

Immunotherapy throughout the decades: from Noon to now

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Objective: To review major milestones in the development of subcutaneous allergen immunotherapy in 20-year segments.

Data Sources: Review of the literature available in textbooks and journals.

Study Selection: Articles and books addressing major achievements in the development of subcutaneous allergy immunotherapy were selected for inclusion in this review.

Results: Immunotherapy administration has improved the lives of possibly millions of patients with hay fever. Asthmatic symptoms have been relieved if not ablated in millions as well. Insect venom hypersensitivity became treatable and highly effective. In the beginning years of immunotherapy, it was clear that immunotherapy worked; in the later years, the mechanisms for this efficacy were discovered. In this case, the therapy preceded its validation. Methods, materials, and safety have vastly improved. Postulated mechanisms explain much but not everything.

Conclusions: There is still research to be accomplished, improvements to be made, and, of course, patients to be made well.

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INTRODUCTION

This article reviews the major milestones in the development of subcutaneous allergen immunotherapy in 20-year segments from 1911 to 2010. We searched the available literature in textbooks and journals and discuss the material that addresses major achievements in the development of subcutaneous allergy immunotherapy.

THE FIRST 20 YEARS, 1911–1930

One hundred years ago the first article describing successful allergen immunotherapy appeared in *The Lancet*.¹ This was a

2-page article with a crude, hand-drawn graph (Figure 1). It was the first article to show evidence that a new therapy (which would later be called *allergen immunotherapy*) could be successful for the treatment of hay fever in Great Britain. The article was entitled “Prophylactic Inoculation Against Hay Fever” and was written by Leonard Noon, who was an investigator at the laboratory of the Department for Therapeutic Inoculation at St. Mary's Hospital, London, England. Noon initially defined hay fever “as a form of recurrent catarrh affecting certain individuals during the months of May, June, and July.” He ascribed it to what he termed a “soluble toxin found in the pollen of grasses.” He described the patients as having an “idiosyncrasy of being sensitive to this toxin which is innocuous to normal individuals.” Furthermore, he demonstrated this “idiosyncrasy” by dropping a small amount of a solution (extract) of grass pollen into the patient's eye. He used this conjunctival challenge test for diagnosis and determination of therapy response. This test was not new, having originally been described by Blakely² as a way of proving that pollen caused hay fever. Dunbar³ had

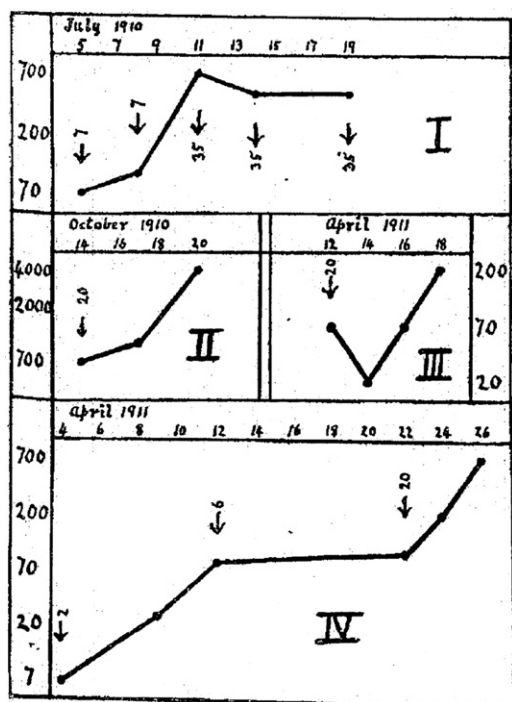
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The numbers at the sides denote the resistance of the patient, given in terms of the strength of pollen extract, one drop of which was sufficient to excite a conjunctival reaction. The arrows indicate subcutaneous inoculations of pollen extract, quantities given in the units described in the text. Figs. 1 and 2 refer to one patient at different periods of treatment; Fig. 3 shows the response obtained after about a month's treatment in another case; and Fig. 4 the early stages of treatment.

