

Perspectives

Some highlights of the first century of immunotherapy

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In 1819, John Bostock, a London physician, presented a paper describing recurrent symptoms that he had experienced since he was 8 years old.¹ In June of each year, he reported that he had had itching and smarting of the eyes, a fullness in the head with violent fits of sneezing, a sensation of tightness in the chest with difficulty breathing, and a degree of general indisposition. All the symptoms disappeared about the end of July except a degree of weakness and languor that persisted for 4 to 6 weeks longer. He noted, "The idea has generally prevailed that it is produced by the effluvium of new hay. Hence the popular name of hay fever." Bostock reported his condition because he considered it such a rare illness. There followed, however, an increasing frequency of the condition and, half a century later, another physician who also suffered from the affliction, Charles Blackley, carried out a number of experiments to determine its cause.² Having excluded several other suggested causes, he demonstrated that applying grass pollen to his scarified skin produced a large wheal, and inhaling grass pollen reproduced his nasal and chest symptoms. He further performed pollen counts during the spring and summer and was able to relate his symptoms to the daily amounts of grass pollen in the air.

Grass pollen was thus established as the precipitant of hay fever, but the mechanism was not clear. Leonard Noon, in a 1911 paper, described his treatment as prophylactic inoculation against hay fever, based on the belief that the symptoms were caused by a soluble toxin found in the pollen of grasses to which hay fever patients were idiosyncratically sensitive.³ Thus he envisioned his injections of increasing amounts of the pollen extract as increasing the patients' resistance to the toxin. He demonstrated this increasing resistance by quantitative challenges of the conjunctiva with timothy extract. Noon was forced to discontinue his work because of tuberculosis, and it was continued by John Freeman, who evaluated the response of 20 treated patients during the grass pollen season of 1911.⁴ All 19 patients who continued the treatment tolerated increasing doses of extract, and all 18 of

the patients who had follow-up conjunctival challenges had an increased threshold to the pollen extract. Clinically almost all the patients reported improvement in hay fever and when present in asthma symptoms as well.

Evidence for a more likely relationship between the pollen and the symptoms was suggested by the work of Carl Prausnitz and Heinz Küstner in 1921.⁵ Küstner was highly allergic to ingestion of fish or intracutaneous injection of fish extract. Küstner's serum was injected intradermally into Prausnitz's arm. The site was challenged 24 hours later by intradermal injection of fish extract, with a resulting cutaneous wheal and flare reaction. This method was employed for the next half century to demonstrate the presence of the reaginic antibody underlying immediate hypersensitivity.

At a time when effective symptomatic treatment for allergic symptoms was lacking, the use of immunotherapy spread rapidly. In 1930, the same John Freeman who had completed the studies initiated by Noon published a paper extolling the convenience of rush inoculations, with injections every hour and ½ to 2 hours over a 14-hour day, achieving maintenance treatment in 2 to 4 days.⁶ The allergens used in the accompanying case reports included, in addition to grass pollen extract administered co-seasonally, extracts of horse dander, autogenous house dust, and cod fish.

After more than 4 decades of use based on testimonial results, Frankland and Augustin reported the first controlled trial of grass pollen extract in 1954.⁷ They compared the response to grass pollen extract, its purified proteins, the ultrafiltrate with no intact proteins, and phenol saline. The results were favorable for the extract and the purified pollen proteins, compared with the ultrafiltrate and phenol saline for both seasonal hay fever and seasonal pollen asthma. Francis Lowell and William Franklin conducted an even more rigorous controlled trial some 10 years later.⁸ They wished to assure complete blinding. Therefore, they selected patients sensitive to ragweed but receiving a multiple-allergen treatment extract. After monitoring them through 1 ragweed season and pairing them for severity of symptoms, they removed the ragweed from the extract of 1 member of each pair and observed their symptoms during the following ragweed season. Complete blinding was assured because the ragweed extract was replaced with caramelized sugar to mimic the color, and the other allergens in the treatment mixture could produce local symptoms on injection, creating an effective

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placebo. In the ensuing ragweed pollen season, despite only 12 subjects in either treatment arm, there were significant differences during 6 consecutive weeks of the pollen season (Fig 1). The same authors then repeated the study, this time reducing the ragweed dose by 95% rather than removing it completely.⁹ Again those who continued to receive the full dose fared better during 3 consecutive weeks of the ragweed season. The 2 studies by Lowell and Franklin firmly established the effectiveness of injection immunotherapy for hay fever but also established that the benefit was very dose-dependent. Furthermore, because the ragweed extract was in a mixture with multiple other pollen extracts, yet was clearly effective, their studies are among the most convincing that multiple allergen immunotherapy is effective and that immunotherapy is allergen specific.

