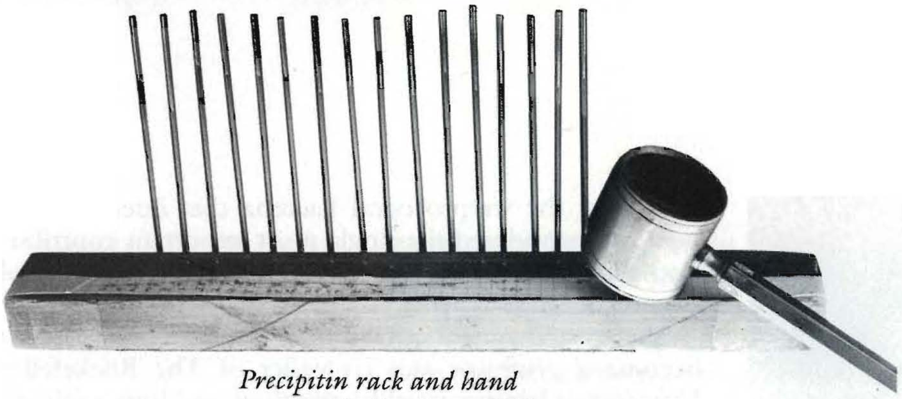
Summer 1990

"Mrs. L." : [Dr. Rebecca Lancefield]

Judith N. Schwartz



Precipitin rack and hand lens used by Dr. Lancefield

THE ROCKEFELLER UNIVERSITY

RESEARCH PROFILES

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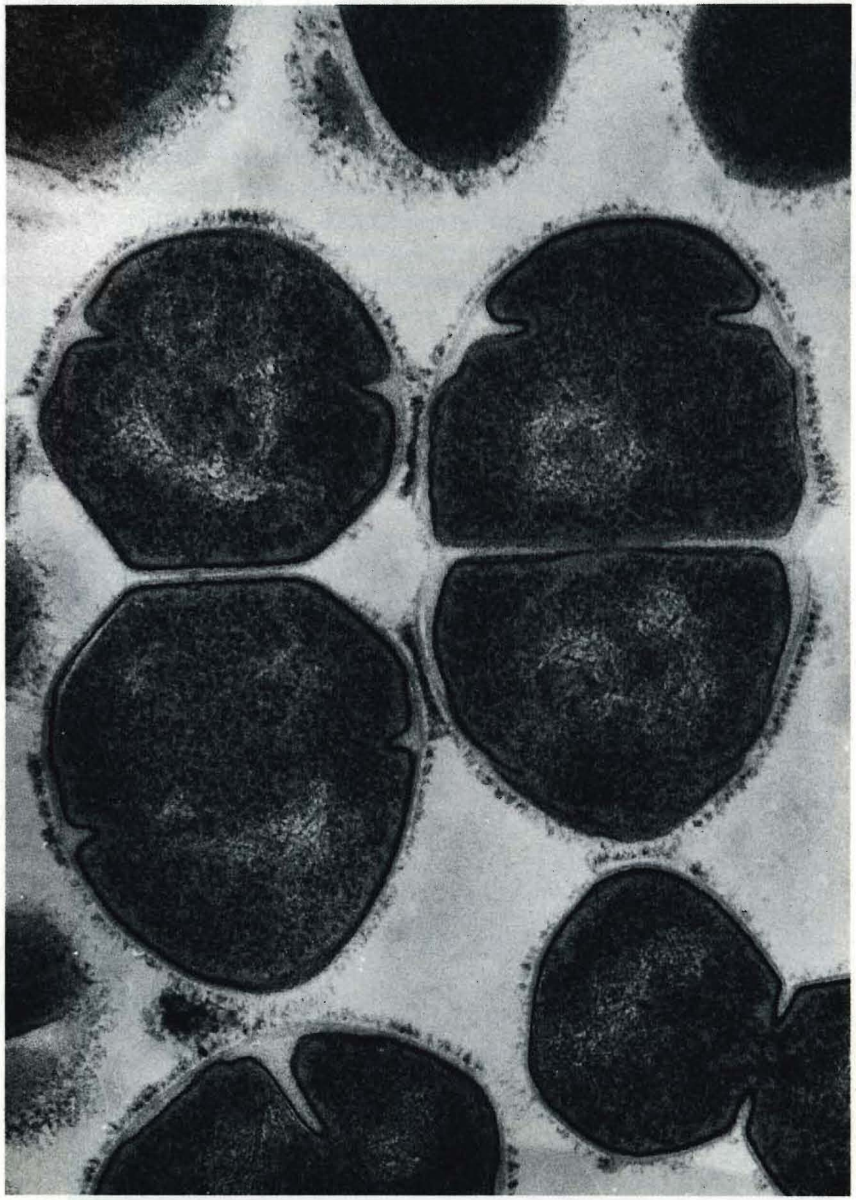
"Mrs. L."

