

The ALLERGY ARCHIVES

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Pioneers and Milestones

Lowell and Franklin on double-blind hyposensitization therapy for ragweed hay fever: The people

*What's in a name?*¹

—Shakespeare (1564-1616)

In the name of Francis Cabot Lowell (1909-1979) (Fig 1) were the connotation and representation of 2 centuries of Massachusetts' economic, cultural, and philanthropic histories. From about 1700, when John Cabot arrived in Salem from the English Isle of Jersey, his early descendants found sources of wealth in privateering and commerce: trading in slaves, rum, and opium. They also followed the custom of intermarriage with other of Massachusetts' first families and joined the evolved upper class of highest social standing, culture, tastes, and intellect, whose members were referred to as "Boston Brahmins."^a

A member of the merged Cabot and Lowell line, Francis Cabot Lowell (1775-1817), with a copy of the design of the English power loom^b and its application to the manufacture of cotton cloth, founded the textile industry in the United States. The textile-center city of Lowell was named in his honor. His century-later namesake, Francis Cabot Lowell, (1909-1979) would relate to Cabots prominent in architecture, politics, government and medicine; to Lowells distinguished in poetry, literature, law, diplomatic service, university education, and the science of astronomy; and to both family branches as foremost donors to major regional social, cultural, and educational enterprises.^c

This common perception of an aristocratic family was responsible for the creation and wide circulation of a popular verse.

And this is good old Boston,
The home of the bean and the Cod,
Where the Lowells talk to the Cabots,
And the Cabots talk only to God.²

However, as those who would cross paths and interact with Francis (Frank) C. Lowell in everyday life—classmates, mentors, colleagues, staff, trainees,



Fig 1. Francis C. Lowell (1909-1979).

and students—were to find out for themselves, it would be deceptive and unfounded to prejudge or conceptualize him in an image of affluent snobbery.

At Harvard, where Frank Lowell was educated (BS 1928, MD 1932), his first college roommate, Lincoln Kirstein,^d thus described him:

The first people I had as friends at Harvard were admired purely for their physical endowment, for their good looks, for their families, because they were very old New England families who had meant the embodiment of a tradition . . . they were naturally personified. There were three or four people that I knew who were actually heirs of great tradition. I lived with a boy Francis Cabot Lowell, who personified to me everything that you could possibly imagine in an aristocrat. He was the nephew of the president of Harvard,^e he became a great doctor, but when I knew him he was merely an extraordinary boy who was unconsciously personifying the very best of New England. And he reminded me of the Abolitionists and the people who had inherited wealth but who were extremely responsible. I was always amazed at how, without any kind of vanity, he behaved in the most extraordinary correct manner; his considerateness was fantastic. He had no prejudices of any sort. He had no curiosity. He knew what he would do. He had no

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doubts. He was the least neurotic person I ever met, and he gave you the feeling that if everybody had as much money as he had and the kind of background he had there would be no trouble.³

In 1933, Frank Lowell began an 18-month internship in the Harvard Medical Service of the Boston City Hospital, the first stage of a professional career spent in association with Boston teaching hospitals. In the setting of integrated expert patient care and clinical investigation, the direction of his special interests were largely influenced and shaped by 2 of the institution's accomplished staff. Bringing him into the study of infectious diseases was Maxwell Finland of the Thorndike Memorial Laboratory.

From an autobiographical note by Lowell⁴:

Pneumococcal pneumonia was a common disease at Boston City Hospital At the instigation of Max Finland, an exceptionally important role in our lives was the purveyor of antipneumococcal serum (rabbit mostly) to be administered intravenously to selected cases of pneumococcal pneumonia. Reactions, either nonspecific (chills and high fever) or allergic were frequent enough for us to regard the serum proffered with some dismay, tempered of course by the excitement that it might induce a dramatic recovery—otherwise rare enough in those days. Also turned up from time to time [was] a tray of syringes, some loaded with multiple skin test doses of various types of pneumococcal polysaccharide and an alcohol flame to sterilize the platinum needle between subjects of which I was of course, one. It was only years later that it crossed my mind that there might have been a connection between this and my second attack of hepatitis (my first at age fourteen when I spent the summer on a thoroughly unsanitary farm in England) which followed a number of weeks later. Granted a connection, I suppose this was by all odds my most intimate and certainly my most impressive experience with research up to that time. More was to come. In the fall of 1938, I joined the paper mill, becoming the junior member of Max Finland's pneumonia service. The pneumonia service was a very active one. Physically active . . . drawing blood for cultures and serology and collecting sputum . . . and treating with either (anti) serum or a sulfonamide We typed innumerable strains of pneumococci, a lost art today.

