

6. Cohen SG. The American Academy of Allergy: an historical review. *J Allergy* 1979;64:412-23.
7. Cohen SG. Firsts in allergy; Boston remembered. *N Engl Reg Allergy Proc* 1984;5:75-7.
8. Franklin W. Biography of Francis Cabot Lowell. *N Engl Soc Allergy Proc* 1982;3:234-8.
9. Franklin W, Lowell FC. Experimentally induced insulin resistance and allergy in the rabbit. *J Allergy Clin Immunol* 1949;20:400-3.
10. Franklin W, Michelson AL, Lowell FC. The reversibility of pulmonary emphysema. *BMQ* 1955;6:14-20.
11. Michelson AL, Franklin W, Lowell FC. Clinical value of tracing of forced expiration (expirogram); cardiac disease. *N Engl J Med* 1955;253:852-5.
12. Lowell FC, Franklin W, Michelson AL, Schiller IW. Chronic obstructive pulmonary emphysema; disease of smokers. *Ann Intern Med* 1956;45:268-74.
13. US Department of Health, Education, and Welfare. Smoking, its role in allergy and immunity: a report of the surgeon general. Washington, DC: US Department of Health, Education and Welfare; 1979. p. 10.1-10.32.
14. Franklin W, Lowell FC, Michelson AL, Schiller IW. Aerosolized steroids in bronchial asthma. *J Allergy Clin Immunol* 1958; 29:214-21.
15. Cohen SG. Firsts in allergy, Boston remembered. *New Engl Soc Allergy Proc* 1983; 4:317-350.
16. Franklin W, Lowell FC. The expiratory rate during the third quarter of a maximal forced expiration. *J Allergy Clin Immunol* 1961;32: 162-8.
17. Lowell FC. American Academy of Allergy Presidential Address. *J Allergy* 1960;31:185.
18. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. *N Engl J Med* 1965;273:675-9.
19. Lowell FC. Observations on heaves. An asthma-like syndrome in the horse. *J Allergy* 1964;35:322-30.
20. Franklin W, Salvaggio J. In memoriam, Francis Cabot Lowell (1909-1979). *J Allergy Clin Immunol* 1990;65:317-8.
21. Franklin W. Treatment of severe asthma. *N Engl J Med* 1974;290: 1469-72.
22. Campbell T. Pleasures of hope. Part 2, line 5; 1799.

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.
- h. Dworetzky M. Personal communication, 2002. (A personal observation and assessment with which this author is in total agreement.)
- i. Lowell FC. Personal communication to M. Dworetzky, 1976.
- 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.

Lowell and Franklin's initial study was designed to compare treatment with aqueous ragweed pollen extract and with placebo in Massachusetts General Hospital Allergy Clinic patients who had objectively verified seasonal allergic rhinitis, asthma, or both.⁹ Careful attention was paid to spelling out details of scoring and reporting symptoms and medication needs, monitoring, evaluating, and masking. In the random assignment of paired subjects receiving individualized mixtures of varied allergens, one group received extract containing ragweed. In the other ragweed was omitted and replaced with caramelized glucose to match the color of the extracts and histamine in a concentration that gave a local reaction similar to that produced by the active extracts. This placebo feature was stressed as absolutely essential in preventing the blind from detection, a point not noted in earlier reports. In their introduction Lowell and Franklin credited the double-blind element in earlier studies with aqueous extracts for injection treatments.¹⁰⁻¹³ In fact, the concept had been introduced by Brunn¹⁰ in studies of asthma and by Frankland and Augustin¹¹ in patients with grass hay fever. However, as Lowell and Franklin also noted, "the means used to achieve and maintain experimental control [had] not been described in sufficient detail for the reader to be able to judge their success."

Of the 164 subjects enrolled in the 3-year seasonal study (1959, 1960, and 1961), higher symptom scores in the first year were noted among those receiving ragweed extract than in the paired placebo group. Commenting that the cause was not clear, the investigators offered 2 possibilities: (1) injections of allergenic extracts actually provoked symptoms early in therapy, and (2) despite randomization, there was a dissimilarity in that the placebo group contained a greater number of young subjects. Retrospective analysis of all subjects indicated that the younger individuals tended to have higher-than-average scores. Observations that during the next 2 ragweed seasons patients receiving specific therapy reported fewer symptoms than did their control subjects led Lowell and Franklin to express the belief that the study strongly suggested the superiority of allergenic extract over placebo.