Her laboratory was called "the Scotland Yard of streptococcal mysteries." In it, for more than sixty years, Rebecca Lancefield stalked a devious, multifarious adversary: the streptococcal bacteria.

For those with access to modern medical care and antibiotics, a touch of "strep" may not seem a particularly serious threat. In 1918, when Rebecca Lancefield first came to The Rockefeller Institute for Medical Research (later The Rockefeller University), the diseases caused by streptococcal infection, among them rheumatic fever, scarlet fever, and acute nephritis, were common and dangerous ailments. Millions of people, mostly children, developed crippling heart disease in the wake of rheumatic fever. Millions in Africa, Asia, and Latin America still do.

When she began her research no one knew how many kinds of streptococci existed, which ones were dangerous to man, or how they did their damage. The link between strep infection and rheumatic fever had been postulated but not proven. Her work provided the basis for answering those questions and for the development of effective diagnosis and treatment. The system she devised for

Rebecca Lancefield, 1895-1981



Electron micrograph of streptococcal bacteria, magnified about 70,000 times. Fuzz around the bacteria is composed of M protein molecules.

classifying the streptococcal bacteria that infect human beings is considered the single most important contribution that has been made to medical understanding of streptococcal disease.

She started out as a technical assistant. She rose to become a professor and co-leader of The Rockefeller University's laboratory of bacteriology and immunology, a member of the National Academy of Sciences, and an Honorary Fellow of the Royal College of Pathologists. Two scientific societies bear her name. The woman they honor worked at her laboratory bench, continuing to solve mysteries, until shortly before her death in 1981, at the age of eighty-six.

FIRST ASSIGNMENT

Rebecca Lancefield always insisted that she went to work at the Rockefeller because it was the only place that answered her job letters. If so, it was a piece of very good luck— for her and for the Rockefeller. She had been hired to assist Oswald Avery, a happenstance she described as the "most fortunate" of her scientific career. Avery is best known today for the identification of DNA as the genetic material, a discovery he made with Colin MacLeod and Maclyn McCarty in the 1940s as an outgrowth of their studies of pneumonia bacteria. Long before the DNA finding, however, Avery was revered among microbiologists as possibly the most brilliant bacteriological investigator and mentor of his era.

Although his interest was the pneumococcus bacterium, Avery, along with other Rockefeller researchers, had turned his attention during World War I to the medical needs of the military. Following severe outbreaks of strep infections at military camps in Texas, he and his colleague Alphonse Dochez were attempting to determine whether one or several types of streptococci were involved in the epidemic. Within a year after Rebecca Lancefield's arrival, the team had found four distinct types. The inclusion of

her name on the paper reporting their results was, according to Maclyn McCarty, later to be Dr. Lancefield's laboratory associate, "a type of recognition seldom accorded to technical assistants in those days."

