Merrill W. Chase

1905–2004

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Carol L. Moberg

NATIONAL ACADEMY OF SCIENCES

MERRILL WALLACE **CHASE**

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Merrill Chase in 1965.
Photograph courtesy of The Rockefeller Archive Center.

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By Carol L. Moberg

With his discovery of the second arm of the immune system—cell-mediated immunity—immunologist Merrill W. Chase brought an end to the early 20th-century belief that antibodies alone protected the body from allergies and disease-causing pathogens. This finding laid the groundwork for subsequent discoveries that pinpointed B cells, T cells, dendritic cells, and other types of white blood cells as the body's central safeguards against infection. Chase's later research greatly clarified the nature of delayed type hypersensitivity to poison ivy and tuberculin as well as of contact sensitivity to simple chemical allergens.

Merrill was born and raised in Providence, RI, the only child of John Whitman and Bertha Wallace Chase. His father, an insurance salesman and owner of several rental properties, built the family's three-story home. His mother graduated from the Rhode Island teacher's college, then called the Normal School, and taught junior high school science. A curious and enterprising child, Merrill built a crystal radio, devised an electrical instrument to test how much current a person could endure, kept detailed records for his egg-selling business, and created several family genealogies. A love of classical music and photography engendered lifelong hobbies. Due to his father's poor health (and death when Merrill was 20), the repair jobs on rental properties and their own house fell to young Merrill. This meant living at home during his undergraduate years and not fully participating in college life. An excellent student, he graduated summa cum laude from high school and Phi Beta Kappa from college.

Chase received B.A. (1927) and M.S. (1929) degrees from Brown University, where he studied toxins liberated from enteric bacteria. Then, when he was in Chicago during the following year, he took two bacteriology courses at the University of Chicago and was based in the laboratory of Edwin O. Jordan, who was studying water- and milkborne diseases that cause food poisoning. Chase volunteered to be a subject in an experiment

to learn whether repeated exposures to drinking milk with staphylotoxin would lead to resistance. Despite early intestinal problems with reactions to the toxin, he was able to drink more and more of the contaminated milk because he became tolerant to the toxin; no antibody was ever found to explain this tolerance. The induction of tolerance to allergenic chemicals eventually became one of Chase's lifelong scientific interests. In 1931, Chase returned to Brown and completed his Ph.D. in bacteriology, with the thesis "Further Studies on the Liberation of Toxins from *Salmonella schottmuelleri*" (which causes an acute infectious disease similar to typhoid fever).

While in Chicago, he met his future wife, Edith Steele Bowen, who had a master's degree in biology from Pembroke College at Brown University and was finishing her studies for a Ph.D. in ecology at the University of Chicago. Her findings on sense organs and behaviors of catfish were published in 1931 as the first article in the first issue of *Ecological Monographs*. Merrill and Edith married on September 5, 1931, in Providence.

Merrill Chase in 1932, the year he joined The Rockefeller Institute . (Photo courtesy of The Rockefeller Archive Center.)

Beginning a career in immunology

Following a year as a biology instructor at Brown, Chase was hired in 1932 by Simon Flexner, the first director of The Rockefeller Institute for Medical Research (now The Rockefeller University) to work with Karl Landsteiner (1868–1943). Before joining the Institute in 1922, Landsteiner had discovered, in Vienna, that he could group humans

on the basis of serologic reactivity to red blood cells, now designated as A, B, and O blood types. He found that each group has distinct antigens and corresponding antibodies that react against the other blood groups, a discovery for which Landsteiner won a Nobel Prize in 1930.

Chase described Landsteiner as a strict laboratory head who insisted that his coworkers do research on projects under his explicit direction.

On Chase's arrival at Rockefeller, during the depth of the Great Depression, he first received a lecture about such economies as the costs of glassware, before being escorted to the Landsteiner suite in the newly built "North Building" (now Theobald Smith Hall). Chase later recalled the chemical laboratory showed signs of heavy use where a vast number of organic syntheses were being carried out to prepare artificial antigens: vacuum distillations, flasks in water-filled enameled pots on tripods over Bunsen burners, draft hoods where solutions were evaporated in porcelain dishes set over steam funnels. There was an oxygen tank and a torch for fashioning their own glassware and pipettes. The few motor-driven instruments used DC current generated by the Institute.