Even before the studies by Lowell and Franklin, Douglas Johnstone began a remarkable study of the value of immunotherapy in childhood asthma.¹⁰ He enrolled every child with perennial bronchial asthma referred to the pediatric allergy clinic of the Strong Memorial Hospital in Rochester, New York, over an 18-month period. Children were divided into 4 equal groups who received either buffered saline or all the inhalant allergens to which they had positive skin tests. The active treatment group was divided into 3 maintenance doses: 1:10,000,000 w/v, 1:5,000 w/v, and 1:250 w/v. Neither the parents nor the evaluating physicians knew to which group the children were assigned. Two hundred ten were originally randomized, 173 completed 4 years of treatment, and 130 were still on treatment on reaching 16 years of age. The results in the saline and 1:10,000,000 groups were the same, so they were considered together. After 4 years, 18% of

the control group were free of asthma, compared with 58% in the 1:5,000 w/v and 81% in the 1:250 w/v groups (Table 1). On reaching age 16 years, 22% of the control group, 66% of the 1:5,000 w/v, and 78% of the 1:250 w/v groups were free of asthma. In view of the current discussions on the lower age for immunotherapy in children, that 5% of the children were younger than 2 years of age and another 32% were between 2 and 5 years of age at enrollment in the study is interesting. Not only did the study by Johnstone demonstrate the potential efficacy of immunotherapy in the treatment of asthma, it again reinforced the dose dependency of this treatment and the effectiveness of multiple-allergen mixes in immunotherapy.

Although allergen specificity was suggested by the studies of Lowell and Franklin, the definitive proof was provided by a study by Phil Norman and Larry Lichtenstein.¹¹ They recruited 42 patients clinically sensitive to both ragweed and grass pollens. One half received injections of ragweed pollen extract for a total of 3 years, and the others received placebo. The active treatment group experienced significant reduction in symptoms during the ragweed pollen season compared with the placebo-treated group, but no difference was seen between the 2 groups during the grass pollen season, even after 3 years of treatment.

The main advantage of immunotherapy over symptomatic therapy is that it alone is disease modifying. Clinically, patients completing a successful course of immunotherapy continued to do well, often for many years, after treatment was discontinued. The definitive proof of this came only in 1999, when Stephen Durham reported on a controlled trial of discontinuation of immunotherapy.¹² The subjects had received 3 or 4 years of high-dose timothy immunotherapy for allergic rhinitis. They were then randomized either to continue to receive monthly maintenance injections of timothy extract or injections of placebo for an additional 3 years. No clinical evidence was found for loss of efficacy in the placebo group over the course of the study. Other less-well-controlled studies of discontinuation of immunotherapy have shown some additional interesting information. One hundred eight patients who had responded well to 3 or 4 years of immunotherapy

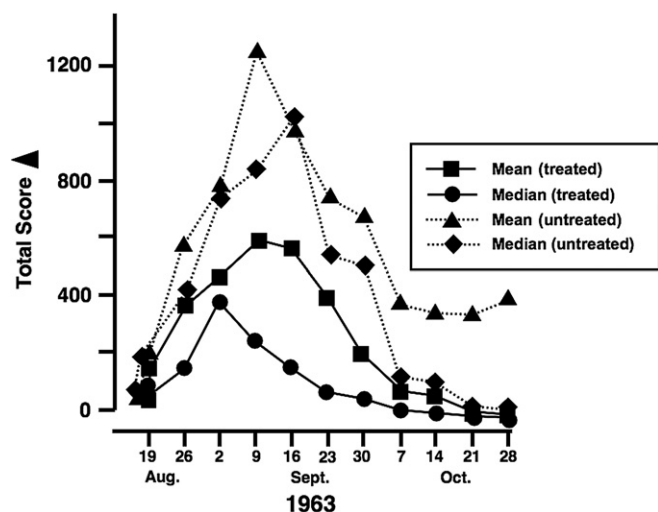


Figure 1. Response to removal of ragweed from immunotherapy extract. Ragweed was removed from the multiple allergen immunotherapy extract of 1 of each pair of patients. *Dashed lines* are the mean and median symptoms/medication scores of those not receiving ragweed, and the *solid lines* are for those who continued to receive ragweed. Groups were significantly different from September 9 through October 14.

