, various forms of occupational therapy and a close, cordial relationship among patients, nurses and physicians. Patients often expressed their gratitude for the opportunity to be treated with such competence and kindness by the Hospital staff and also for the special privilege of being able to make a contribution to the advancement of medical science.

One of the great Metropolitan Opera sopranos, Alma Gluck, came to the Hospital for treatment of liver disease. In a note of thanks to Mr. Rockefeller, her daughter Marcia Davenport wrote, "The care and understanding that my mother received from the Rockefeller Institute were far beyond the realm of benefits for which one can express gratitude in words."[35] To the young Rockefeller Hospital physician-scientist who worked with Alma Gluck, Marcia Davenport wrote indicating how important it had been for her mother to feel that she was contributing to medical science.

On page 46: Rebecca Lancefield was a world-renowned authority on the streptococcal bacteria that cause rheumatic fever, scarlet fever, sore throats and other illnesses.

Such relationships among the staff, patients and their relatives created a unique atmosphere, carefully nurtured by the Hospital throughout its history, demonstrating the advantages of studying human disease and the assurance that this can be done with no compromise in the excellence of medical care in a warm, reassuring ambience. Two components made up this special bond between the staff and the patients. The first was the total commitment of the treating physician to the patient, in the firm belief that this was a

The nursing staff, circa 1935. For 100 years, nurses have been essential partners in the clinical research studies at the Rockefeller Hospital.

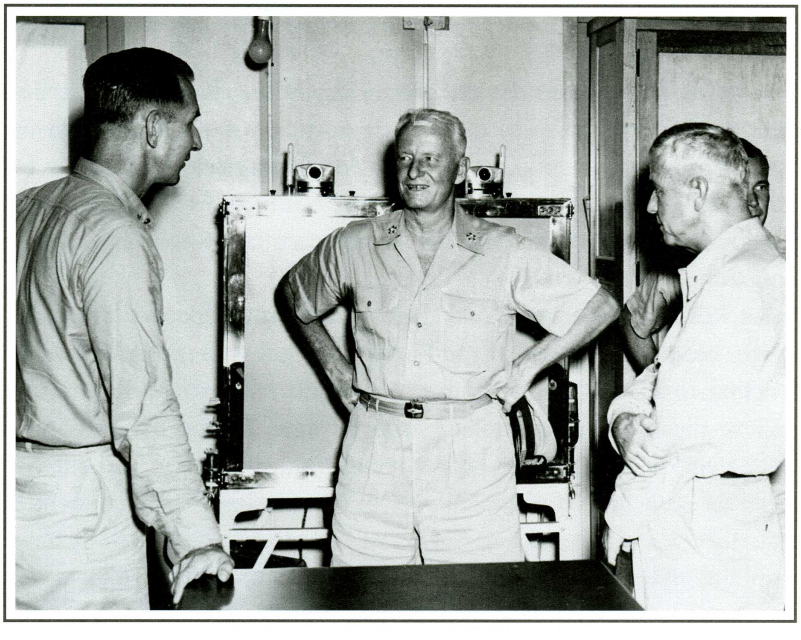
rewarding pathway to the understanding of the disease. The second was the patients' wish to make their participation a weapon in the ultimate defeat of the disease, if not for themselves, then surely for those who would have the disease in the future. At the Rockefeller Hospital, patients were best described as collaborators rather than research subjects.

As Rufus Cole noted: "Although investigation has been stressed, it has been the purpose of the Hospital to provide the best possible nursing care, and the use of every procedure known to benefit and relieve disease. The methods employed have been those of clinical investigation, not human experimentation, and every patient has been safeguarded from anything which might be to his detriment. It has been one of the strong beliefs of the Hospital staff that even if experimentation on patients were morally justifiable, which it is not, the increase in knowledge derived thereby would be negligible."[36]