Figure 1. Noon's original hand-drawn chart.

shown that not only were mucous membranes such as the conjunctiva sensitive but also that the skin of hay fever patients was sensitive. Dunbar also showed that the injection of the pollen "toxin" gives rise in animals to the production of what was termed *antitoxin*. He even recognized that after treating patients with the pollen extracts that soluble precipitates could be found in the serum. Noon's hypothesis was that by injecting small amounts of this pollen "toxin," he could induce a state of immunity and the patient would get better. This goal of immunotherapy has not changed in the century of its use. The plan of Noon's experiment in his own words "was to obtain numerical measure of the sensitiveness of the patients to the pollen toxin and to observe whether this was increased or decreased by subcutaneous inoculations of various quantities of pollen toxin." The pollen extract was prepared by extraction with distilled water aided by freezing and thawing several times and then boiling the extracts for 10 minutes in sealed glass tubes according to the method of Dunbar. Noon found that boiling did not decrease activity of his reagents. He used several different species of grass and found all of them "capable of exciting an energetic reaction when instilled into the conjunctival sac of hay fever patients." Timothy grass, *Phleum pratense*, was found to yield the most active extract and that is what he used in his experiments. He

began with 1 g of pollen in 50 mL of water. One drop of that mixture diluted 5,000-fold was found to be sufficient to excite a distinct reaction in the more sensitive patients.

He defined a unit of pollen toxin as that amount of "pollen toxin which could be extracted from the thousandth part of a milligram of *Phleum* pollen." Using his Noon units, he found that the most sensitive patients reacted to 4 units, the least sensitive to 70. Healthy individuals failed to respond to the strongest extract, which was 20,000 units.

He began his subcutaneous injection with small doses every 3 to 4 days and increased the dose and the interval between doses. Figure 1 shows his initial chart for treatment in 1910 and 1911. He found out in the early stages of immunization that an overdose could induce a severe attack of hay fever, lasting nearly 24 hours, which was not observed in the later stages. He was able to show that after the inoculations there was an increase in tolerance (Figure 1). Unfortunately, this was the only paper written by this brilliant investigator because he died of tuberculosis in 1913.

John Freeman had been a classmate of Leonard Noon and had worked in the same laboratory with him. He continued Noon's work.⁴ He wrote a personal note about Noon and included interesting facts, such as his sister was the one who collected the grass pollen for his studies. He describes his untimely death from tuberculosis in 1913 and includes a picture of him (Figure 2).⁵

Robert A. Cooke (Figure 3), who is considered the father of American allergy, began his studies of pollen and sensitization in 1910, before Noon's paper was published. When Cooke was honored at a dinner on February 27, 1958, on the 40th anniversary of the founding of the first allergy clinic, he spoke about the factors that led him to medicine and allergy.⁶ The first factor was family predetermination. His great grandfather, the first Dr Cooke, was a physician during the Revo-



Figure 2. Leonard Noon.



Figure 3. Robert A. Cooke.

lutionary War. Robert A. Cooke was the last Dr Cooke in a continuing lineage of eldest sons expected to be physicians. The second factor he cited was that he had asthma since 8 years of age. He found out when he was sent to boarding school in 1890 that his asthma disappeared and could be traced to animals at his home, particularly horses. The third factor that committed him to his future allergy career was an exposure to diphtheria in 1908 that required him to have an injection of horse antitoxin, which resulted in severe anaphylaxis, necessitating epinephrine injections and artificial respiration to save his life. He did not mention Noon's work.

In 1910 Cooke, who had asthma, and Albert Vander Veer, who had hay fever, began studies of "hypersensitivities in humans." Cooke related that in 1911 he began experiments that culminated in his article with Vander Veer in 1915 on "Human Sensitization."⁷ In 1911 he had "extracted a pollen protein that caused skin reactions in his patients."⁸ Among the contributions Cooke and Vander Veer made were inheritance of sensitization, development of the intradermal skin test, methods of collecting pollen and making extracts for testing and treatment, antibodies in hay fever, constitutional reactions, drug idiosyncrasy, elucidation of house dust as an important allergen, and classifications of hypersensitiveness.⁸

During the next 20 years the materials and methods for allergen immunotherapy were defined. In 1912, Schloss⁹ applied the skin test to food allergy. Wodehouse¹⁰ developed extract preparation methods in 1917. Walker¹¹ extended desensitization to substances other than pollen.