She had been lucky in other ways. Her background and childhood might not have seemed to provide fertile soil for the cultivation of a scientist, particularly a woman scientist. Her family, on both sides, had deep roots in the provincial, tradition-bound South. With their Army-officer father, Colonel William E. Craighill, Rebecca and her five sisters led a peripatetic life that resulted in erratic early schooling. But Mrs. Craighill was a strong believer in education for women, a conviction which laid the foundation for the careers of Rebecca and another daughter, Margaret, who became a successful physician.

At Wellesley College, Rebecca Craighill happened to room with a zoology major. Originally intending to study French or English, she'd peer over her roommate's shoulder and decided that doing science was more to her taste than conjugating verbs. Later, while working toward her master's degree in bacteriology and genetics at Columbia University, she met a fellow student, Donald Lancefield, with whom she would share a love of science and a loving partnership to the end of her life.

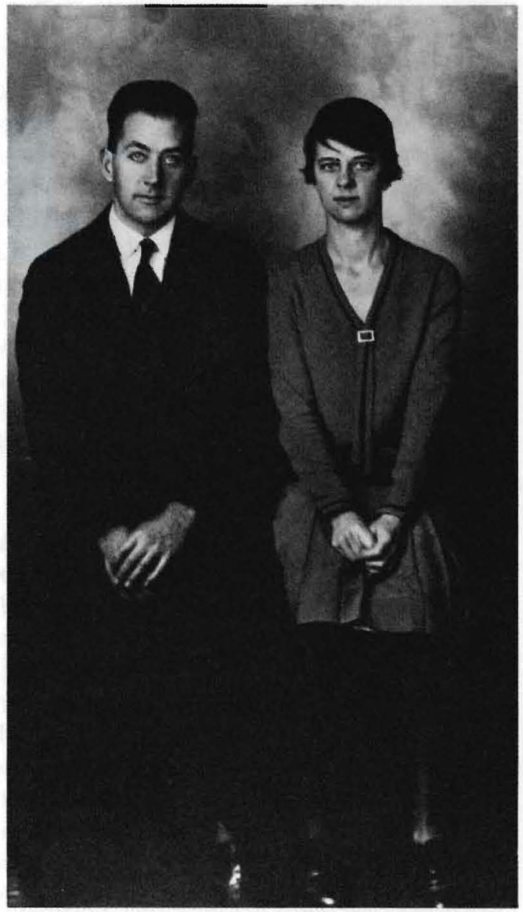
The Lancefields' daughter, Jane Hersey, an editor, remembers a mother of "extraordinary energy" and idealistic commitment to science "for the thing itself," and a father who, in those pre-feminist days, could find his way around the kitchen when "Mrs. L," as her Rockefeller colleagues affectionately called her, had to work late at the lab. At a young age Mrs. Hersey recalls the pride she felt towards her mother because she was "different" from the other mothers in their suburban Long Island community.

With the close of World War I and the termination of Army funds for Avery's streptococcal research, Rebecca Lancefield's first assignment at the Rockefeller came to an end. She returned to Columbia as a research assistant while her husband completed his Ph.D. Following his graduation, both accepted teaching positions at the University of Oregon, Donald's home state. In 1922 Donald Lancefield received an appointment to the Columbia faculty where he remained for many years before assuming the chairmanship of the Department of Zoology at Queens College in New York. Rebecca Lancefield was offered a second chance to do research at the Rockefeller, working with streptococci bacteria to determine their role in rheumatic fever.