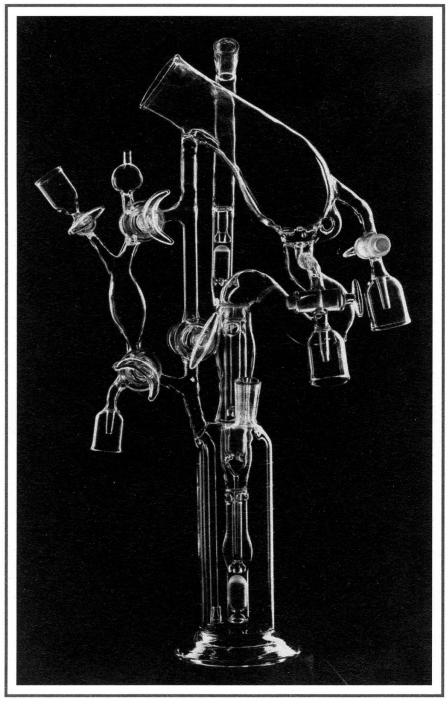
Thus, the Rockefeller physician-scientists, patients and staff were comrades in a battle against disease: a small army of dedicated soldiers using and reshaping the powerful weapons of science.

Thomas Rivers and a New Focus on Viruses

As Cole's scientific and administrative achievements became known, he was asked to serve on various national commissions. While consulting with the U.S. Surgeon General concerning a commission, he learned of the work of Thomas Rivers, who was serving on an Army committee studying the development of pneumonia in patients with measles. Rivers, a graduate of Emory University and Johns Hopkins



Rockefeller virologists Thomas Rivers (right) and Richard Shope (left) on Guam, in 1946, with Admiral Chester Nimitz.



The Carrel-Lindbergh pump, invented by Alexis Carrel and aviator Charles Lindbergh, made it possible to maintain and study organs and tissues in culture.

Medical School, and thereafter a highly respected resident in pediatrics at Hopkins, was given an offer from Cole to come to the Rockefeller Hospital to establish a laboratory in virology. Clearly, any earlier difficulties working with poliomyelitis had not dampened Cole's enthusiasm for pursuing studies of viral disease at the Rockefeller Hospital.

In March 1922, Rivers began studies of patients with viral diseases. Over the next 15 years, he and his group examined the virus of chicken pox, demonstrated that lymphocytic choriomeningitis is a human as well as an animal disease, characterized the mode of transfer of psittacosis and explored the pathogenesis of Rift Valley fever. The development and use of virus cultures was an important feature of these studies. Alexis Carrel was then pioneering tissue culture at Rockefeller, maintaining living chicken hearts *in vitro* in a device that he and Charles Lindbergh had designed. Rivers, inspired by their work, grew viruses in small pieces of tissue, maintained in buffered solutions. In this way the vaccinia virus was maintained and became the first cultivated virus for immunizing humans.

Physician-scientists who worked with Rivers filled prominent positions in virology, infectious disease research and medical education. In June 1937, on Cole's retirement, Rivers became the director and head of the Rockefeller Hospital. He continued his efforts as a distinguished writer and promoter of research in virology, and also as a key figure in advisory groups involved in the ultimate conquest of poliomyelitis.

As director of the Hospital, Rivers organized and recruited people to carry out new Hospital activities. Maclyn McCarty, who had studied streptococcal disease in Homer Swift's group, inaugurated a program on rheumatic fever. Frank Horsfall expanded his viral work to include the study of nonbacterial primary atypical pneumonia and the adenoviruses, one cause of such pneumonia. Charles Hoagland, who was initially in the Cole-Avery group, began independent studies of viral hepatitis. After Hoagland's untimely death, Henry Kunkel and E. H. Ahrens from his laboratory began independent clinical programs on fundamental issues in clinical immunology and lipid metabolism. Vincent Dole and Reginald Archibald, originally with Van Slyke, developed new Hospital research programs. Rivers lent his enthusiasm and skills to these activities during World War II and immediately thereafter.

