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THE ROCKEFELLER UNIVERSITY

RESEARCH

PROFILES

*What is now proved
was once only imagin'd*
—WILLIAM BLAKE

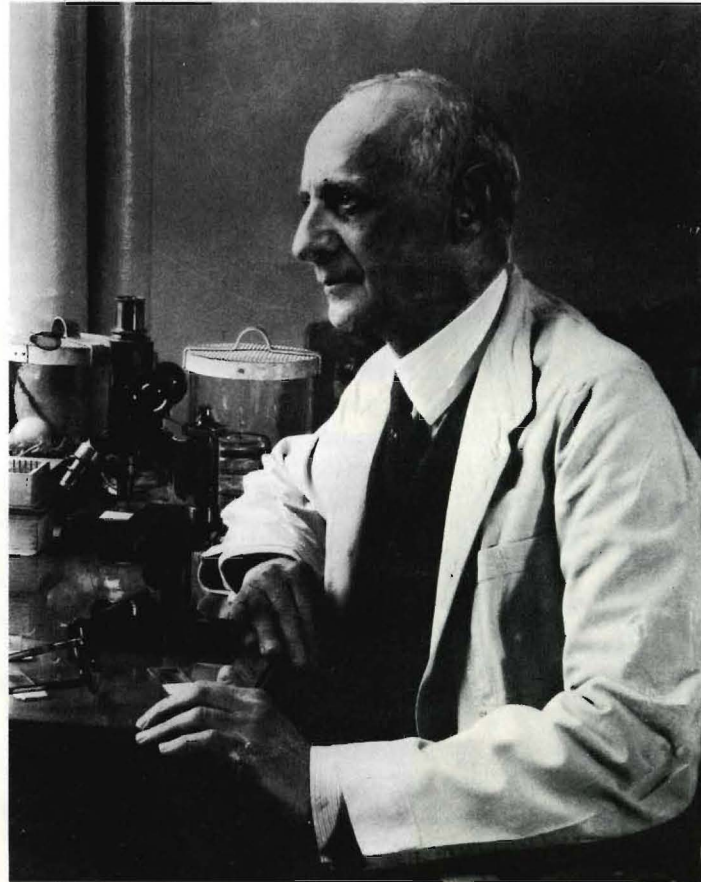
SUMMER 1987

Dr. Flexner's Experiment

When Simon Flexner retired in 1935 as the first director of The Rockefeller Institute for Medical Research, his colleagues wanted to organize a testimonial in his honor. But Flexner, in keeping with his characteristic reserve, politely declined. He had been director for thirty-three years, during which time the Institute had grown from a handful of scientists working in rented quarters to a world-renowned research center. As he passed through its gates for the last time, he left behind, on its library shelves, the most durable and eloquent tribute to his career: one hundred bound volumes containing the reports of the scientists whose research he had guided, encouraged, and nurtured.

Within the pages of the volumes were his own considerable contributions to the understanding of meningitis and polio, Hideyo Noguchi's studies of syphilis, Peyton Rous's demonstrations of virus-caused cancer, Karl Landsteiner's discovery of the Rh factor, Eugene Opie's descriptions of the process of inflammation, and the research on pneumonia that culminated in Oswald Avery's identification of DNA as the material of the genes.

With this issue, *Research Profiles* introduces what will be an occasional glance backward at the history of The Rockefeller Institute for Medical Research, now The Rockefeller University, as exemplified by some of its most remarkable figures. We begin, appropriately, with Simon Flexner.



Simon Flexner, 1863-1946



First board of directors. From left, T. Mitchell Prudden, Christian A. Herter, L. Emmett Holt, Simon Flexner, William H. Welch, Hermann M. Biggs, and Theobald Smith.



Flexner and Frederick T. Gates, confidential advisor to John D. Rockefeller, Sr.

“AM I THE MAN FOR THE PLACE?”

The idea for an institute for medical research was first proposed to oil magnate John D. Rockefeller by his confidential advisor, Frederick T. Gates. During his early years as a clergyman, visiting the sick and dying, Gates had had ample opportunity to see at first hand how ineffective was the medicine of the time. By the late nineteenth century, with the discovery that microbes cause infectious disease, a true medical science was beginning to emerge in such places as the Pasteur Institute, in Paris, and the Koch Institute, in Berlin. No such institutes existed in the United States. Gates's vision of an American institute comparable to the great research centers of Europe was shared by John D. Rockefeller, Jr., who was instrumental in organizing The Rockefeller Institute's first board of directors and acted as an intermediary between the board and his father.