Chase described Landsteiner as a strict laboratory head who insisted that his coworkers do research on projects under his explicit direction: He

> *manifested an endless flow of ideas, stimulated by constant reading, which he wrote on slips of paper. His assistants were encouraged to try various things while working on particular problems he assigned. Idleness was intolerable, curiosity was insatiable. With this high standard of work, he was scrupulous about publications, demanding they must be 'thick' so their results could be repeated by others.*

Further, in a 1950 letter to George Mackenzie, who was writing a biography of Landsteiner, Chase described his own sense of powerlessness and criticized Landsteiner's failure to train or encourage independent scientific inquiry among his numerous associates (Chase 1950). Nonetheless, this experience had an influence on Chase, who also became known as a rigorous, controlling, and demanding lab head. One of his later colleagues referred to him as a "one-man surveillance mechanism" who often caused lab members to squirm under his scrutiny.

At Rockefeller, Landsteiner continued to study the biochemical specificity of the various blood groups. Chase's initial experiments with him involved separating enzymes from these groups and trying to identify the substances responsible for particular adverse effects in humans.

Another line of research, begun with John L. Jacobs and taken over by Chase in 1936, concerned skin-sensitization and allergy. This effort reflected a new science of immnochemistry emerging at Rockefeller, whereby antibodies were found to be proteins whose reactions depended on the chemical constitution of the antigen. Such work during the 1920s and 1930s was carried out not only by Landsteiner but also by Institute colleagues Oswald Avery, Michael Heidelberger, Walther Goebel, and René Dubos.

The relationships between contact dermatitis and environmental agents were well known at the time to dermatologists, who observed that chemical industry workers commonly had skin eruptions. However, the laboratory-based study of human allergies had made little progress because it was so difficult to reproduce them in animals. To reduce this barrier, Landsteiner pioneered a method for systematically investigating the relation between serological specificity and the chemical structure of antigens. He and Chase prepared synthetic antigens, called haptens or incomplete antigens, by combining a particular antigenic protein with a simple chemical substance—such as the known human allergens chlorodinitrobenzene or picryl chloride—that stimulated the production of antibodies. Intradermal injections of trace amounts of these haptens sensitized guinea pigs. The known chemical composition of the hapten provided specificity, so that when exposed to the substance again, animals produced an immune reaction reflecting their prior contact with it.

On reapplication of the substance, not only did hypersensitivity result but also, in some cases, a state of anaphylaxis was induced. Although anaphylaxis and allergy were once considered distinct events, these experiments showed that the same basic principles of immunology underlie both processes. The experiments shed light as well on allergies such as serum sickness following transfusion with an incompatible blood group, and on allergies to certain foods, drugs, pollens, and plants (such as poison ivy). Some reactions began immediately after exposure while others were delayed and appeared after hours or days.

In 1936, a personal tragedy propelled Chase's interest and research in allergy—in particular, the relationship between sensitization and immunity—even further. His wife Edith was eight months pregnant with a second set of twins. After developing Type III lobar pneu-

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monia (from the most dangerous strain, *S. pneumoniae*), she was treated with a serum therapy that was prepared from animals and contained specific antipneumococcal antibodies. Within a short time Edith suffered anaphylactic shock that caused the twins to be born prematurely. With severely underdeveloped lungs, David lived three days and Mary four months.

Passive transfer of sensitivity

Landsteiner reasoned that if sensitization with a simple chemical produced an immune reaction, a cell-bound antibody would reside in the tissues of the sensitized animal and could be transferred, by injections of clarified serum from peritoneal exudates, to a normal one. Using the exudates, Chase was able to transfer hypersensitivity; the exudate recipients produced a positive allergic skin reaction when the original sensitizing chemical was later applied to their skin. However, there was no detectable antibody. Moreover, transfers of killed exudate cells failed to produce hypersensitivity.