In 1922 the *Journal of Immunology* (founded by Arthur Coca) published an entire issue dedicated to allergy (a first). This landmark issue contained a number of articles of major

significance; among them was Cooke's paper on constitutional (systemic) reactions.¹² This paper described causes and treatment of systemic reactions. Concerning adrenalin, Cooke advocated adrenalin (1:1,000), 1 mL in adults and 0.4 to 0.6 mL in children. He wrote, "The writer has never seen any ill effects from these large doses of adrenalin and is confident that if it is used early enough and in large enough dose, the serious results of a reaction can be avoided."

In another article in that issue, Coca¹³ reported on improved methods of allergen extraction, and to this day Coca's solution or modifications of it are still in use. Allergens were prepared by some institutions for their own use, and allergen extract manufacturers appeared as early as 1921.¹⁴

Despite Cooke's article on the possibility of reactions with intradermal testing, in that same issue in 1922, Brown¹⁵ discussed whether puncture tests or intradermal tests were better. In the last article in that issue of the journal, Cooke¹⁶ wrote about the desensitizing effects of allergen injections. He wrote, "The writer has had numerous opportunities to make such a study following subcutaneous injections in hay fever and asthma for therapeutic purpose. The effect of those injections has usually been a specific lessening of the general cutaneous reactivity, which, however, never approached extinction."

Philip Levine and Arthur Coca,¹⁷ in 1926, showed that an increase in serum reaginic antibodies after hyposensitization injection treatments helped to explain the nature of reactions to injections of pollen vaccines.

By 1927, Vander Veer, Cooke, and Spain¹⁸ published a summary article on the diagnosis and treatment of seasonal hay fever. The article summarized pollen seasons and sensitivity of patients according to 5 classes. They analyzed the results of 1,070 cases. They described local reactions and 96 "constitutional reactions" in the 1,070 cases (9%) or 1% of all injections. Treatment recommended for severe reactions was 0.5 mL of epinephrine subcutaneously and in extreme cases given intravenously. Allergy symptoms improved in 85% of the patients treated (in a preantihistamine era), and treatment was unsuccessful in 15%. In their series 30% of allergic rhinitis patients had allergic asthma; 75% of this subgroup improved with pre-seasonal therapy of at least 3 months' duration. These investigators also described encouraging results using continuing (perennial) therapy instead of only preseasonal therapy.

Twenty years after Noon published his first article on allergen immunotherapy, methods had become refined, large number of patients had been treated, and this novel therapy had helped many patients overcome allergic and asthmatic illness. The next 20 years would result in continued research, applications, and understanding of allergen immunotherapy.

1931–1950

In 1930, Freeman introduced "rush desensitization" in which injections of pollen vaccines were given at 1.5- to 2-hour intervals during a 14-hour period.¹⁹ Robert Cooke, in 1932, incorporated bacterial vaccines in hyposensitization treatments. This concept was influenced by immunologic mechanisms in infectious asthma. In 1932, Cooke reported that

cutaneous reactivity was not eliminated in patients receiving injection treatments for asthma or allergic conditions due to horse and rabbit dander. This contrasted with desensitization that accomplished complete inactivation of antibody actions in animal models of anaphylaxis.

In 1933, Arthur Stull and Robert Cooke introduced a laboratory technique to assay allergenic vaccines for protein nitrogen units. They also introduced a guide for standardization of hyposensitization schedules.²⁰

In 1935, Robert Cooke's group relocated to a new Department of Allergy at New York's Roosevelt Hospital. This group presented evidence in favor of a protective serum factor induced by injection treatments.²¹ In 1935, Robert Cooke and Arthur Stull identified this "blocking antibody" as a product of hyposensitization treatments. They also identified its chemical and immunologic differentiation and inhibiting action on atopic reagin plus allergen.²⁰

