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EDITORIAL



Immunotherapy coming of age: notable advances during the first hundred years

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In 1911, Leonard Noon published a paper in the *Lancet* entitled 'Prophylactic inoculation against hay fever' [1]. Hay fever had first been described in 1819 by John Bostock [2] and had been shown to be caused by grass pollen by Dr James Blackley [3]. Noon believed that the symptoms were caused by a soluble toxin in the grass pollen to which only some persons were sensitive. He believed that inoculations of timothy pollen extract would relieve patients by inducing antitoxins and proceeded with this treatment, the efficacy of which was subsequently reported by John Freeman, also in the *Lancet* in 1911 [4].

Grass pollen was the major cause of allergic rhinitis (as we now properly call hay fever) in England. In the Eastern United States, similar symptoms occurred later in the summer and were termed autumnal catarrh. This condition had been shown by Wyman to be caused by ragweed pollen [5]. The practice of immunotherapy was rapidly adopted in the United States and applied to ragweed and a number of other pollens as reported by Robert Cooke of New York in 1915 [6]. By 1917, I Chandler Walker of the Peter Bent Brigham Hospital in Boston reported using immunotherapy to treat asthma, employing extracts of cat, dog, and horse dander for treatment [7].

A major addition to the allergens employed for immunotherapy was the introduction of house dust. In 1917, Robert Cooke observed a patient whose asthma remitted on going to Texas for army training and relapsed on returning to New York. He prepared an extract of the patient's house dust and found not only that the patient reacted to the extract on skin testing, but so also did about 30% of the asthmatic patients in his clinic [8]. Over succeeding decades, it was recognized that house dust from all over the world contained a common allergen to which many allergic patients reacted, but the nature of the allergen remained elusive until the 1960s, when workers in the Netherlands discovered the mite, *Dermatophagoides pteronyssinus*, in house dust and demonstrated that extracts of the mite produced positive skin tests that paralleled those produced by house dust extracts from around the world [9].

Noon originally prepared his material by extracting timothy pollen in distilled water and then boiling it for 10 min. More standardized and gentler extraction methods were developed by Arthur Fernandez Coca, including a sodium bisulfate-buffered saline solution with phenol as a preservative still known as Coca's solution [10].

Subsequently, the use of glycerin was introduced to prolong potency of the extracts, although at the expense of painful injections when the concentration was too high [11]. Aluminum precipitation was introduced producing a depot-effect and reducing systemic reactions. Although widely employed in Europe, alum-precipitation has had limited use in the US [12]. To further reduce systemic reactions, extracts were converted to allergoids by the addition of formaldehyde or glutaraldehyde [13]. These preparations would require approval by the US FDA for use in the United States. So, although increasingly employed in Europe, they are not available in this country. In the 1980s and 1990s, the FDA undertook to standardize a number of allergen extracts [14]. Cat pelt and cat hair and dander were standardized to contain a certain amount of the major allergen Fel d 1. Short ragweed was also standardized by the content of its major allergen, Amb a 1. For a group of northern pasture grasses, Bermuda grass, and the house dust mites *D. pteronyssinus* and *D. farinae*, on the other hand, potency of the FDA standard preparation was determined by titrated intradermal skin testing. There has been no further progress with standardization in the US in the last two decades.

Noon, and those who immediately followed him, administered injections on a preseasonal schedule. Perennial injections for pollen allergy were introduced in the 1920s. The advantages of perennial immunotherapy were that it could be started at any time of year, there was less urgency in reaching maintenance doses, it was more convenient for the patient and the physician, and, furthermore, it appeared to more often be effective since higher doses were achieved. In 1937, Spain and Fuchs reported on their experience with preseasonal and perennial regimens over the previous 5 years [15]. They reported that 73% of the 692 patients treated preseasonally had good results compared to 95% of the 258 treated perennially. Further alternative treatment schedules were introduced by John Freeman who described cluster and rush protocols in 1930 [16]. He reported rushing subjects, in hospital, with extracts of grass pollen, autogenous house dust, codfish, and horse dandruff extracts. He also described the occurrence of frequent systemic reactions during rush protocols.