The old procedure used by Landsteiner and Chase involved "clarifying" the peritoneal exudates, using a centrifuge to remove the cells. Only the serum was injected into recipient animals. However, as Chase explained,

> *In the course of these futile exercises, I once transferred the sticky exudate when it was not fully clarified, but had a hint of opacity. The recipient of this became beautifully positive. The following experiment, with fully clarified fluid, was negative—and then I knew. When Landsteiner looked through the microscope and saw lymphocytes, he did an abrupt about-face and said with dignity, "Yes, I thought so!" (Chase 1985).*

He was, Chase added, likely recalling James B. Murphy's 1920s experiments at Rockefeller that associated lymphocytes with graft rejection as well as resistance to experimental tuberculosis. Landsteiner then complimented Chase for providing him with what he termed an "*embarras de richesses.*"

In retrospect, it may seem curious why full details of this significant discovery were never reported and thus not widely known for a long time, though the work did appear as a brief notice in *Proceedings of the Society for Experimental Biology and Medicine* in 1942. Chase said Landsteiner was skeptical that anyone could reproduce their results. Even though Chase knew that seven other scientists almost immediately confirmed those results, his own insecurity on Landsteiner's death in 1943 and his uncertain future at Rockefeller kept him from writing up the experiments—something he much later regretted.

The René Dubos laboratory group at The Rockefeller Institute for Medical Research in 1946. Dubos is standing with hands on both hips. To his left is Merrill W. Chase and to Chase's left is Cynthia Pierce.
(Photograph courtesy of Carol L. Moberg)

When Dubos reported to Rockefeller Scientific Director Herbert Gasser that Chase's linking of the lymphocyte to the formation of hypersensitivity opened "an entirely new immunological vista," Gasser appointed Chase to the Dubos laboratory, which was just beginning a study of tuberculosis. In an extension of his experiments with Landsteiner, Chase transferred hypersensitivity to tuberculin (a purified protein derived from mycobacteria) from a sensitized guinea pig to a nonsensitized one by injecting sensitized white blood cells. Chase and Dubos then realized that certain white cells were not mere carriers of antibody but served in its production; and, importantly, that hypersensitivity to tuberculin was not equivalent to having tuberculosis. In other words, a positive tuberculin test does not necessarily measure active disease, only allergy or previous sensitization to the protein. This reaction, shown by Chase in guinea pigs, was soon secured in humans by H. S. Lawrence and W. S. Tillett at New York University.

Chase's landmark discovery of the passive transfer of sensitivity uncovered an entirely new class of immune responses called "cell-mediated immunity." This work also showed

that, in complementarity to humoral immunity, cell-mediated immunity was not innate but adaptive—after being activated by an outside stimulus.

In further studies of passive transfer, Chase found that washed cells from the spleen, lymph nodes, and the buffy coat of centrifuged blood transferred sensitization effectively. A study on the origin of diphtheria antitoxin production in rabbits also showed that the antibody that was appearing in the recipient was not present in the transferred cells but was newly produced. Further studies focused on the timing and measurement of antibody production under controlled experimental conditions. He followed the appearance of antibody in a single recipient guinea pig and reported that the antibody was being synthesized de novo and slowly. He also found that lymph nodes were the source of cells leading to the first appearance of antibody, followed a few weeks later by the spleen. Although described only in meeting abstracts and a few lectures, Chase pointed to the lymphocytes as a special intermediate in the formation of antibodies.

An independent laboratory

By 1956, recognizing that many other scientists were discovering multiple functions in the immune system, Chase said he no longer wanted to belong to "the school of lymphomaniacs." At this point he established an independent Rockefeller laboratory, called Immunology, that focused on ways to inhibit sensitivity to chemicals/drugs, the role of heredity in allergy, and the allergic basis for the production of experimental granulomas.