Table 1. The Value of Immunotherapy for Bronchial Asthma in Children

"Free of asthma" after 4 years	
Placebo and lowest dose	18%
1:5,000 w/v	58%
1:250 w/v	81%
"Free of asthma" at end of study (age 16 years)	
Placebo and lowest dose	22%
1:5,000 w/v	66%
1:250 w/v	78%

Two hundred ten children with asthma were randomized to 4 immunotherapy doses. Results did not differ between those receiving placebo and the lowest allergen dose (10^{-7}). The outcome was assessed after 4 years of treatment ($n = 173$) and at the end of treatment on reaching age 16 ($n = 130$).¹⁰

with grass pollen extract were followed after its discontinuation.¹³ The rate of clinical relapse was 2.7% the first year, 16.7% the second, 30.6% the third, and 32.8% the fourth (Fig 2). In 40 asthmatic patients who had responded well, house dust mite immunotherapy was discontinued, and the patients were followed for 3 years.¹⁴ Approximately half relapsed. Predictors of a favorable outcome were immunotherapy for 36 months or more and even more so a decrease in the titer of titrated prick skin test to house dust mite extract during the course of immunotherapy.

Further evidence of a disease-modifying effect of immunotherapy came from studies of new sensitizations in monosensitized children. The first report was on 44 children 2 to 6 years of age, half of whom received immunotherapy with house dust mite while the others were observational controls.¹⁵ After 3 years of immunotherapy, 10 of the monosensitized children who received immunotherapy had not developed new sensitivities, whereas all of the control children had. The total number of new sensitivities was 13 in the treated and 32 in the control group. A later study included 134 children ages 5 to 8 years with asthma who were also monosensitized to house dust mite.¹⁶ Randomization was by parent choice for immunotherapy or only medical therapy. The children received treatment for 3 years and were then retested 3 years after the completion of treatment. At that time, 2/3 of the control but only 1/4 of the treated children had developed new skin test sensitivity.

Another study that supported a disease-modifying effect of immunotherapy was the Preventive Allergy Treatment study.¹⁷ This study was conducted in children age 6 to 14 years, allergic to timothy or birch pollen, who during an observational year only had symptoms of allergic rhinitis. They received 3 years of immunotherapy with 1 or both pollen extracts, or were observational controls. After 3 years

of immunotherapy, the actively treated children were less likely to have developed asthma symptoms (odds ratio 2.52). They were then followed for a total of 7 years after discontinuation of active treatment.¹⁸ At that time, the actively treated group was still less likely to have developed asthma (OR 2.5). Thus, both lines of evidence showed a reduction in new manifestations both during and for years after the discontinuation of immunotherapy, true disease modification.

The clinical potential of immunotherapy in seasonal allergic rhinitis was reemphasized in a study from England in 1991.¹⁹ A group of patients with grass pollen allergic rhinitis that had been resistant to medical treatment were given a preseasonal course of timothy grass pollen extract or placebo. During the ensuing grass pollen season, symptoms were reduced in the active group, as compared with placebo, by over 60% and medication use by over 80%. Despite such impressive results in allergic rhinitis, there was still some doubt that immunotherapy was effective in asthma. This was dispelled by a series of meta-analyses examining all the published, randomized, controlled studies of immunotherapy for asthma.²⁰⁻²² The first of these meta-analyses supporting immunotherapy as a treatment for asthma appeared in 1995.²⁰ The most recent, in 2010, included data from 88 clinical trials.²² It concluded that a significant improvement occurred in asthma symptoms scores (standardized mean difference -0.59) with a significant reduction in medication use, in allergen-specific bronchial hyperreactivity, and some reduction in nonspecific bronchial hyperreactivity as well.