However, in a self-critical evaluation of the study itself, they noted its shortcomings, pointing to the relatively small number of cases, possible error of selection, and the possibility that some of the study was unmasked by patients who reported systemic reactions after their visits. Nonetheless, the thrust of this article was recognized as pivotal in that it clearly set the stage and requirements for follow-up study to deal with questionable and controversial issues that remained to be addressed.

Drawing on that experience with experimental control and design, Lowell and Franklin, in their second study,¹⁴ attempted to meet the recognized need

of a better selection of patients, determine means of assessing severity of symptoms, and obtain evidence on the specificity and efficacy of ragweed pollen extract injection treatments. For the next study, undertaken during the ragweed season of August through October 1963, a carefully selected group of 24 subjects was selected. In addition to each having had their required clinical sensitivity verified during prior observation in the allergy clinic, possible confounding factors were bypassed; any who had been treated with ragweed pollen extract and did not have any symptoms during the previous year of 1962 were eliminated. Patients paired primarily for comparable intensity of symptoms were randomly assigned to one of 2 groups. One received injections of unchanged mixtures of their treatment extracts (including ragweed). In the other group ragweed was eliminated and again replaced by the color- and sting-simulating caramelized glucose and histamine, respectively. All were administered in double-blind fashion.

Statistical analysis of symptom scores this time was definitive in demonstrating that the group receiving the mixture containing ragweed extract fared better than its nonragweed counterpart, that the difference was highly significant, and that the ragweed effect was specific to the extent that tree, grass, and plantain pollens, which all subjects received, could not substitute for ragweed. However, the benefit of the injections was lost wholly or in part within 5 months. Not only did this precisely controlled study confirm the concluding impression of their earlier investigation of the issue of efficacy, it also established the allergen specificity of the treatment and demonstrated the effectiveness of extracts containing multiple allergens in polysensitized patients.

Of their view of the still-unanswered questions of optimal dosages, intervals between injections, and length of time over which injection therapy should be maintained, Franklin and Lowell¹⁵ 2 years later next attacked the first of these. Many allergists had been using relatively small doses, mainly because of safety concerns, especially in children. In a mid-May through mid-August double-blind protocol, they compared previously established maximally tolerated doses of ragweed extract with those of one twentieth of that amount in 25 paired patients. Their findings strongly suggested that the small or very small dosages recommended by some would have been ineffective in the representative study population, an evaluation that led many allergists to rethink their positions relating to practice patterns.

From the data generated in these studies, most concluded that therapy was helpful but far from dramatic. The opinion of allergists varied. Some believed that the studies showed that the benefits, although significant, were so slight that the value of injection therapy was limited; others were convinced that it proved its efficacy and continued to use it

enthusiastically. Through subsequent years, countless double-blind studies consistently showed the statistical advantages of injection treatment, but study of the data also showed its limitation.

A detailed and characteristically accurate article in *Consumer Reports* in 1966¹⁶ was entitled "The shot doctors," with the following headline statement: "Although advances in drug therapy now offer help for most allergies, some doctors are building an allergy practice on the dubious use of shots." Interspersed within the article were cautionary notes that reflected the more responsible use of injection therapy, but the major portion of the article dealt with highly questionable practices, which was to the detriment of the field. This highly critical article was fair and balanced when published in 1966. However, it must be recognized that injection therapy, when introduced by Noon and Freeman more than 60 years before, was an important advance at a time when so little else was available to treat what was a very disabling affliction; its sufferers were rendered dysfunctional for weeks or months and sometimes year round. As late as 1941, a year before antihistamines were first introduced, the foremost pharmacology book of the time¹⁷ included only 4 medications for treating hay fever: ephedrine, topical epinephrine, neosynephrine, atropine, and, for troublesome eye symptoms, topical cocaine. The subsequent introduction of a wide variety of efficacious medications, ultimately corticosteroids, gradually reduced the need for injection therapy.