Chase then studied other aspects of allergic sensitivity—fever and asthma in particular. As early as 1936, Chase and Landsteiner had found individual differences in those guinea pigs acquiring hypersensitivity to an inciting drug (chemical, allergen), even under uniform housing and dietary conditions. Others had demonstrated strong hereditary influence for hay fever and common forms of asthma, but not for drug allergies. Consequently, Chase established two colonies of albino guinea pigs by selective breeding, one highly susceptible to and the other resistant to poison ivy, tuberculin, and a mycobacterium. Within four generations he found that one line responded intensely to the allergen while the other only slightly. Although it was not possible to make an analysis of genetic factors at the time, they postulated that more than one genetic factor was responsible, given that the sensitivities did not fall into a few sharply discrete grades but showed continuous transitions.

By the late 1950s, Chase was maintaining several colonies of genetically variant guinea pigs that served his experiments in special ways, in particular for separating the mechanisms involved in transitory and in delayed allergic manifestations. His research with inbred strains played a fundamental role for later immunologists to identify key genes involved in the immune response.

In the early 1950s, Chase made a study similar to his personal experiment as a graduate student of drinking toxic milk. To prevent primary sensitization to other drugs/chemicals, he fed a chemical incitant (such as picryl chloride) to a normal animal prior to starting the sensitizing injections. This action decreased sensitivity up to the point of preventing its appearance. A condition of "non-responsiveness" occurred when he then tried to sensitize the animals to the same chemical: no antibody and no sensitive cells were produced. The effect was durable and extended far beyond the time when feedings ended. It became clear that when the allergen was absorbed through the intestine it interacted with the host tissues in a different way than do chemicals entering by the parenteral route.

This and other studies in the 1960s with colleagues in his laboratory prepared the way for future developments, now taken for granted, that allowed others to elaborate on the nature and significance of the antibody response and the various cells involved in immune reactions.

One such Chase lab study was performed by his graduate student Barry Bloom. Unlike Chase, who used living white blood cells to make a passive transfer of sensitivity in guinea pigs, Bloom tried using disrupted or killed cells and subcellular materials. He found no reproducible method to make a passive transfer with the nonliving materials. This research contradicted results of other scientists, who claimed to have found such a "transfer factor" in humans.

Bloom's thesis advisors accepted his research as a significant contribution to immunology. However, a manuscript prepared for *The Journal of Experimental Medicine* was rejected by its editor, Peyton Rous, who wrote that the journal "is reserved for positive papers" (Chase 1963). Chase and Bloom then published a highly critical review of the transfer factor in *Progress in Allergy* (1967) to prevent others from wasting time and effort on a wrong path. The monograph provided detailed analyses of the criteria, technical procedures, and conflicting data that were being used by those scientists who had been making the claims. In 1983, Chase reviewed the continuing "enigma of transfer factor," citing inconclusive results by transfer-factor advocates that had not defined its precise chemical

composition or its mode of action. Importantly, Chase and Bloom's critical observations pointed the way for researchers to show that immune cells make products, initially called lymphokines but better known today as interleukins and cytokines, that give rise to antibodies. By 2009, science historian Arthur Silverstein reported the transfer factor was no longer even a curiosity (Silverstein 2009).

Another important Chase lab study, by German dermatologist Egon Macher, involved the initiation of cell-mediated immunity by means of the skin. Macher and Chase found the stimulus or allergen only had to be in the skin for a short time, even though the immune response took days to develop. Chase's research with Huminori Kawata and Mark Kaplan on serum immunoglobulins showed that these agents could reinforce, alter, or imitate true delayed type hypersensitivity. A byproduct of these efforts was their isolation of multiple tuberculin antigens, which led to ways to monitor the biochemical steps in separating them and to test the dynamics of their antibody responses. By the time of his retirement in 1976, Chase had greatly clarified the nature of allergic sensitivity of the skin and had showed that this type of irritation is closely related to allergies of other kinds—a conclusion that has become increasingly important in medical practice as new drugs and chemicals continue to be introduced by industry. More generally, his work established a detailed understanding of the body's reactions to foreign proteins and other allergenic substances.