In 2 years of original studies as a hospital assistant resident and research fellow with Finland, Lowell was credited with 19 publications. Finland's section of the history of the Harvard Unit mentions Lowell in 2 other connections. One, in the only reference to social background, reads, "as the name implies, (he) was of



Fig 2. William Franklin (1919-).

a proper Boston family." Second that he played the viola in a staff, chamber music quartet that gathered in the back of a Thorndike storeroom some evenings and on Saturday afternoons.⁵

The second clinical faculty member was Chester Keefer, who had arrived at Harvard and the Thorndike Laboratories in 1930 after holding positions at Johns Hopkins, the University of Chicago, and in China at the Peking Union Medical College and who rose to become chief of Harvard's Boston City Medical services. He subsequently was appointed Professor of Medicine and Dean of Boston University School of Medicine and director of medical services at the affiliated Massachusetts Memorial and Evans Memorial Hospitals.

Keefer, influenced by the concept of coordinated structure and function, moved to transform Boston University Medical Center to an identical unit system. With a cadre from Thorndike, he initiated integrated clinical, teaching, and research sections in the various branches of internal medicine. Included in the design was a section of allergy and asthma, but that plan required a delay in implementation. The study of allergy was still emerging.⁶ Programs within medical schools and university centers to furnish academic leaders for the new field were still in the formative stages, and National Institutes of Health grants to recruit full-time medical scientists to the study of hypersensitivity disorders were still a few years away. A step ahead of the time, Keefer identified the requisite potential in one of Thorndike's rising staff in his own field of infection and immunity,[†] Frank Lowell.

At Evans Memorial-Massachusetts Memorial hospitals, an immunization clinic had gotten underway earlier with Sanford Hooker, Boston University's first professor of immunology, and his associate, Mathew Derow, professor of microbiology.⁷ Because both had extended themselves in developing interests in human hypersensitivity,⁸ their part-time availability provided a starting point for Lowell's indoctrination. When Keefer felt that Lowell had learned the necessary minimum, he put him in charge of the clinic and the allergy unit.⁴ Reflecting the influence of Lowell's on-the-job learning was his acquisition of interest and initiation of studies in applied immunology: techniques of antibody measurements, allergy and resistance to insulin, and isoagglutinin responses to blood group substances.⁸

In developing a model of full-time academic allergy, Lowell's initiative and originality made it attractive to physicians exploring the potential of a new field. In his expanding clinical and research programs were 2 physicians in particular.

Irving Schiller (1907-1972) joined him in 1943 as instructor in medicine after completion of a teaching fellowship at Tufts University Medical School. Working with Lowell, he advanced to assistant professor of medicine at Boston University; held staff positions in allergy at the Boston Floating, New England Center, University, and Beth Israel Hospitals; served as president of the New England Allergy Society; and as reflected in society memberships, pursued interests in internal medicine, chest diseases, and clinical pharmacology.

In 1950, William Franklin (1919- ; Fig 2) became Lowell's first fellow. Franklin was a native New Yorker who had initially studied chemical engineering at the College of the City of New York (BChE 1939). After receiving an MS in Sanitary Engineering from Harvard in 1940, Franklin joined the US Public Health Service and was detailed to the Massachusetts Department of Labor to survey health hazards in defense industries for the Division of Occupational Diseases. In 1943, he turned to the study of medicine at Boston University (MD, 1946). During subsequent residency training in internal medicine at (Boston) University Hospital, his introduction to Lowell's work progressed to clinical and research fellowships in allergy and immunology. In 1950, with an appointment to the Boston University faculty as instructor in medicine, he became a Lowell associate, and within a few years, he became assistant professor of medicine and advanced on the University Hospital visiting staff.

The publications Lowell and his group produced while at Boston University⁸—during part of which time he also served as assistant dean for admissions—reflected a wide scope of subjects in allergy. There was nevertheless a consistent line of focused interest reflected in their work. Among pioneering undertakings were the earliest on insulin allergy

and immune-mediated insulin resistance,⁹ reversibility of pulmonary emphysema,¹⁰ pulmonary function tests that demonstrated patterns characteristic of asthma, and obstructive lung disease.¹¹ Their study of smoking as a cause of pulmonary emphysema and its relationship to airways obstruction¹² was cited in the US Public Health Service Surgeon General's first report on smoking and health.¹³ Considered by Franklin and Lowell at the top of their important contributions was the first double-blind study showing that topical steroids could act effectively at the respiratory membrane level,¹⁴ a contribution documented well before inhalational steroids became commercially available for the treatment of asthma and allergic rhinitis.