MAKING ORDER

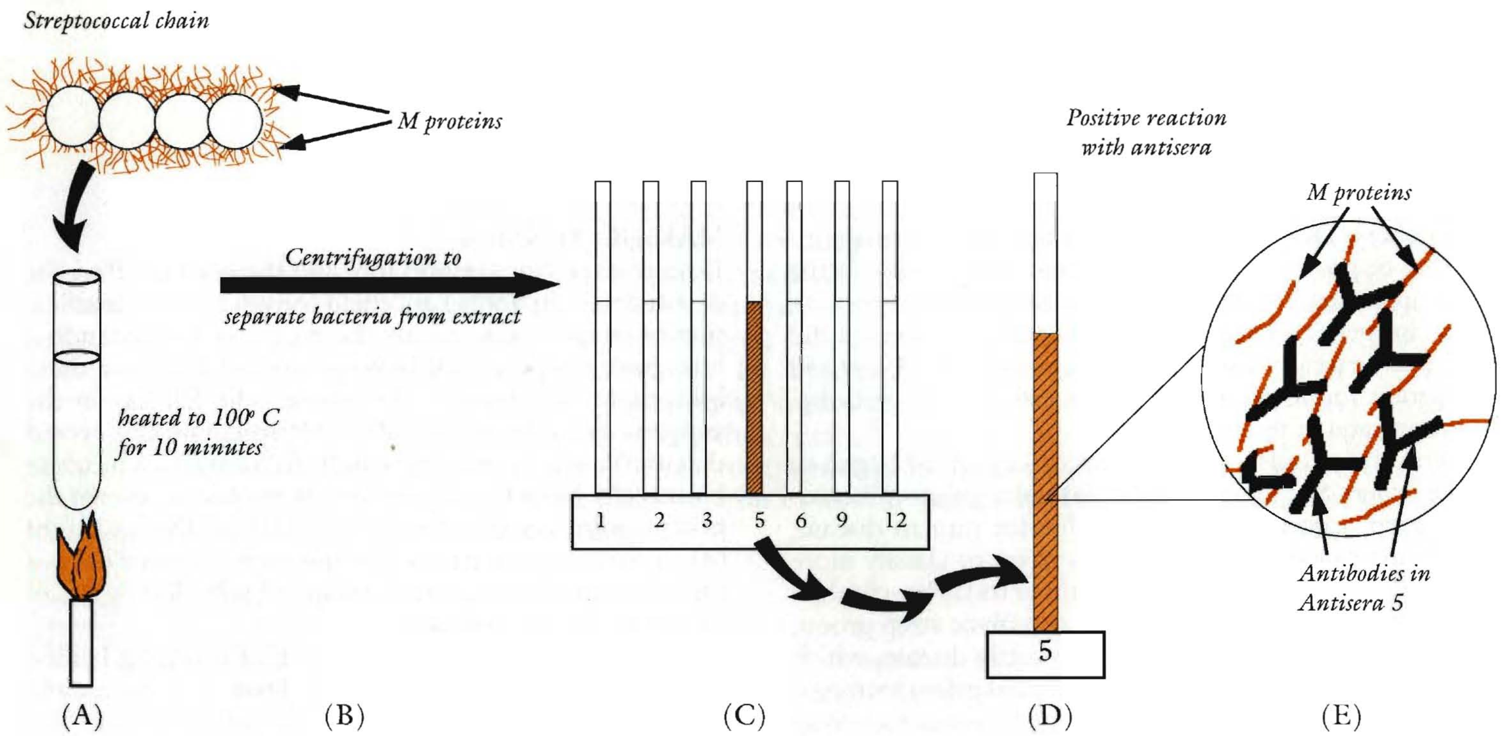
Some species of microorganisms exist as one-of-a-kind. Others come in many different varieties—streptococci notorious among them—as Rebecca Lancefield would learn.

She had been invited to participate in rheumatic fever studies being initiated at The Rockefeller Institute's research hospital by Homer Swift, a deliberate, painstaking physician-researcher fated to be nicknamed "Speedy" by his laboratory juniors. Before the war, Swift had tried without success to recover a specific bacterium from rheumatic fever patients that could be definitively identified as the causative agent of the disease. When Dr. Lancefield joined his laboratory, the bacterial bugs under suspicion were a streptococcal group called "green" or viridans.