Chase made two other important contributions in the 1960s regarding specific human allergies. Following his inquiry into the allergic basis for the production of experimental granulomas in guinea pigs, he joined clinicians James Hirsch, Louis Siltzbach, and Zanvil Cohn in The Rockefeller University Hospital to evaluate the Kveim skin test in sarcoidosis patients. This was a 10-year study of 200 patients with the immune disorder, of unknown cause, characterized by inflamed granulomas throughout the body. Chase prepared and standardized a purified test antigen from a single human sarcoidal spleen. It helped establish the test's usefulness as a diagnosis of early-onset disease and as a tool for investigating the disease's pathogenesis.

In the late 1960s, the Federal Trade Administration asked René Dubos to perform experiments on bacterial enzymes from *Bacillus subtilis* that he had earlier found toxic to red and white blood cells. These enzymes were being added to laundry detergents without prior testing and were causing severe skin and respiratory ailments in workers in the manufacturing plants as well as in consumers. Dubos enlisted Chase, who quickly found the enzymes were both toxic to blood cells and that low levels of exposure to them

sensitized individuals, aggravated allergies, and provoked subclinical respiratory disease. Consequently, the FTA's ruling on enzymes changed the way they were handled by workers but, despite warnings from Dubos, Chase, and many others, it did not ban them from detergents or require warnings on the packages (Moberg 2005).

The Merrill W. Chase Historic Scientific Instrument Collection

Respected as a rigorous experimentalist, Chase also showed a keen interest in scientific instruments themselves. He was driven by great curiosity to know in detail how things worked, and he liked to ask other scientists about their tools and the experiments for which they were used. Perhaps an inkling of this interest was stirred by what he wrote about his first glimpse of Landsteiner making detailed readings of delicate skin reactions.

> *The first thing that struck my eyes was a dilapidated microscope of antique vintage, of which only the 10-power objective was functional. He had 'scrounged' it without cost in order to spare wear and tear on a better microscope.*

Throughout his career, Chase quietly collected instruments after they were no longer used in the Rockefeller laboratories, including Landsteiner's microscope. Knowing that the Institute's directors rejected the idea of a museum in the community, he stored them carefully in various locked closets and empty rooms without publicizing the collection or making requests for support. Handwritten cards documented who had used or donated the instruments and gave insights into the work of the corresponding particular laboratory. In 1976, on the occasion of the University's 75th anniversary, Chase planned an exhibition and wrote a booklet about 60 instruments displayed in a specially constructed gallery space in Caspary Auditorium. These instruments, he noted, played critical roles in the progress of biomedical research during the 20th century, they were associated with significant discoveries, and they were integral pieces in the mosaic that helped define the rich history of Rockefeller. By 1997, Chase had collected 262 instruments, many of them designed and constructed by scientists and master craftsmen in Rockefeller's machine, electronics, and glassblowing shops to address scientific questions for which no tools existed.

The Merrill W. Chase Historic Scientific Instrument Collection, named in his honor in 1997 by President Torsten Wiesel, has grown to 366 instruments at this writing. In 2010, a historic laboratory, vintage 1950s, was also named for Chase as a place to study and

Merrill Chase with guinea pig. (Photo courtesy of The Rockefeller Archive Center.)

exhibit selected items from the collection. Of the many "instruments" acquired from his own laboratory, one has an unusual charm: it is a cotton jacket, beautifully constructed and handsewn by Chase's wife Edith, for gently restraining the guinea pigs during his allergy experiments.

"A Medical Gamble"

At the age of 80, Chase became proficient in using the UNIX "vi editor" to prepare a history of Rockefeller, intended to complement the scientific history, written by George Corner, of Rockefeller's first 50 years. Thus Chase extended his rigorous interest in how things work in the laboratory to the institution itself, and he spent long hours watching what individuals throughout Rockefeller were doing to make it productive. The result was an unfinished manuscript, called "A Medical Gamble," that described how the largesse of the Rockefeller family and its venture to enter the virgin field of medical research in 1901 grew into a world-famous organization specializing in biomedical sciences. In its large compendium of stories recreating the daily life of the community, Chase's document revealed the numerous nuts and bolts of how things got done at Rockefeller—how a building got built, the thankless tasks of ordering earthworms, blowing and molding glass for the Alexis Carrel and Charles Lindbergh perfusion pump, and routine functions such as library, mail, security, cleaning services, even the Rockefeller baseball team. The stories celebrated scientists, artisans, telephone operators, nurses, carpenters, stokers of the boiler house, and many others, with the common thread being an emphasis on how each person contributes to getting Rockefeller research done right.