Summing Up: 1910 to 1950

The achievements of Cole, Van Slyke and Rivers exemplify the work at the Hospital between World Wars I and II. The Hospital had grown from an idea into a productive research venture, and also a training ground that was transforming American medicine from a craft into a scientific discipline. Individuals who wished to investigate disease no longer needed to turn to the great laboratories of Europe for training. Physicians were increasingly able to study human disease productively by bringing scientific precision to bear on problems encountered at the sick bed. The unending varieties of human disease generated important questions that could be answered by these physician-scientists, leading to basic biologic advances. The birth of molecular genetics, cell biology and sophisticated human biochemistry resulted from the efforts of these physicians; a new chapter in the history of medicine and science had begun.

The triumphs and hopes of medical science became publicly known. Sinclair Lewis with help from Paul de Kruif, who had been at The Rockefeller Institute, wrote the popular book *Arrowsmith*, a fictional account of the Rockefeller Hospital. It influenced a generation of young students, as did de Kruif's widely read book *Microbe Hunters*. Descriptions of the Rockefeller Hospital experience helped to mobilize the creative energy of American youth at a time when science and clinical medicine were becoming integrated and opening new vistas of research and understanding. This gave a ray of hope for a better future during the depressing years of the 1930s.

World War II brought a pause in Hospital activities as the medical manpower of the nation became harnessed to the war effort. New leadership had recently come to both the Hospital and the Institute. Not only was Cole replaced by Rivers as Hospital director in 1937, but Flexner had relinquished leadership of the laboratories in 1935 and was succeeded by Herbert Gasser, who later received a Nobel Prize. The new leaders were dedicated to continuing the Hospital and the Institute as originally planned, and they maintained Hospital traditions successfully. With the coming of peace in 1945, however, it became evident that a new period in medicine and science had begun.

The New Frontier: 1950 and Beyond

In 1945, Vannevar Bush, who had been a principal science adviser to President Roosevelt, prepared a document entitled "Science: The Endless Frontier," in which he advocated a new linkage of government and academia.[37] The frontiers of science were to be explored not only to harness the energy of the atom, but to create new opportunities for intellectual and industrial growth, hopefully generating a new prosperity based on scientific information. There

was a national consensus that science would hasten the conquest of disease, and in the Truman administration the advance to the new frontier was quickened. The National Institutes of Health grew exponentially, fueled by generous congressional support, and a large research hospital was built on the Bethesda, Maryland, campus of the National Institutes—following on the model of the Rockefeller Hospital.

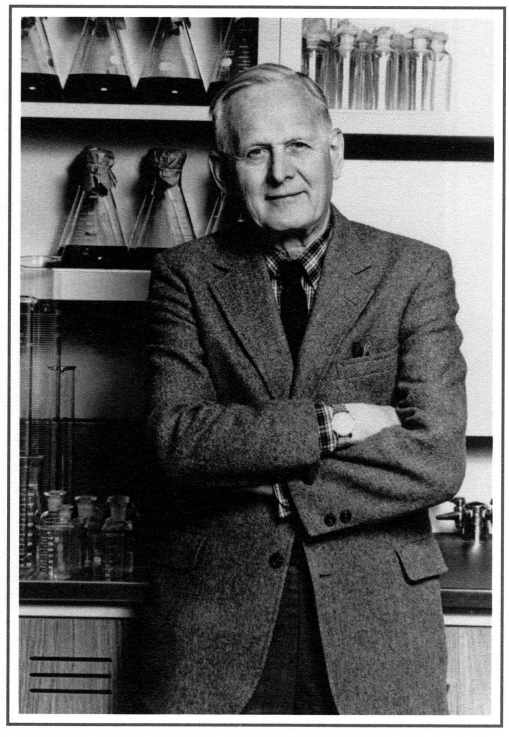
The roots of the new biologic science planted at the Rockefeller Hospital were now growing in many gardens. Laboratories of enzymology and biochemistry were enlarged, greatly enriched by the availability of isotopic tracers, new instrumentation and advanced analytical techniques. During the Korean War, when physicians were again drafted into national service, some spent time at the National Institutes of Health developing a scientific laboratory orientation to enhance their clinical research. There was a sharp increase in the number of medical schools and hospitals receiving federal funds. In this expanded arena, the findings of physician-scientists were transforming medicine into a well-grounded scientific endeavor. Chemical treatment of cancers, the conquest of many infectious diseases by antibiotics and chemotherapeutic agents, and new diagnostic procedures came on the scene, as did cardiac surgery and organ transplantation. Construction, expansion and optimism spread across the nation.