The first choice for the position of director was not Simon Flexner but the distinguished animal pathologist Theobald Smith. To no one's great surprise, Smith declined to leave his post at Harvard. When the board approached Flexner, he, too, was not sure he wanted the job. Two years earlier, he had been appointed director of pathology at the University of Pennsylvania School of Medicine. At the age of thirty-eight, he was on the faculty of the nation's oldest medical school in the most prestigious position a pathologist could hope for. Also, he was skeptical as to whether the proposed institute could be successfully established with a benefactor who was proceeding so cautiously it seemed his support might vanish at any moment.

Flexner had doubts as well about his own competence to lead such an endeavor. For within the mind of the accomplished scientist lingered memories of the unpromising boy he had been growing up in Louisville, Kentucky. (When he was ten, his delinquency so worried his parents that his father, an immigrant Jewish peddler, arranged a private tour of the town jail as a warning to his son of where he would end up if he did not change his ways.) He had dropped out of school in the eighth grade, and until he fell victim, at sixteen, to typhoid fever, he had drifted from one menial job to another.

His nearly fatal illness and long convalescence transformed the indolent adolescent. As he himself expressed it, “I appear

to have become wide awake almost at once.” From a job as a drugstore apprentice he went on to earn a degree, with highest grades, at the Louisville College of Pharmacy and was soon sharing ownership of a drugstore with one of his brothers.

Greater achievements followed, but he never completely conquered his early sense of inadequacy. All his life he remained shy and reticent, unsure of his capabilities. Writing to a friend for advice as to whether or not to take the Rockefeller post, he wondered, “Am I the man for the place? Have I the originality to keep it going?”

Also in need of assurances was the man being asked to bankroll this experiment in scientific philanthropy. An institute devoted entirely to laboratory science was, after all, an unproven concept in the United States, regarded even by members of the medical establishment with suspicion. At that point, Rockefeller was prepared to give twenty thousand dollars a year for ten years, a sum just enough for the board to begin moving ahead by small steps.

The first question the board pondered was whether there were enough able scientists to fill an institute. To find out, they provided funds to support young researchers working in existing medical school laboratories. The papers that followed convinced them there was no lack of talent.

Since Rockefeller had asserted that his primary interest in research was humanitarian rather than scientific, the board also allotted part of the first year's budget to an immediate medical problem. Infant illness and death from dysentery were widespread in New York, as in other large cities. Researchers enlisted by the Institute began an investigation that quickly demonstrated an alarmingly high level of bacterial contamination in the milk sold from open cans to tenement dwellers. Before the study was officially submitted, the Board of Health had issued rigorous new regulations for milk inspection and the dysentery epidemics in New York halted.

The practical value of medical research had been demonstrated, as well as the existence of sufficient expertise to carry it forward. But what finally decided the matter was news that rival industrialist Andrew Carnegie was planning his own philanthropic enterprise. On June 13, 1902, John D. Rocke-

feller donated one million dollars to The Rockefeller Institute for Medical Research. The next day, Simon Flexner accepted its directorship.

“GIVE THEM PERFECT FREEDOM”

Since his formal employment was not to start until the following year, Flexner used the intervening months to visit research institutes in Europe and meet with prominent scientists in order to clarify his ideas. It was from Anton Dohrn of the Naples Zoological Society that he received the most pointed advice. “Men work here in a dozen different branches of biological science,” Dohrn told him. “Can I be an authority on them all? No, no. Give them perfect freedom. Let them search where and how they will. Help in every way you can, but do not pretend to be master of them. . . . Unless you permit workers in the medical institute to make perfect fools of themselves,” he warned Flexner, “you will make no great discoveries.”

It was a point of view consonant with Flexner’s own development. Tending the pharmacy in Louisville, he had taught himself to use a microscope, and without books or teacher, with only tissue specimens given him by local doctors, had mastered the basics of histology and pathology. His self-directed approach changed little when he entered the scientific community.