Mary Loveless (Figure 4) had arrived at Cooke's laboratory planning on staying 3 weeks but instead stayed 3 years.²² Dr Loveless worked with Stull and others studying blocking antibodies.²³ Additional studies showed the transferable nature of these blocking antibodies in Loveless' report when she demonstrated that blood transfusions from ragweed-sensitive donors treated with pollen vaccine injections conferred equivalent beneficial effects on untreated ragweed-sensitive recipients during the hay fever season.²⁴

In 1937, Louis Tuft developed guidelines for prevention of precipitin-mediated serum disease by desensitization. Horse serum products were common at that time. Tuft's guidelines advocated mandatory skin testing before its use. He also recommended a desensitization procedure incorporating epinephrine to prevent systemic reactions with injections of the horse antiserum.²⁵



Figure 4. Mary Loveless.

Efforts to make allergenic extracts less allergenic began in the 1934, with Harrison's work on alum precipitated extracts.²⁶ In 1940, Arthur Stull, Robert Cooke, and William Sherman developed depot allergenic vaccines for delayed absorption. The depot mechanism used alum to delay absorption.²⁷ There are alum precipitated allergenic extracts still available today. Mary Loveless reported on repository adjuvant therapy with a single injection of water-in-oil emulsified vaccines.²⁸

The first controlled studies on the efficacy of immunotherapy were published in 1949.²⁹ The 1950s brought new possibilities for allergen immunotherapy. These included desensitization to stinging insects and to drugs such as penicillin.

1951–1970

Several critical studies between 1951 and 1970 helped demonstrate the utility of immunotherapy for respiratory and venom allergies and laid to rest the claims of efficacy for bacterial vaccines. Advances in our understanding of the basic immunology of the allergic response during that time also paved the way for future research and improvement in therapy.

Perhaps the most important study for the validation of immunotherapy for aeroallergen sensitivity was conducted by Lowell and Franklin.³⁰ They performed a double-blind trial of immunotherapy for ragweed hay fever, demonstrating its efficacy. This trial established the efficacy for allergic rhinitis.

Venom immunotherapy was also pioneered during this time by Mary Loveless.³¹ She treated patients with venom derived from extirpated venom sacs (she called various Hymenoptera species *wasps*). She was able to show hypersensitivity to venom in patients using skin, conjunctival, and sting challenge tests. Treatment with venom injections rendered these reactions to be about the same as in control subjects. She used a version of rush immunotherapy, treating with up to 6 sacs administered in a single, prolonged visit. It would be another 22 years before the double-blind studies of Hunt et al³² confirmed these observations.

Bacterial vaccines had been used to treat allergic and nonallergic rhinitis ever since 1913, it having been reasoned that bacterial infections of the nose and sinuses were factors in the pathogenesis of hay fever.³³ Several years later, Walker³⁴ popularized the notion that bacterial allergy had a role in asthma based on his observations of scratch tests with bacterial antigens and with inhalants and foods. He therefore introduced immunotherapy with autogenous bacterial vaccines. The first controlled trial appeared in 1955³⁵ and failed to show efficacy of bacterial vaccine in asthma triggered by respiratory infections. This was confirmed by several subsequent controlled studies.^{36,37} However, it was not until 2000 when the Food and Drug Administration revoked the license for the manufacturing of bacterial vaccines.³⁸

Exploration of immunologic adjuvants for allergen immunotherapy was begun in the 1930s and furthered by Mary Loveless, who studied repository treatment using Freund's adjuvant.³⁹ She continued to pursue this line of treatment enthusiastically and published her experience in the *Journal of Immunology* in 1957.²³ Others also wrote glowingly of the use of emulsified

vaccines.⁴⁰ Unfortunately, many of these patients developed sterile abscesses, granulomas, and persistent nodules. Finally, Potter and Boyce⁴¹ in 1962 showed that mineral oil and mineral oil adjuvants produced plasma cell neoplasms in BALB/c mice, and this caused the eventual elimination of emulsions for allergy treatment.