Rebecca Lancefield and her husband Donald Lancefield in 1928

Rebecca Lancefield endured two years of frustration. The myriad green strains proved to be a lawless, perverse morass. With the patience and persistence that would become her hallmark, she worked simultaneously for Swift at the Rockefeller and for her doctoral degree at Columbia, carrying racks of test tubes back and forth between labs.



Precipitation reaction for determining streptococcal serotypes:

(A) The antigen, or M protein, is extracted from streptococcal chains by heating them for 10 minutes in an acid solution.

(B) The bacterial portion is separated from the M protein extract through centrifugation. The bacteria are discarded.

(C) To determine the serotype of the streptococcus from which the M protein was prepared, the extract is placed in capillary tubes and mixed with each of a battery of antisera reactive with known serotypes.

(D) In this example, antisera 5 shows a positive reaction with the extract. Thus, the serotype of the streptococcus from which the extract was derived is Type 5.

(E) A white cloudy sediment forms in the capillary tube indicating a positive precipitation reaction. This occurs when the antibodies contained in the antisera bind to the M proteins from the streptococci being tested, forming an insoluble complex.

She finally managed to ascertain that viridans was not the culprit in rheumatic fever. Fortunately for science, she returned to work on hemolytic strep, the kind of strep she had studied with Avery.

The method she used, based on Avery's approach to the sorting out of pneumococcal types, is called serological analysis. Simply stated, it works this way: Antigens are molecules on the surface of invader cells, like bacteria, that a host organism recognizes as foreign. Strains of bacteria differing on the basis of their antigens are called serotypes. Serotypes are identified by means of antibodies that combine only with the antigens of that serotype. The antibodies are obtained by injecting an experimental animal with antigens from a known serotype. Antibodies form in the animal's blood, or serum, which is then called antiserum.

Antiserum mixed with an extract of the bacteria of a specific serotype causes the type-specific protein in the extract to precipitate, producing a whitish sediment in the test tube. This is called a precipitation reaction. If a precipitation reaction occurs with the extract of an unknown serotype, it can be concluded that the serotype is the same as the known one that was used to make the antiserum.

By the mid-1920s, Dr. Lancefield had isolated two antigens from hemolytic streptococci. One was type-specific, that is, it was responsible for the differences in the various strains of strep that had been obtained from the patients of a Texas epidemic. The other antigen was species-specific; it appeared to be present in all human strep strains.

Oswald Avery (just down the hall from Lancefield on the same floor of the hospital) had determined earlier that the type-specific antigens of pneumococci were made of polysaccharides, which are complex carbohydrates. To her surprise, and to the initial disbelief of some of her fellow

researchers, Dr. Lancefield found her type-specific antigens to be proteins. She labeled them M proteins (for the matt appearance of the colonies formed by bacteria with these antigens). Her species-specific antigen, however, did prove to be a carbohydrate, and not long after, Avery and his group found an analogous species-specific carbohydrate antigen in pneumococci.

With these tools in hand, Rebecca Lancefield began to make order. She identified the particular group of hemolytic streptococci chiefly responsible for human disease, which she called Group A, and went on to classify more than sixty distinct strains. (The number today has climbed to eighty). She identified another hemolytic strep group, Group B, originally encountered in cattle disease, which was found could also cause septicemia and infant meningitis in human beings. In later years, she returned to Group B and initiated studies that investigators are still pursuing.

John J. Sampson presents Rebecca Lancefield with the American Heart Association Research Achievement Award in October 1964.

MAKING SENSE

Despite its obvious importance and the years of effort she devoted to it, Rebecca Lancefield considered the classification of streptococci as only the means of understanding how basic streptococcal biology worked and how these bacteria caused disease. The answer, she felt, lay in the antigens. From her studies of the M protein she discovered that its role was to protect the bacteria from attack by white blood cells. Since the M protein is type-specific, even if the host's antibodies did manage to overcome the onslaught of one particular strep type, the immunity acquired did not provide protection against subsequent infection by any of the other Group A serotypes.