Rational use of immunotherapy reached its apogee with the publication in 2003 of the report by the Task Force on Practice Parameters of the American Academy of Allergy, Asthma and Immunology; the American College of Allergy and Immunology; and the Joint Council of Allergy, Asthma and Immunology.¹⁸ With respect to hay fever, the Council stated that "the decision to begin allergen immunotherapy depends on the degree to which the symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effect of medications." It is likely that members of the task force and responsible allergists had been practicing this way for a long time, but it was a statement that was badly needed and served as the most recent milestone in a form of therapy that began in 1911 with Noon² and Freeman.³ It was a fitting resolution of the concerns expressed by Lowell and Franklin, whose classical studies moved allergists to view the results of injection therapy with skepticism and accept only placebo controlled double blind studies. For this, all allergists and their allergic patients are in their debt.

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REFERENCES

1. Lowell FC. American Academy of Allergy Presidential address. *J Allergy* 1960;31:185-7.
2. Noon L. Prophylactic inoculation against hayfever. *Lancet* 1911;1: 1572-3.
3. Freeman J. Further observations on the treatment of hayfever. *Lancet* 1911;2:814-7.
4. Páfe A. La Method de Traichter les Playes. Paris: C'hes Viuant Gaullterst, 1545. Cited in Chalmers I. Control of selection biases: comparing like with like. In: Chalmers I, Milne L, Trohler U, editors. *Tr James Lind Library*. Available at: www.JamesLindLibrary.org.
5. Semmelweis LP. Die Aetiologia, der Begriff und die Prophylaxis des Kinderbett Fiebers. Wein und Leipzig: Hartleben; 1861. Cited in Chalmers I, Milne L, Trohler U, editors. *Tr James Lind Library*. Available at: <http://www.JamesLindLibrary.org>.
6. Pasteur L. La vaccine du charbon. De l'attenuation des virus et le retour a la virulence. *Comp Rend Acad d sc* 1881;92:429-35. Cited in Chalmers I, Milne L, Trohler U, editors. *Tr James Lind Library*. Available at: www.JamesLindLibrary.org.
7. Bingel A. Über behandlung der diphtherie mit gewöhnlichem pferdeserum. *Deutsch Arch f Klin Med Leipz* 1918;125:284-332. Cited in Chalmers I, Milne L, Trohler U, editors. *Tr James Lind Library*. Available at: www.JamesLindLibrary.org.
8. Potter S, Storke EF. Final report on the Milwaukee test of the thirtieth dilution. *Homeopathic Times: A Monthly Journal of Medicine Surgery and the Collateral Sciences* 1880;7:280-1. Cited in Kaptchuk T. Control of observer biases: masking (blinding) and placebos. Cited in Chalmers I, Milne L, Trahler U, editors. *Tr James Lind Library*. Available at: www.JamesLindLibrary.org.
9. Lowell FC, Franklin W. A double study with treatment with aqueous allergenic extracts in cases of allergic rhinitis. *J Allergy* 1963;34:165-82.
10. Brunn E. Control examination of the specialty of specific desensitization in asthma. *Acta Allergol* 1949;2:122-8.
11. Frankland AW, Augustin R. Prophylaxis of summer hay fever and asthma. A controlled trial comparing crude grass pollen extracts with the isolated main protein component. *Lancet* 1954;1:1055-7.
12. Johnstone DE. Study of the role of antigen dosage in the treatment of pollenosis and pollen asthma. *AMA J Dis Child* 1957;94:1-5.
13. Johnstone DE. Value of hyposensitization therapy for perennial bronchial asthma in children. *Pediatrics* 1961;27:39-44.
14. Lowell FC, Franklin W. Double blind study of the effectiveness and specificity of injection therapy in ragweed hayfever. *N Engl J Med* 1965;273:675-9.
15. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. *JAMA* 1967;201:915-7.
16. The shot doctors. *Consumer Reports* 1966;Feb:96-100.
17. Goodman L, Gilman A. The pharmacological basis of therapeutics. New York: MacMillan; 1941. p. 413, 432, 447, 448, 475.
18. Li TJ, Lockett RT, Bernstein IL, et al. Allergen immunotherapy: a practice parameter. *Ann Allergy Asthma Immunol* 2003; 90(suppl 1):1-35.

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