Ever since the studies by Noon, immunotherapy has been known to cause rapid changes in the tissue threshold for the allergen injected. These changes in sensitivity of the skin and nasal mucosa to challenge were carefully documented by Jean Bousquet.²³ He performed titrated prick skin testing,

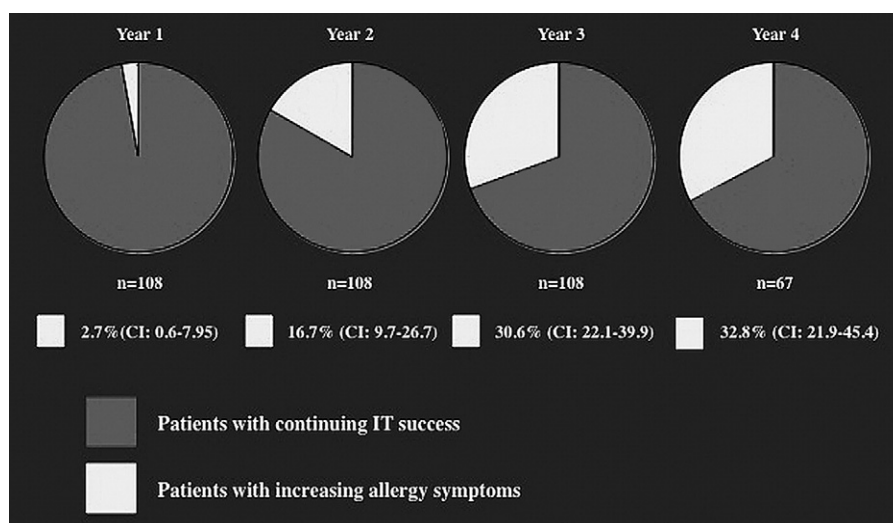


Figure 2. Recurrence of symptoms on stopping immunotherapy with grass pollen extract. Subjects were free of symptoms of allergic rhinitis after 3 or 4 years of grass pollen immunotherapy. Treatment was discontinued, and patients were followed for recurrence of symptoms during the ensuing grass pollen seasons.

titrated nasal challenge, and measured immunoglobulin G (IgG) antibody to grass pollen before and after a preseasonal course of immunotherapy with grass pollen extract. He then recorded the subjects' symptoms during the ensuing grass pollen season. He demonstrated a highly significant negative correlation between the threshold for nasal challenge (R_s , 0.66) and for titrated prick skin test (R_s , 0.84) and the number of days with symptoms during the grass pollen season. There was not a significant correlation, however, between grass-specific IgG and symptoms.

The generation of a "blocking antibody," later shown to be in the IgG₁ and IgG₄ subclasses, had been demonstrated by Robert Cooke in 1935.²⁴ Attempts to correlate the blocking antibody response with clinical improvement were generally unsuccessful. Studies on reaginic antibody, later designated IgE, also failed to establish a significant correlation between its response to immunotherapy and the observed clinical improvement. After the discovery of IgE allowed in vitro measurements, the initial response to immunotherapy was found to be a rise in allergen-specific IgE, which then declined slowly, as subsequent seasonal increases were blocked.²⁵ Still, specific IgE often took several years even to return to the baseline level, whereas symptoms had shown improvement within the first year of treatment.

The first evidence of an effect of immunotherapy on T lymphocytes was demonstration of suppression of the T-lymphocyte proliferative response to the allergen injected.²⁶ Somewhat later this suppression of the T-lymphocytes was shown to be attributable to allergen-specific "suppressor cells."²⁷ Somewhat later, evidence suggested that immunotherapy through increased production of interleukin (IL)-12 resulted in an immune deviation, such that allergen-stimulated T-lymphocytes produced increased amounts of interferon-gamma and lesser amounts of IL-4.²⁸ Recently attention has again been directed toward the suppressor cell, now known as an inducible regulatory T-cell.²⁹ These cells, by secretion of both IL-10 and transforming growth factor beta, suppressed allergen-induced lymphocyte proliferation and secretion of both interferon gamma and IL-4, while causing immunoglobulin production to shift from IgE to IgG₄ and IgA. Some incompatibility occurs in these 2 responses, 1 suppressing and 1 enhancing the release of interferon-gamma. The regulatory T-cell response appears to occur early, but it tends to wane after a year or 2, at which time the immune deviation becomes dominant.

Thus, over the last 2 centuries, allergic diseases have emerged as major health problems in the developed countries of the world. In response, medications have been developed for symptomatic treatment. However, allergen immunotherapy, first introduced 100 years ago, remains not only the most effective treatment, but also the only one that addresses the underlying immunologic derangement and offers the possibility of a cure.

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