The growth of information about the immune system during the era from 1950 to 1970 was extraordinary. Burnet's clonal selection theory,⁴² the discovery that different kinds of lymphocytes (T and B cells) had different roles in immune responses, and the structure of immunoglobulins^{43,44} were all critical to our understanding of immune function. It was the discovery of IgE by Ishizaka and Ishizaka⁴⁵ and the recognition that this immunoglobulin class carried reaginic activity that finally brought our knowledge of allergy to a cellular and molecular level, helping give it the scientific credibility it enjoys today and paving the way for all the other advances that continue to the present.

1971–1991

The 1970s and 1980s saw the publication of further randomized and controlled trials demonstrating efficacy to specific allergens, investigations into the mechanisms of immunotherapy, adverse reactions, and the development of venom immunotherapy. In 1978, Norman and Lichtenstein⁴⁶ published a study conducted in a population of allergic rhinitis patients sensitized to both grass and ragweed pollen. One group was treated with ragweed immunotherapy only, whereas the control group was untreated. Grass symptom scores remained the same in both groups, whereas ragweed scores significantly improved in the treatment group, providing evidence that the benefit of allergen immunotherapy is specific to an individual allergen. The specificity of immunotherapy and the efficacy of multiple vs single allergens had been demonstrated in an earlier study by Lowell and Franklin.⁴⁷ Johnstone and Crump⁴⁸ had demonstrated that targeted immunotherapy to inhalant allergens after skin prick testing could improve asthma symptoms in a dose response manner.

The capability of immunotherapy to modify the humoral immune response was demonstrated by Grammer et al,⁴⁹ who reported that titers of “blocking antibodies” to ragweed increased in response to specific immunotherapy treatment. This elevation was shown to persist for at least 3 months after treatment. Clinically, the treatment group continued to report consistent improvement in symptom scores for more than 3 years without additional therapy. Reid et al⁵⁰ also showed elevations in antibody titers in response to immunotherapy and specific clinical improvement to grass allergy in sensitized patients with asthma. In 1981, Norman et al⁵¹ provided additional evidence for the specificity of immunotherapy when they demonstrated elevations in specific IgE after initiating allergen immunotherapy followed by a slow overall decrease with continued treatment. Creticos et al⁵² examined the response of IgG and IgE production in vivo in response to immunotherapy. In both cases, significant elevations in immunoglobulin production were elicited in a dose response

fashion. Furthermore, the IgE elevation and suppression were more sensitive than IgG to consistent treatment. A separate prospective study of ragweed immunotherapy at the Mayo Clinic also demonstrated initial increases in specific IgG and IgE after initiating treatment. Continued therapy resulted in blunting of seasonal increases in specific IgE and gradual suppression of total IgE that was inversely related to the increase in serum specific IgG.⁵³ These results confirmed earlier findings that weekly immunotherapy is more effective in eliciting antibody responses that mirrored clinical improvements in skin and conjunctival sensitivity than monthly treatment.⁵⁴

Evidence that immunotherapy could induce regulatory effects on cell-mediated immunity was demonstrated by increases in “suppressor cells” after treatment with ragweed monotherapy.⁵⁵ This same subset of cells was later shown to be increased in patients receiving immunotherapy and that this increase was accompanied by decreases in serum IgE levels.⁵⁶ In vitro studies of lymphocytes by Nagaya⁵⁷ revealed that antigen-specific lymphocyte proliferation could be suppressed by a regulatory T-cell population induced by immunotherapy. In a separate study, Hsieh⁵⁸ showed that dust mite immunotherapy could decrease the production of interleukin (IL) 2 in lymphocytes cultured from treated patients to prevent antigen-specific clonal expansion of T cells in sensitized patients.

The efficacy of immunotherapy as a treatment was shown by demonstrable changes in end-organ sensitivity. Decreased sensitivity on skin testing and nasal allergen challenge sensitivity was present in persons receiving immunotherapy vs untreated controls.^{59,60} Decreases in bronchial hyperresponsiveness and a decrease in eosinophils seen in bronchial alveolar lavage fluid and nasal secretions were found in patients treated with immunotherapy.^{61–63} The evidence provided by these studies defined immunotherapy as immunomodulatory, allergen specific, and efficacious, validating its use in the treatment of allergic disease.