In 1893, the Johns Hopkins University, in Baltimore, had established a medical school with research laboratories that quickly become famous as a proving ground for young physicians interested in pursuing medicine as a science. The teaching staff, as Flexner learned, placed strong emphasis on independent investigation. It seemed to him the ideal place to expand his knowledge. But to become eligible to study pathology at Hopkins, he needed an M.D. degree.

Such a requirement was easier to fulfill then than now. Medical schools in those days were by and large spurious affairs, little more than trade schools in which instruction typically consisted of rote lectures delivered by practitioners turned part-time “professors” in return for a share of the students’ fees. (It was this system of medical education that Simon’s brother Abraham was to criticize harshly in the now famous “Flexner



Report” of 1910. The impact of the report closed hundreds of medical schools and impelled those that remained to upgrade their methods.) Simon Flexner received a medical degree in Louisville without ever having performed a physical examination. In September of 1890, with five hundred dollars lent him by his brother Abraham, he arrived in Baltimore.

The pathology department at Hopkins was headed by William Henry Welch, whose idiosyncratic and freewheeling style suited Flexner perfectly. After brief lectures, the students were given tissue sections to stain, mount, and study. Welch moved among them, sometimes discussing what they were seeing under the microscope, but for the most part leaving them to puzzle out problems for themselves. The result was a harvest of original research, including a major finding by Flexner.

The lecture topic of the day had been diphtheria. Welch had explained that Friedrich Loeffler, the discoverer of the diphtheria bacillus, had been unable to confirm a report of diphtheria lesions in lymphoid glands. After the lecture, Flexner decided to try the experiment on his own. Obtaining an infected guinea pig, he removed the lymphoid glands, took a cutting, and mounted it. As he turned the knobs of the microscope, the image sharpened. With a shock of surprise, he saw the lesions.

Upper left, the Schermerhorn farm purchased in 1903 as the permanent site for The Rockefeller Institute, and, lower left, the Institute as it appeared during the time of Flexner’s administration. Above, The Rockefeller University today.

The significance of this, his first major discovery, was twofold: it confirmed Loeffler's bacillus, which had been under dispute for years, and it solved a controversy concerning whether the disease was local or constitutional in origin. (Flexner showed that the bacilli proliferated only at the point of infection and then produced a poison that passed into the body.) Flexner became Welch's favorite student, and when a position became available as Welch's assistant, he got the job.

Although Flexner often commented that he had consciously modeled himself after Welch, the two men could not have been more different. Flexner was punctilious to details; Welch's rooms were cluttered with books, papers, and unread manuscripts. Flexner was self-contained, soft-spoken, and slightly built; Welch was rotund, gregarious, fond of cheap cigars, amusement park rides, and baseball. A Baltimore Orioles fan, he could be found regularly at the ballpark on summer afternoons correcting proofs of *The Journal of Experimental Medicine* between innings. Their differences notwithstanding, the two men, working together, redirected pathology training at Hopkins from the traditional style of reading, listening, and memorizing to that of seeing and doing. Welch served on the board of scientific advisors of The Rockefeller Institute for thirty-two years.

FINDING THE BEST

The initial staff Flexner recruited for The Rockefeller Institute for Medical Research began work in 1904 in a converted three-storey apartment building on Lexington Avenue and 50th Street in Manhattan. Until the Institute could prove itself, established investigators and those with promise could not be expected to be easily wooed from university positions. Flexner's mission was to convince them to take a chance on the future of the fledgling institution.

Samuel Meltzer was one of the men Flexner doubted would accept his invitation. At fifty-three, Meltzer had long before distinguished himself as a pathologist in his native Germany. Because, as a Jew, he could not hope for a university chair there, he had come to New York and had been supporting his research with a medical practice. Flexner could offer only a half-time job. Meltzer responded, "I have always paid



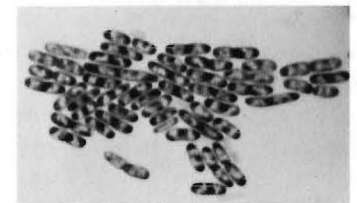
Scientific and administrative staff, circa 1912. Front row, from left, P.A.T. Levene, Alexis Carrel, Simon Flexner, and Samuel Meltzer. Hideyo Noguchi appears in the second row, between Flexner and Meltzer.

laboratories to be permitted to work in them; now you propose to pay me to work. Of course I will come."