The Hospital After World War II

At the Rockefeller Hospital, the pavilion originally designated for the isolation of patients with infectious diseases was enlarged and refitted to house an increased number of nurses. In 1951, a new wing was added to the Hospital and the original building was fully modernized.

By 1952, Hospital studies were conducted in 56 beds on the third and fourth floors; the second, fifth and sixth floors housed the resident staff and employees. Leadership at the Institute was placed in the hands of Detlev W. Bronk, a biophysicist who was elected Rockefeller's president in 1953, with Rivers as vice president and director of the Institute.

The rebuilt Hospital at that time was home to five research groups investigating respiratory diseases, rheumatic fever, cardiovascular diseases, endocrine disorders and acute and chronic diseases of the liver. Mentors leading these groups were Horsfall, McCarty, Dole, Archibald and Kunkel, with 24 physician-scientists in training. The physicians in training mostly lived in the Hospital, caring for patients and conducting research in their own laboratories. Hospital work continued as Detlev Bronk, after a distinguished career as president of Johns Hopkins and investigator at the University of Pennsylvania, brought other changes to the Rockefeller campus. While the basic structure of the Hospital and laboratories remained, a new graduate university for biologic sciences was opened. Small numbers of students were invited for graduate training in the laboratories to obtain Ph.D. degrees, and The Rockefeller Institute for Medical Research was transformed into The Rockefeller University.



Maclyn McCarty worked on the landmark experiments showing that DNA carries hereditary information. He was physician-in-chief of the Hospital from 1960 to 1974.

The Rockefeller University

Many of Rockefeller's early Ph.D. students arrived with medical degrees, but took the opportunity to develop laboratory-based scientific skills, thereby in effect beginning an M.D.-Ph.D. program, as was occurring at other universities. The newly expanded Rockefeller University grew rapidly; laboratories were added in cell biology, biochemistry, genetics, and behavioral sciences, as well as mathematics and philosophy. Some

of the first Rockefeller students worked with Hospital groups. Over time, however, most students elected to study with the more numerous laboratory groups not directly involved in Hospital-based, patient-oriented investigations; thus, the Hospital did not enlarge its physician-scientist group or the number of patients under study.

The Rockefeller Hospital was one of the first general clinical research centers sponsored by the National Institutes of Health, and its success inspired the creation of many other federally funded centers for clinical investigation. The rise of these new clinical research centers, combined with the rapid growth of Rockefeller's own graduate school, had the effect of challenging the centrality and singular quality of the Rockefeller Hospital. Nevertheless, the Hospital maintained unique and excellent work in such areas as nutrition, metabolism, immunology and addiction, all adding luster to the University.

This account of the Hospital gives greatest weight to the first half century, when a new variety of clinical science was forged, merging the bedside and the laboratory, with ardor and devotion emanating from the clinic, but using and creating new tools of science to understand and conquer disease. The second half of the century gave repeated proof of the value of the new clinical science.

Detlev Bronk (left) and David Rockefeller, who together guided the Institute's transformation into The Rockefeller University.

As a devotee of patient-oriented clinical research, I have always argued for the expansion and further development of the Hospital, which I view as "the heart" of the University. Many scientists agree with me, while others have debated the point. Fortunately, in recent years, the leaders of The Rockefeller University have made major investments to modernize the Hospital's facilities and recruit physician-scientists who head new laboratories that make use of its unique resources. While patient-based clinical research is being nurtured at Rockefeller, the same is not necessarily true beyond our campus.