In 1959, Keefer retired from active administrative positions at Boston University Medical School and Center, and Lowell left to become an associate professor of medicine at Harvard and chief of the allergy unit at Massachusetts General Hospital. Franklin moved with Lowell. In converting the clinic and service that Francis Rackemann had established¹⁵ into a full-time teaching, clinical, and research section, the thrust of Lowell's work and his investigations with Franklin were transferred; only the setting had changed. In detection of airway dysfunction, 20 years before the flow-volume loop became a standard test, they had demonstrated the importance of tracing the latter portion of forced expiration.¹⁶

As a naturalist with a personal interest and informed base in botany, Lowell moved into perceptive studies of hay fever. In his presidential address to the American Academy of Allergy in 1959, Lowell called attention to a longstanding deficit and fault in the rationale for injection therapy that was arbitrarily based on assumed relevance to immunologic concepts. Lacking the validation of rigid control, use of that modality failed to exclude the possibilities of chance or bias.¹⁷ Concluding with the need for controlled investigative protocols in ragweed immunotherapy, he and Franklin then embarked on a series of studies dealing with dose-related factors, efficacy, and specificity, an initiative that demonstrated the double-blind approach to be a classic model.¹⁸ Among other firsts were interpretation and application of changes followed in total circulating eosinophil counts as a guide in the management of asthma and Lowell's demonstration of hypersensitivity pneumonitis in horses, induced by inhalational exposure to a mold contaminant of hay, in the pathogenesis of heaves rather than emphysema, as heretofore believed by veterinarians.¹⁹

The quality of Lowell's work was recognized in his election to selective society memberships—the American Association of Immunologists and American Society of Clinical Investigation—as he moved to the forefront of professional leadership. At the national level, he served as President of the American Academy

of Allergy, a 6-year term as editor of the Journal of Allergy, chairman of the American Board of Internal Medicine Subspecialty Board of Allergy, and chairman of the Medical Advisory Committee of the Allergy Foundation of America. He was one of allergy's earliest representatives to the National Institutes of Health in study section membership and the Advisory Council of the then newly created National Institute of Allergy and Infectious Diseases.

Although Lowell's scientific achievements are a matter of record and documentation, his persona and character are best understood and appreciated in the words of those who interacted closely with him as associates, colleagues, and trainees. His advantaged background had never gotten in the way of his being "a serious researcher, a fine and caring physician . . . and one of the most remarkably fine people I had come to know in our field. He had all the credentials of a patrician, tall, handsome, highly educated and socially prominent. Yet he was enlightened and liberal in politics . . . (and had) a marvelous dry wit."^h There was even a light side to his dealing with personal health problems. Subject to postural hypotension as an adverse reaction to his antihypertensive medication, he recounted a slight episode of faintness experienced during an out-of-town visit with the comment, "It's amazing what a crowd you gather when you lie down on the sidewalk in New York."ⁱ

On first meeting, a reserved and dignified carriage might have projected as stern and intimidating but certainly not to his group to whom he personified the description "gentleman and scholar" and to whom his leadership, concerns, and integrity spontaneously generated respect and affection. Intellectual independence might have been misinterpreted as aloofness: "he was his own man."^j First-hand information on Lowell's role as a mentor comes directly from recall of former fellows in speaking of "his scientific and humanitarian achievements and personal qualities."^{8,20,j}

"Integrity in investigation was stressed; he was primarily interested in insuring accuracy and honesty. As a mentor, his style was to look on fellows as colleagues and less than that of a teacher. Although his objective was to interest fellows in research, rather than to direct or push, he encouraged us to explore on our own."^k

"His qualities of wisdom, patience and quiet strength were ever present He taught far more by example than by didactic lecture . . . (we) remember his disciplined and creative mind, meticulous attention to detail, clarity of expression, and drive for perfection — one of a kind, ahead of his time. In addition to medical activities, he was a dedicated conservationist, worked with state agencies to regulate use of pesticides, was an avid gardener, and concerned with preservation of woods. He loved to teach us about his hobbies as well as his profession. In happy weekends

with him on his sailing boat on Cape Cod, he taught us the ways of the sea."^{8,20}

In 1976, Lowell retired from his positions at Harvard and Massachusetts General Hospital and joined Tufts University Medical Center. By then his publications reached 157 in number, and 27 post-graduate fellows had trained under his direction.