The group was soon joined by Phoebus Aaron Theodor Levene, a Russian-born chemist who had studied in the prestigious laboratory of Emil Fischer in Berlin. Flexner showed courage in taking him on, for Levene had recently spent more than two years nursing a tubercular lung.

Flexner also invited his former protégé from the University of Pennsylvania, Hideyo Noguchi. A rice farmer's son from Japan, Noguchi had put himself through medical school and in 1899 traveled halfway across the world to present himself, with twenty dollars in his pocket, on the doorstep of "the great Dr. Flexner." Under Flexner's guidance, Noguchi became a master microbiologist and pathologist. Among his achievements, he was the first to demonstrate that paresis resulted from syphilis and to grow pure cultures of the syphilis spirochetes. (At Pennsylvania, he had begun studies on the effects of snake venom on red blood cells. He continued these investigations at Rockefeller, keeping live rattlers in dry-goods boxes to the consternation of his colleagues and the delight of newspaper reporters.)

His dream was to conquer yellow fever. The agent of yellow fever is a virus, and very little was then understood about viruses. In 1928, he died of the disease, contracted in Africa, where he had journeyed at the height of an epidemic, still hoping to solve its mystery. By the time of his death, he had



Shigella flexneri, a major bacillus of dysentery. Flexner made the study of dysentery a lifelong project. The organism, named for him, was among the samples he brought back from an expedition to the Phillipines in 1899.



Alexis Carrel, in white hat standing behind operating table, at the War Demonstration Hospital, circa 1917. Carrel, who received the first Nobel prize in Medicine awarded in the United States, in 1912, taught military surgeons a new method he helped to develop for treating bacterial infections from combat wounds.

attained world recognition. In his native country, half a century later, his name retains its heroic stature and The Rockefeller a special esteem.

In pursuit of the best, Flexner recognized no boundary of race, religion, nationality, or sex, not a policy common to all institutions in those days. And he selected his staff to represent the broadest base of scientific inquiry, making no attempt to fashion the Institute after his own particular interests. Nor did he press for immediate results. But while publicly asserting that “there is no royal road to discovery,” privately he harbored doubts. “The first years,” he later confessed, “were nervous ones for all concerned.” He felt pressed to deliver himself some important and highly visible result.

The opportunity soon presented itself in the form of an epidemic of cerebrospinal meningitis that struck New York in 1904. Before it was done, it had claimed three thousand lives. Flexner had studied the disease at Hopkins and was well-acquainted with the bacterium that inflamed the brain and spinal cord membranes of its victims. He took up the challenge again.

Investigators in Europe and at the Board of Health

laboratories in New York had developed a serum that raised antibodies to the bacterium but failed to stop the course of the disease. Flexner struggled with the problem without success until he was inspired to try a novel mode of inoculation. Instead of injecting the serum under the skin, which was the usual procedure, he injected it directly into the spinal canal at the site of inflamed membranes. After successful trials with laboratory animals, this method was used with human patients during a meningitis outbreak in Ohio in 1907. Of those thus treated, three in four survived, as opposed to one in four in previous epidemics.

For a number of years, Flexner personally supervised the manufacture of the Flexner serum, as it came to be known. In one twelve-month period the Institute distributed seven thousand bottles. Although results were not always as impressive as in Ohio, the serum remained the only means for reducing deaths from meningitis until the advent of antibiotics.

During those years, Flexner also conducted some of the earliest studies of polio, discovering, among other things, its viral origins and its mode of transmission. His work provided what Jonas Salk later called the “conceptual framework” for the development of polio vaccines.

In 1906, The Rockefeller Institute moved to its permanent home on York Avenue and 66th Street. In 1910, it opened the first hospital in the country devoted solely to clinical research. At the Rockefeller Hospital, long before his DNA discovery, Oswald Avery explored the mechanisms of pneumonic infection and developed the first effective treatment for it, and Rebecca Lancefield classified the bacteria responsible for human streptococcal infection. A laboratory of animal and plant pathology was established in 1914, in Princeton, New Jersey, where, John Northrop and Wendell Stanley conducted enzyme research that led to a Nobel Prize in 1946.