The larger medical research scene and, in particular, its hero, the physician-scientist, have been in peril for some time now. In 1979,

James Wyngaarden wrote a widely quoted warning entitled "The Clinical Investigator as an Endangered Species,"[38] and E. H. Ahrens provided convincing data on the decline in the number of physician-scientists.[39] What happened? Why were those who had brought science and medicine together now disappearing?

Surprisingly, two of the Hospital's greatest successes became major elements in the decline of the physician-scientist. First, a century of productivity in the Hospital gave clear demonstration of the value of science at the bedside and laboratory. Medical science came of age with increasing demand for health care and a national commitment to provide the fruits of scientific medicine as a fundamental right for all. The pressure grew to train physicians skilled in subspecialties to administer new, complex and often costly treatments. The health care industry expanded dramatically, providing new diagnostic devices and treatments, and accounting for a growing portion of the national economy. There were fewer opportunities for the reflective and meditative aspects of medical research, as practiced at the bedside and in associated laboratories. Physicians, often in debt with loans taken out during their schooling and prolonged postgraduate training, were obliged to turn away from research and enter the full-time practice of medicine. These forces created an environment no longer conducive to the search for new knowledge and understanding by physicians at the bedside.

A second factor affecting the prominence of the physician-scientist was the rise of molecular genetics, which was launched, in large part, by the Rockefeller Hospital's success at bringing startling insights into human biology. It became possible to forgo human studies, as molecular genetics showed that there is only one genetic code for all living systems, from plants to unicellular animals, worms and mice, all the way to humans. Curiosity about disease, it was reasoned, could be as well satisfied by examining animal models and tissue cultures as by the analysis of human disease at the bedside of the sick.

In 1998, an organization called the Association for Patient-Oriented Research was founded to maintain science at the bedside,[40] but nationwide the vector had already turned 180 degrees. No longer pointing from bedside to laboratory, the new arrow of translation began to fly primarily from the laboratory to the bedside. Today, a national effort aims to bring the findings of basic science from the laboratory to humans in translational science centers, prompted by the burgeoning health care needs of an aging population.

In the face of these trends and pressures, it has become more important than ever to safeguard the initial great experiment of the Rockefeller Hospital and its commitment to patient-oriented research.

Jules Hirsch (left) with physician-scientists Attallah Kappas (center) and E. H. Ahrens in the 1980s. Kappas served as the Hospital's physician-in-chief from 1974 to 1991, preceding Hirsch.

LOOKING AHEAD

"Many enduring mysteries await our understanding. How do we think and feel? What is the nature of our consciousness? How do early developmental events remold our genetic endowment, generating behaviors that lead to better or worse outcomes? Physicians who address these matters scientifically will maintain the core of scholarly integrity in medicine. Without them, medicine will no longer be a profession, but a technology."

Birthday Greetings and a Reaffirmation

What are we celebrating? Are we reminiscing about great accomplishments and honoring past heroes? Or are we pausing for only a moment to recall historic achievements, before leaping into the next chapter of a never-dying account of innovation and discovery driven by physician-scientists? We have learned much from the opening chapters of our account; clinical observation joined to laboratory science, carried out by physician-scientists, has been immensely productive, maintaining the scholarly integrity of medicine while enriching biological science. I believe there is much more to come.

The next 100 years will see a need stronger than ever for an observation post amid the persistent perils of human disease. Just as we depend on physicists and their technological marvels to help us understand the mysteries of the universe, we need disease watchers. One might argue that all physicists should be put to work discovering new sources of energy. However important that may be, we also need those who will give us riches from as yet unimagined findings, as physics has repeatedly done in earlier centuries.