Franklin remained at Massachusetts General Hospital and Harvard Medical School until his retirement. During the years of his association with Lowell in patient care, clinical research, training fellows, and teaching medical students, Franklin became highly regarded in his own right, reaching the Harvard faculty rank of associate professor of clinical medicine. He had been coinvestigator with Lowell in 30 published reports, and both in collaboration and independently, he pursued research interests in immunotherapy, insulin resistance, pulmonary function, obstructive bronchial disease, treatment of asthma, and clinical relevance of eosinophilia. His review on the treatment of severe asthma, written and published at the invitation of the editors of the *New England Journal of Medicine*,²¹ received 10,000 requests for reprints. His prominence in his field of specialization was reflected in his extensive organizational committee leadership activities for the Asthma and Allergy Foundation of America and the Massachusetts Medical Society and his obtaining the office of the presidency of the New England Allergy Society, the vice presidency of the American Academy of Allergy and Immunology, and staff attending and consulting appointments at regional hospitals.

Lowell, associated with Tufts Medical Center, continued to write and practice medicine until his death at age 70. He had spent most of his life commuting between Boston and his homes and lands in Concord and Cape Cod, explaining, "Why go anywhere else, I am already here."

*The power of grace; the magic of a name.*²²

—Thomas Campbell (1777-1844)

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Lowell and Franklin on double-blind hyposensitization therapy for ragweed hay fever: The paper

In January 1960, in his presidential address at the annual meeting of the American Academy of Allergy, Francis Lowell commented on the "sorry plight of allergy and allergists in many teaching institutions" and suggested that the identification of allergy with "shots" had seriously undermined their reputations. He went on to state that in his opinion, "this sorry state would continue until such time as careful evaluation through rigid double-blind studies demonstrated the value of injection therapy."¹

Forty-some years had gone by since Noon and Freeman's reports of pioneering immunization against grass hay fever pollens had launched the continuing empiric use of the modality.^{2,3} Lowell's words resonated with many of the Academy members in the audience, who were already beginning to sense that injection therapy for hay fever was being overused. Most were unaware that he and William Franklin were already embarking on a classic series of studies that would affect the thinking and practice of responsible allergists.

NOTES

- a. Derived from India; name given to the highest Hindu caste.
- b. Reputed to be the result of one of the early cases of industrial espionage.
- c. Cabots were major supporters of the Boston Symphony, Harvard University, and Massachusetts General Hospital; Lowells were founders of the Lowell Institute and the Lowell Observatory.
- d. Lincoln Kirstein (1907-1996), son of the head of Boston's Filene's department store; he became cofounder (with George Balanchine), president, and general director of the New York City Ballet at Lincoln Center of Music and Drama and the School of American Ballet.
- e. A(bott) Lawrence Lowell (1856-1943). President of Harvard University (1909-1933). Advanced Harvard through restructuring the majors studies curriculum, adding a tutorial plan to supplement lectures, creating houses modeled after the Oxford system, and adding professional schools of architecture, business administration, education, and public health.
- f. Chester Keefer was one of the leading clinical investigators in infectious diseases both before and during the antibiotic era. During World War II, he oversaw medical research to combat infectious diseases in the military services. Through his role in directing clinical evaluation and distribution of penicillin, use of that antibiotic agent was rapidly developed from a laboratory phenomenon to an important therapeutic modality.
- g. Hooker had attended Cooke's New York Hospital Clinic and served in the prestigious presidencies of both the Society for the Study of Asthma and Allied Conditions, forerunner of the American Academy of Allergy in 1935, and in the following year the American Association of Immunologists.⁷ Derow's work in medical parasitology, bacterial toxins, and blood groups expanded to interests in immunochemistry and allergy. Active in the New England Society of Allergy, he served in its presidency.
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- j. Franklin W. Personal communication, 2003.
- k. Banov C. Personal communication, 2003.

Controlled studies of one sort or another had been ongoing for centuries, beginning in 1545, when Pa  ⁴ compared crushed onions with no intervention or with traditional treatment by using boiling oil as a dressing for wounds or burns. Many reports during ensuing years included that of Semmelweis,⁵ who in 1861 showed that fatalities from labor were higher under the care of doctors than midwives, and Pasteur,⁶ who in 1881 compared the results of anthrax vaccination in sheep with no attempted preventive measures to prove its effectiveness in establishing protection. It was not until 1918 that Bingel⁷ first carried out a double-blind study with diphtheria antitoxin versus normal serum during a diphtheria epidemic. Although placebos had been used for 3 centuries, they were blinded only to the patient, with the exception of a study in 1879 and 1880 by the Milwaukee Academy of Medicine in which experimenters and patients were both masked in comparing a homeopathic remedy with a sugar pill; the results were the same in both groups.⁸ However, it was not until the 1930s that double-blind studies began to appear in the literature and not until the second half of the 20th century that they became virtually obligatory for acceptance by peer-review journals.