Investigations into the safety of immunotherapy conducted during this period have provided valuable insight for today's clinician. Two separate articles in 1986 examined adverse reactions to inhalant allergen immunotherapy. In a retrospective review, Greenberg et al⁶⁴ reported a series of more than 20,000 immunotherapy injections among 628 patients, showing that 7% of patients experienced a systemic reaction and that 38% experienced late systemic reactions after immunotherapy injections. Most late reactions were urticarial in nature; however, a significant number involved respiratory symptoms and were treated with epinephrine. The overall reaction rate was 0.3% of injections for systemic reactions and 0.2% for late systemic reactions. This group also reported that the incidence of reactions did not vary with season or between escalation and maintenance dosing. A prospective study published by Reid et al⁶⁵ and Nelson et al⁶⁶ included a total of 416 patients who received 26,645 immunotherapy injections using pollen extracts. They reported a systemic reaction rate overall of 0.3% with a local reaction rate of 4%. Most reactions occurred in patients who had previously

experienced reactions, and most were local reactions only and not found to be predictive of future systemic reactions.

The Committee on Allergen Standardization report published in 1987 provided a review of fatalities related to immunotherapy and helped define the associated fatality risks. This was the first review of its kind, providing evidence that fatal reactions to immunotherapy, although rare, can occur in certain subsets of patients, such as those with asthma taking β -blockers or those symptomatic from seasonal exacerbations. Furthermore, most fatal reactions occurred within 30 minutes of receiving an injection. Additional high-risk patients were identified as having previous severe reactions, highly sensitized patients, or patients receiving pollen extracts from new preparations. The potency of grass pollen extracts was reflected in the higher number of fatalities associated with this specific treatment.⁶⁷ To further underscore the risks of immunotherapy with asthma, Bousquet^{68,69} showed that in study patients receiving rush dust mite immunotherapy, asthma exacerbations were the most common adverse event, particularly in those with a forced expiratory volume in 1 second less than 80%, leading to a recommendation that asthmatic patients should not receive an immunotherapy injection if they have a forced expiratory volume in 1 second less than 70% predicted. The safety of immunotherapy in pregnancy was assessed by Metzger et al⁷⁰ during a retrospective review in 1978. They found no increases in pregnancy complications, such as preeclampsia, abortion, fetal demise, prematurity, and congenital abnormality, or in the rate of adverse reactions to immunotherapy. Taken as a whole, these studies provide the basis for counseling patients on the risks and benefits of immunotherapy, the potential for fatal reactions, and the need for observation after receiving an injection.

Treatment of stinging insect hypersensitivity was another area of investigation during this period. Several studies published in the early 1970s demonstrated increases in venom specific IgG, IgE, and histamine release in response to venom injection that were not seen with injections of whole body extract.^{71,72} In the first controlled study using venom immunotherapy vs whole body extract for hymenoptera hypersensitivity, 59 patients with verifiable evidence of sensitization were divided into placebo, whole body, and venom treatment groups followed by sting challenge tests.⁷³ The authors found marked elevations in venom specific IgG to phospholipase A in the venom treatment group without any increase or difference between placebo and whole body extract groups. Sting challenges in the venom treatment group resulted in 1 systemic reaction of 19 patients, whereas challenges in the whole body and placebo arms were halted because of systemic reactions in more than 50% of the patients.

The risks associated with venom skin testing and immunotherapy were also a subject of research during the 20 years between 1971 and 1991. Lockey et al⁷⁴ published a series of reports on the epidemiology of stings, safety of venom skin testing, and venom immunotherapy. As a result of their work, it is now known that the patients at highest risk of stings are males, work as beekeepers, and are usually atopic. Patients reported that systemic reactions occurred less often with honeybee and wasp stings. However, during the study, no

difference in reaction rates was noted among wasps, hornets, yellow jackets, and honeybees, indicating that historical accounts could not be relied on diagnostically. In addition, Schwartz et al^{75,76} demonstrated that venom-related anaphylaxis may often be a cause of unexplained fatalities. Adverse reactions with venom skin testing were found to be rare and typically mild. Venom immunotherapy was associated with systemic reactions at initial and maintenance dosing and more often with honeybee and wasp venom; however, overall reaction rates were similar to those reported with inhalant immunotherapy.^{77,78} Finally, the safety of venom immunotherapy in pregnancy was examined. A survey of practicing allergists reported on 26 women receiving venom immunotherapy while pregnant, and no increases in pregnancy-related complications or adverse reaction rates to immunotherapy were found.⁷⁹