Chase's career at Rockefeller lasted 71 years, two-thirds of the institution's first century, and he worked under six directors/presidents. At the end of a long life dedicated to science, he wrote how grateful he was for his early experiences at the Institute, with its endowed facilities and staff pledged to full-time research. In contrast to later years of grant-writing for government support, he emphasized its special values that gave scientists the freedom to pursue a problem, explore a novel question, and change course when warranted.

Chase published many scholarly reviews during his career, and, in the Landsteiner tradition, they were thick with details. From 1935 to 1938, he and Landsteiner reviewed the literature on immunochemistry as a way to help promote this burgeoning new science. From 1948 to 1965, Chase contributed extensive chapters on "The Allergic State" to the four editions of Dubos' classic text *Bacterial and Mycotic Infections of Man*, updating his own field with each successive edition. Then, in the final decade of his laboratory, Chase and Rockefeller colleague Curtis A. Williams published five volumes of *Methods in Immunology and Immunochemistry,* which conveyed the state of the art of these sciences. All these publications were not only major contributions to science in themselves but also provided a useful service for keeping immunologists up to date.

A passionate supporter of immunology, Chase was well known to an international community of scientists for his faithful abstracts and cheerful presence at annual meetings. He was on the editorial board of the *Journal of Allergy*, served as president of the American Association of Immunologists (1956–57), and was a member of the National Institutes of Health's Committee on Standardization of Allergens (1959–1967). Chase was elected to the American Academy of Arts and Sciences in 1974 and to the National Academy of Sciences in 1975. He received three honorary degrees—from the University of Münster (1974), his alma mater Brown University (1977), and The Rockefeller University (1988).

Chase married twice. His first wife Edith became a biology professor and assistant dean of students at Hunter College, which was then exclusively for women. She died of cancer on January 8, 1961. Their twins Nancy and John were born in 1933; a daughter Susan, born in 1937 with Down syndrome, died of cancer in 1985. On July 8, 1961, Chase married a long-time family friend, Cynthia Hambury Pierce, who earned a Ph.D. in bacteriology at Yale University in 1942. Cynthia had been his colleague in the Dubos laboratory, where her studies of tuberculosis included developing a rapid test of drug resistance and a standardized BCG tuberculosis vaccine. She died on April 13, 1997, of

post-polio syndrome. Chase himself, who died on January 5, 2004, is survived by his twin children, five grandchildren, and three great-grandchildren.

Dubos referred admiringly to Merrill Chase as "Old Faithful" because he could be counted on to ensure that every experiment was sound. Chase was usually friendly and engaging, but he could be inflexible, even irascible, in maintaining an opposing opinion. He enjoyed giving short but detailed lectures to students he found on campus who were improperly using animals, separating compounds, or making antigens. And his lectures could be directed at colleagues as well. During Rockefeller scientist Ralph Steinman's first meeting with Chase, he received a lengthy "chastening" about immunological questions. Merrill was critical, said Steinman (who was awarded a Nobel Prize in 2011),

> *but he was always constructive and genuine in his intent, and he had so much experience at his fingertips. He was a master of experimentation, attending to every variable and detail of dose, timing, route of administration, diet, even the season of the year, and the use of inbred animals.*

Chase took a genuine interest in all who worked with him and always had time to share family stories and current events. Having had two wives with strong scientific backgrounds, he was an early and encouraging supporter of women in science. One scientist in his laboratory recalled that she learned from him the importance of attention to detail so that even the faintest trace that might make an experiment fall apart could not be ignored. With his personal penchant for meticulousness, Chase wrote his own obituary and took it to the Public Affairs office with the stern admonition to use it or they would hear from him!

Chase spent his final days in his apartment near The Rockefeller University resting comfortably, eager to receive colleagues, and delighted to tell detailed stories about the people and places that had meant so much to him during his 98 years. His abiding zest for life had great influence on all of his friends and colleagues.

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