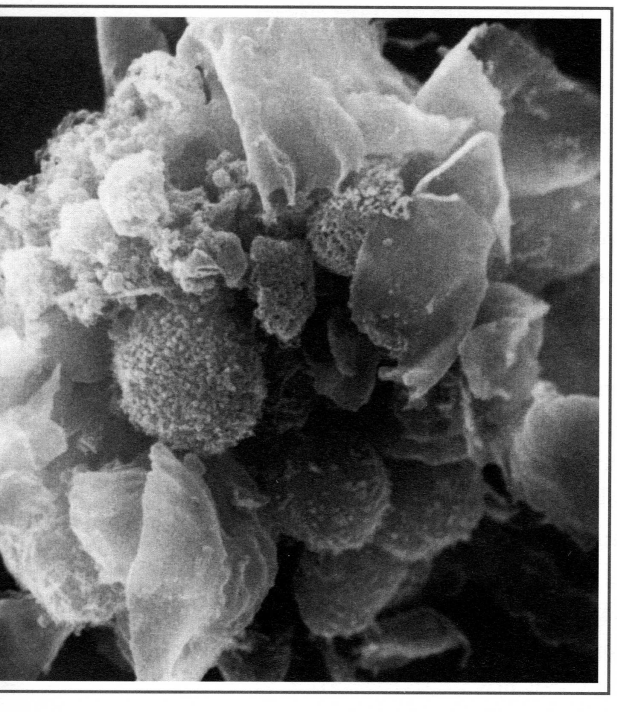
On page 60: Physician-scientists Sohail Tavazoie and Agata Smogorzewska joined the Rockefeller faculty in 2009. Their new laboratories focus on cancer metastasis and DNA repair, respectively.

One might likewise argue that the need to distribute health care will require all the time and effort of every physician. According to this reasoning, new drugs and other treatments can come from basic laboratory scientists; physicians should stick to their fundamental professional imperative: to examine, diagnose and treat, because reflection, observation and scientific inquiry will now be carried out by others. If this becomes the new medical modus operandi, then a great natural resource—the curiosity and creativity of physician-scientists—will be lost.

More optimistically, methods of imaging, microscopy and genomic analysis that have been made available, in part, by the clinical investigations of yesterday can be applied to the problems of today

and tomorrow, by those physician-scientists who continue to ask relevant questions and are deeply motivated to study human disease.

There is no shortage of puzzles and problems generated at the sickbed of afflicted, suffering and aged patients. As Rufus Cole noted more than 80 years ago at the dedication of the Billings Hospital at the University of Chicago: "It has not infrequently happened that the unused and bizarre in nature have stimulated man's imagination and have led him to undertake investigations which have finally resulted in the formulation of general laws. Observations of the rainbow led to important discoveries in the field of optics, observation of lightning directed man's attention to the study of electricity."[41]



Dendritic cells, interacting here with round T cells, are crucial components of the immune system. Discovered at Rockefeller by Ralph Steinman and Zanvil Cohn in 1973, dendritic cells are now a focus of efforts to fight cancer, AIDS, diabetes and other disorders.

Many enduring mysteries await our understanding. How do we think and feel? What is the nature of our consciousness? How do early developmental events remold our genetic endowment, generating behaviors that lead to better or worse outcomes? Debates about mind and matter must ultimately be enriched by the study of fellow humans as they live, age and enjoy health or suffer sickness and sadness. Physicians who address these matters scientifically will maintain the core of scholarly integrity in medicine. Without them, medicine will no longer be a profession, but a technology.

Many of our current clinical centers have been designed to take the work of translation in only one direction: from the laboratory to the clinic. The necessary protocols are tightly structured activities, as required for statistically valid analyses of the efficacy of new therapeutic agents. But as history has shown, the results of patient-oriented studies—carried from the clinic into the laboratory—can give an invaluable "peek" behind the curtain of confusion and uncertainty of disease. Such was the case when attempts to explain the peculiar blue skin coloring of dying influenza patients gave rise to the new science of blood chemistry, or when studies of sputum from pneumonia patients led to the discovery that genes are made of DNA.

Observant physician-scientists—with a passion for fathoming the secrets of disease—are our great hope for a future that will produce revelational and sometimes revolutionary research.