The years from 1971 to 1991 recognized the immunomodulatory effects and overall safety of immunotherapy. The scientific findings of these decades have contributed to the validation of immunotherapy as a treatment modality. Although generally safe and effective, the small but definite risk of adverse events associated with therapy underscores the need to have specially trained physicians supervise the treatment of patients receiving immunotherapy.

1991–2010

The last 2 decades have seen an escalation in research regarding immunotherapy. During this period, PubMed and MEDLINE searches using the Keywords *allergy immunotherapy* disclosed several thousand articles.

Although many studies have shown efficacy of subcutaneous immunotherapy in allergic rhinitis, questions remain regarding its utility in the treatment of allergic asthmatic patients. A recent Cochrane database evaluation examined 75 trials involving more than 3,000 asthmatic patients and found that subcutaneous immunotherapy not only resulted in a reduction in symptoms and medicines required but also demonstrated modest improvement in nonspecific bronchial hyperresponsiveness.⁸⁰ It has always been the hope of allergists that the use of immunotherapy can modify disease progression, and several recent studies have shown this to be true. Des Roches et al⁸¹ showed that there were fewer new sensitizations in youngsters treated with dust mite immunotherapy. Pajno and colleagues⁸² examined 134 children (5–8 years old) with allergic rhinitis monosensitized to house dust mite and stratified them to receive appropriate immunotherapy for 3 years vs standard care with follow-up 3 years later. They found a significantly lower rate of further sensitizations to new allergens in the immunotherapy group (66.7%) compared with the control group (24.5%). Likewise, a recent study corroborated work performed almost 50 years ago by demonstrating that use of subcutaneous immunotherapy in patients with allergic rhinitis could prevent later development of asthma. To do so, Moller and colleagues⁸³ examined 205 children (ages 6–14 years) with a history of grass and/or birch pollen allergy sensitivity manifesting as allergic rhinitis without significant asthma. Patients were randomized to specific subcutaneous im-

munotherapy for 3 years or to open control. At the time of randomization, 20% of children had mild asthma symptoms during the pollen season. In the group without asthma at baseline, there was a significant reduction in asthma symptoms (odds ratio, 2.52; $P < .05$) and bronchial hyperresponsiveness ($P < .05$) measured by methacholine sensitivity in the subcutaneous immunotherapy group compared with standard care at the conclusion of the study.

Durham et al⁸⁴ have published studies that indicate that after 3 years of grass immunotherapy in adults with allergic rhinitis the benefits of immunotherapy persist. With regard to asthma, a number of years ago Johnstone and Dutton⁸⁵ showed that 14 years after immunotherapy was stopped there was less asthma in the immunotherapy-treated group. The specific immunotherapy group had more patients without asthma than the control group. The number of patients who continued to have asthma was higher in the control group than in the immunotherapy-treated groups. Cools et al⁸⁶ showed similar data more than 32 years later. The study population was asthmatic children with a mean (SD) age of 5 (3.8) years who received immunotherapy for a mean (SD) duration of 61 (9.7) months and were reevaluated after stopping immunotherapy at a mean (SD) of 9.3 (2.8) years previously. When compared with a control group treated with appropriate medication and no immunotherapy, frequent asthmatic symptoms were 3 times higher in the non-immunotherapy-treated group (prevalence ratio, 3.43; $P = .0006$).