During the First World War, the Institute ran a War Demonstration Hospital on its grounds to teach surgical methods to medical officers. Among its instructors was Alexis Carrel, whose surgical innovations had won him, in 1912, the first Nobel Prize in Medicine awarded in the United States and the first of the nineteen Nobel Prizes that would come to scientists

AY. AUGUST 6. 1907.

CURE IS FOUND FOR MENINGITIS WITH JOHN D.'S AID

Discovery of Dr. Flexner, of the Rockefeller Institute. Is Declared to Have Positively Succeeded.

From the New York World,
August 6, 1907.

associated with The Rockefeller. During this period, Peyton Rous, who would receive a Nobel Prize in 1966 for his discovery of a cancer virus, developed a method for preserving whole blood for use in transfusion, a vitally important technique for military medicine.

If Flexner found the task of choosing a staff "a difficult and often dubious and baffling undertaking," others were often baffled by his choices. Board member Theobald Smith questioned the appointment of the German physiologist Jacques Loeb. What, Smith asked, did physical chemistry have to do with curing disease? But Loeb, whose demonstration of chemically induced parthenogenesis in sea urchins and frogs had astonished the scientific world, believed that physical chemistry would eventually explain all biological phenomena. The so-called mechanistic theory of life was his religion and he preached it in laboratory and lunchroom.

At the other end of the spectrum, the Frenchman Carrel, ardent Catholic and mystic, who claimed to have had a heavenly vision at Lourdes, tried the director's devotion to "perfect freedom" in other ways. Beyond creating his own miracles of technique, from the suturing of minute blood vessels to new methods for cell and organ cultivation, Carrel's imagination led him in many directions. Observing that cancer rates varied widely from one geographical area to another, he hypothesized that diet played a role, a notion considerably ahead of its time. To test it, he convinced Flexner to build him a "mousery," a huge glass-roofed, air-conditioned labyrinth on the top floor of the Institute's powerhouse. At its peak population, it housed fifty-five thousand mice. The mousery ended in mystery, its appropriations terminated without explanation, Carrel's voluminous records undecipherable. As Dorhn had foreseen, freedom was a philosophy that necessarily combined spectacular success with frequent failure.

THE MAP OF TIME

Simon Flexner achieved the hope he had expressed early in his tenure of putting the work of The Rockefeller Institute on "the map of time." His special genius resided in his respect for individuality and his understanding of the scientific tempera-

ment. Juggling administrative minutiae and budget ledgers, he was always sensitive to how demanding, lonely, and heartbreaking the research life could be. Over thirty-three years, more than one scientist would emerge from the director's office strengthened against despair. "I did not think yesterday morning my nerves could stand the strain much longer," Phoebus Levene wrote to Flexner. "I left your room after our little interview cured and happy."

"Such men," Flexner observed, "when numerous assembled under one roof, may give rise to situations which tax somewhat the administrative staff; but it appears nevertheless that with the high purpose mutually understood and appreciated and the exercise of a fair amount of human wisdom and tact, such a temperamental team is capable of working in close contact and with mutual respect and helpfulness."

Once, in a letter to his future wife, Flexner wrote about a day in the laboratory when a number of his group were "working merrily" and of how he "caught the spirit and puttered among some embers of studies." Suddenly, he observed something through the microscope he had not seen before. "Nature is a tantalizing mistress," the letter concludes, "and gives her fruits only at particular seasons, when the spirit is on her—and you." The cultivation of that spirit, which continues to guide the work of The Rockefeller University, was Dr. Flexner's greatest experiment and his legacy to science. □

EDITOR'S NOTE

For further reading we suggest *An American Saga*, by James Thomas Flexner, published in 1984 by Little Brown and Company, in which the author, an award-winning historical writer, chronicles the lives of his parents, Simon Flexner and Helen Thomas, whose families' members included Simon's equally renowned brother, Abraham, Helen's oldest sister, M. Carey Thomas, president of Bryn Mawr College, and her brothers-in-law, Bertrand Russell and Bernard Berenson. Also, *A History of the Rockefeller Institute* by George W. Corner (Rockefeller University Press, 1964), and *A System of Scientific Medicine* by Howard S. Berliner (Tavistock Publishers, 1985).

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