Best wishes for the Rockefeller Hospital can be found in the words used by Rufus Cole on May 27, 1926, at a celebration of the centennial of the incorporation of the General Hospital Society of Connecticut. "May this hospital," Cole wished, "in the future, as in the past, have the services of the greatest men in the medical profession. May they be guided by the same broad humanitarian spirit as have their predecessors and may the next centennial bring as marked cause for satisfaction to your descendents as this first centennial has brought to you."[42]

Cole had hopes for "the next centennial" and looked to "the greatest men in the medical profession" to bring it to fruition. We have admired his remarkable ability to find and bring great men and women to the Rockefeller Hospital. The financial support provided for this effort must be considered one of the greatest successes of private philanthropy in the 20th century. American medicine left its apothecary, apprenticeship, craft days and took a seat in the academic arena.

Surely, physicians must do service for all and assist industry to develop better drugs and treatments, but the integrity of their

profession demands that they also maintain a corps of their colleagues devoted to observing and probing the nature of disease. There seems to be a never-ending abundance of the sick, aged and dying. We must hope that special hospital-laboratories will always exist as a workplace for creative, imaginative physicians, well endowed by private funds, free of the competing pressures that can hobble and trivialize research.

May the Rockefeller Hospital of 1910–2010 continue to show the way toward creating a new understanding of human biology, through the intensive study of patients and disease, thereby enriching science so as to provide better health for all.

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Dr. Hirsch is a leading authority on the metabolic and behavioral aspects of obesity and its role in degenerative disease. Through studies of fat cells, he has helped to explain why so many people have difficulty losing weight, why many who do lose weight suffer from the physical and emotional symptoms of starvation, why many individuals regain the weight they have lost, and what factors contribute to obesity.

After attending Rutgers University, Dr. Hirsch earned an M.D. from Southwestern Medical School at the University of Texas, which has recognized him with its Distinguished Alumnus Award. He then completed an internship at Duke University Hospital and a residency at the Upstate Medical Center. Dr. Hirsch served for two years with the U.S. Coast Guard, working for the Public Health Service, before joining what was then The Rockefeller Institute in 1954. He was appointed a professor and senior physician in 1967 and the University's Sherman M. Fairchild Professor in 1988.

Dr. Hirsch has served on numerous national advisory councils and held leadership positions with the American Society for Clinical Nutrition, the American Psychosomatic Society and the Association for Patient-Oriented Research. In 1993, he was elected to the U.S. Institute of Medicine. He is the recipient of an honorary doctorate of science from the State University of New York, and he has been named a fellow of the American Association for the Advancement of Science, the New York Academy of Medicine, the American Institute of Nutrition and the Royal College of Physicians in Edinburgh.

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Page 60, Zach Veilleux
Page 63, courtesy of the laboratory of Ralph Steinman

In honor of the Hospital's Centennial, The Rockefeller University has created a special website, **http://centennial.rucares.org.** Visit the page **Discoveries Advancing Medicine** for vignettes describing more than 100 landmark scientific and medical advances made at Rockefeller.

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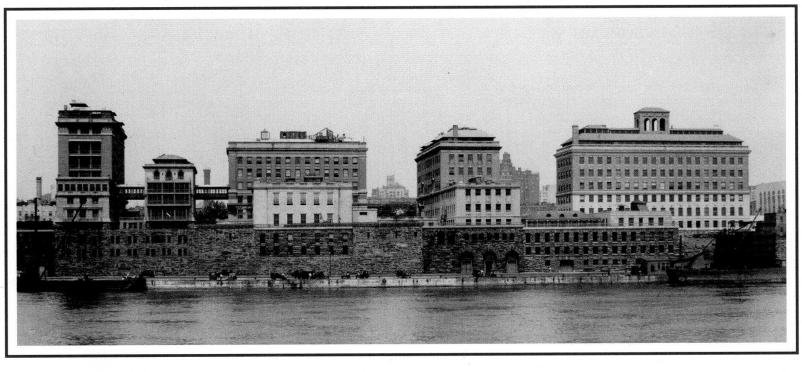

A CENTENNIAL ESSAY

Commemorating the 100th Anniversary of
The Rockefeller University Hospital

On the front cover: The Rockefeller Institute in 1917, with the Hospital at the right.
In the foreground is a War Demonstration Hospital, created during World War I.