Along with proofs of efficacy and disease modification, there has been a growth in understanding the mechanisms of immunotherapy. A recent review on the topic of immunotherapy by Frew⁸⁷ highlights both our understanding and our lack of understanding regarding allergy immunotherapy's mechanism of action. It has been known for some time that although allergen specific IgE levels increase initially, they ultimately return to pretreatment levels during maintenance therapy. Immunotherapy has been shown to increase allergen specific IgG levels, particularly the IgG4 subclass. Although in the past, many believed this increase in IgG level to be the mechanism of immunotherapy efficacy, the so-called blocking antibody, recent data have highlighted that the change in these levels appears to correlate more closely with the dose of allergen compared with clinical efficacy. Studies have also demonstrated that it appears the blockade of the late-phase response to skin testing and nasal challenge may hold the answer to the mechanism of action of immunotherapy.⁸⁸ Much of the recent mechanistic research has focused on T-cell response. Beyond reduction in total T-cell and eosinophil influx, effective immunotherapy is thought to result in a shift from a T_H2 to a T_H1 milieu. This phenomenon was explored in a recent study by Durham et al,⁸⁹ who performed nasal provocation to grass after a 12-month, double-blind, placebo-controlled trial of immunotherapy. They found that immunotherapy to grass-inhibited allergen induced immediate (0–60 minutes) increases in sneezing ($P < .02$) and nasal blocking ($P < .01$), as well as late (0–24 hours) nasal symptoms ($P < .05$). Immunotherapy also inhibited the infiltration of the nasal mucosa by $CD4^+$ T lymphocytes and total (major basic protein-containing) and activated (cationic protein-secreting) eosino-

phils (all $P = .03$). There was a significant ($P = .04$) increase in cells expressing messenger RNA for interferon γ at 24 hours after allergen challenge, which correlated inversely with patients' seasonal symptoms ($r = -0.65$, $P < .05$) and medication requirements ($r = -0.75$, $P < .02$) during the pollen season.

Research has also recently focused on IL-10. Studies have demonstrated its expression by nasal mucosa and peripheral blood $CD4^+$ $CD25^+$ (T-regulatory) cells⁹⁰ and its anti-inflammatory effects, such as inhibition of mast cell as eosinophil activation and inhibition of T-cell cytokine production.⁹¹ In a study by Francis et al,⁹² the relationship among clinical efficacy, regulatory cytokine production, and antibody response was examined during a year of immunotherapy in 18 patients with severe grass-induced allergic rhinitis. Grass pollen immunotherapy was effective in reducing overall symptom scores ($P < .05$) and conjunctival reactivity ($P < .05$). In the active treatment group, significant IL-10 production occurred early (2–4 weeks) at low allergen doses and at a similar time as inhibition of late skin responses, whereas serum allergen specific IgG4 occurred later (6–12 weeks). However, the increase in IL-10, although in line with suppression of cutaneous late-phase response, was seen before clinical efficacy. The authors postulate that IL-10 might contribute clinical protection through development of IgG4⁺ memory B cells. Radulovic et al⁹³ have shown that grass immunotherapy induces increased numbers of $Foxp3^+$ $CD25^+$ ($P = .02$) and $Foxp3^+$ $CD4^+$ ($P = .03$) cells in the nasal mucosa. Within the immunotherapy-treated group, 20% of $CD3^+$ $CD25^+$ cells expressed $Foxp3$, and 18% of $Foxp3^+$ $CD3^+$ cells were IL-10 positive. They concluded that the presence of local $Foxp3^+$ $CD25^+$ $CD3^+$ cells in the nasal mucosa, their increased numbers after immunotherapy, and their association with clinical efficacy and suppression of seasonal allergic inflammation support a putative role for T-regulatory cells in the induction of allergen-specific tolerance in humans.

The development and continued revision of the Practice Parameters of immunotherapy undertaken by the Joint Task Force on Practice Parameters of the American College of Allergy Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology have produced a profound effect on the continued improvement in the practice of immunotherapy in the United States.^{94,95}

CONCLUSION

The past 100 years of immunotherapy administration has improved the lives of possibly millions of hay fever patients. Asthmatic symptoms have been relieved if not ablated in millions as well. Insect venom hypersensitivity is treatable and highly effective. In the beginning years, it was clear that immunotherapy was effective; in the later years, the reasons for this efficacy were discovered. In this case the therapy preceded its validation. Methods, materials, and safety have vastly improved. Postulated mechanisms explain much but not everything. There is still research to be accomplished, improvements to be made, and, of course, patients to be made well. Noon would marvel as to where we are now.

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