This finding clarified the puzzle that had long baffled researchers as to why rheumatic fever is a frequently recurring disease. "Her work on this antigen," Dr. McCarty has written, "provided the basis for a better understanding of the epidemiology of the disease and a more rational approach to its control."

During World War II, Rockefeller scientists were again called to service. Dr. Lancefield was appointed a civilian member of the Office of Scientific Research and Development and a consultant to the Armed Forces Epidemiology Board on the Commission on Streptococcal and Staphylococcal Diseases. When the commission was dissolved in 1972, its members continued to meet as an independent organization and in 1977 they adopted "The Lancefield Society" as its name.

Throughout the war and after, Dr. Lancefield worked tirelessly to identify strep strains and supply antisera to military laboratories. To the end of her career, she responded to all such requests from researchers all over the world. A colleague remembers her jokingly complaining about the endless stream of queries addressed to her "Scotland Yard" at the Rockefeller, saying "nobody ever sends me easy ones."

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Homer Swift retired in 1946. Maclyn McCarty moved across the hall from Avery's laboratory to join forces with Dr. Lancefield. In his early training as a pediatrician he had cared for children with rheumatic fever and considered it one of the most challenging problems in infectious disease. In their laboratory, Dr. McCarty concentrated on clinical aspects of the hospital's rheumatic fever service and on research concerning the course of infection and the chemical and biological properties of the streptococcal cell wall. Dr. Lancefield went on to identify and study other streptococcal antigens.

MORE THAN A LEGEND

Although first and foremost a research scientist, Dr. Lancefield was unavoidably drawn into the larger world of science. She was elected president of the Society of American Bacteriologists in the 1940s and of the American Association of Immunologists in the 1960s. She delivered major lectures in this country and abroad. Those were duties. Her pleasures, when not at the lab bench; were visits to and from fellow "strep hounds," as she called them. To her juniors she was a caring, generous mentor and a model of meticulous science. Dr. Vincent Fischetti, who joined the laboratory of bacteriology and immunology in 1962, has put it succinctly: "If Mrs. L published it, it was right." She never missed a lab celebration, and her family eggnog recipe remains a tradition at the lab's holiday festivities. Hating the New York heat, only in summer did she eagerly abandon her laboratory. At the Marine Biological Laboratory in Cape Cod, she and her husband could do science, swim in the ocean, and enjoy the company of their family, which eventually included two grandsons.

Many honors came to her. She received the T. Duckett Jones Memorial Award of the Helen Hay Whitney Foundation, the American Heart Association Achievement Award "for accomplishment in the cardiovascular field," and the Medal of the New York Academy of Medicine, among others. In 1973, The Rockefeller University, her lifelong scientific home, awarded her an honorary degree, as did Wellesley College in 1976, on the occasion of the college's 100th anniversary, which happened to be the sixtieth anniversary of Lancefield's graduation.

Streptococcal disease is not conquered. Treatment is hard to come by for many poor people, and almost nonexistent in many parts of the world. The search for a vaccine against strep infections, as in the case of influenza and other diseases caused by microorganisms that come in many strains, has been a struggle both scientifically and in terms of financial support.

Laboratories at Rockefeller and elsewhere continue the research for which Rebecca Lancefield laid the foundation. For five days this coming September, scientists from around the world will gather in Siena, Italy, for the eleventh Lancefield International Symposium on Streptococci and Streptococcal Diseases, under the auspices of the International Lancefield Society.

In the newsletter of the American Society of Microbiologists after her death, Lewis Wannamaker of the University of Minnesota Medical School wrote: "Inevitably, 'Mrs. L' became a legendary figure among microbiologists, but she was more than a legend. She was a patient, hardworking scientist and a warm, soft-spoken person who made her contribution without fanfare and without feeling the need to compete with anyone except, possibly, herself." □