Although there had been some attempts at controlled studies of immunotherapy, as for instance Frankland and Augustin in England in 1954 [17], none met the standards of Francis Lowell, largely due to inadequate masking of placebo treatment. Accordingly, he and William Franklin, from Massachusetts General Hospital, undertook, during the early 1960s, two carefully designed studies that they felt overcame the deficiencies of previous attempts [18,19]. In the first study, they monitored patients undergoing immunotherapy through the ragweed season. Twenty-four patients were identified who, despite receiving immunotherapy that included ragweed, experienced rhinitis symptoms during the ragweed pollen season. They were matched, by severity into 12 pairs. Early the next spring, ragweed was removed from the treatment extract of one of each pair and replaced with caramelized sugar saline to mimic the color of ragweed extract [18]. Each subject continued to receive all the other components of their extract. During the ensuing ragweed pollen season, the group still receiving ragweed fared significantly better during each of 6 weeks of the ragweed pollen season. They then repeated the study, but this time reduced the ragweed extract from 1:50 w/v to 1:1000 w/v with similar loss of efficacy [19]. Those subjects with the reduced dose of ragweed had significantly more symptoms during three of the weeks of the ragweed pollen season. In these small but carefully conducted studies, they had proven the efficacy of immunotherapy, they had shown that it was effective when administered in a multiple-allergen mixture, and they had shown that it was immunologically specific since the patients not receiving ragweed received multiple other pollen extracts but lost efficacy with the removal or reduction of only the ragweed content.

In the 1950s, Douglas Johnstone undertook a study of the efficacy of immunotherapy as treatment for allergic asthma in children [20]. He enrolled all children with perennial bronchial asthma and positive skin tests to inhalant allergens who were referred to the pediatric allergy clinic of Strong Memorial Hospital between August 1953 and January 1955 ($n = 230$). Neither children nor parents were told they were in a study. Children were randomized to saline, a very dilute extract, an extract containing each component at 1:5000 weight by volume (w/v) at maintenance, or an extract containing each component at 1:250 w/v at maintenance. The treatment extracts contained all inhalant allergens to which the child reacted on skin testing. Those evaluating the children were unaware to which group they had been assigned. After 4 years, 18% of those receiving saline or the very low-dose extract had been free of asthma for the previous year, while this was true of 58% of those receiving 1:5000 w/v and 81% of those receiving 1:250 w/v extracts. Similar results were reported by those continuing in the study until age 16 years. Again, extracts had been administered as multiallergen mixes and had been effective.

Both the studies of Franklin and Lowell and those of Johnstone showed that there was a dose-response in immunotherapy and that doses recommended by some allergists were partially to totally ineffective. Subsequently, a number of double-blind, placebo-controlled studies have established effective and in many cases less-effective or even totally

ineffective doses by injection for many of the common aeroallergens [21]. Dose-ranging studies with the sublingual tablets have also defined optimal doses [22]. Although there are many double-blind, placebo controlled studies with sublingual immunotherapy (SLIT) liquid preparations that show efficacy, there are few dose-ranging studies and widely varying doses are offered commercially [23].

There was still some question of the specificity of immunotherapy. This was answered by a study conducted in the 1960s by Phillip Norman and Lawrence Lichtenstein [24]. They recruited 42 subjects allergic to both ragweed and grasses. Half received ragweed immunotherapy for 2 years, but neither received grass immunotherapy. After 2 years of immunotherapy, there was marked reduction in symptoms during the ragweed season in the treated, but not in the untreated subjects, while both groups had similar symptoms during the grass pollen season.

In the late 1970s, two empirically based immunotherapy practices came under scientific scrutiny. The first was the time-honored treatment of hymenoptera venom sensitivity with an extract of insect whole bodies. Investigators at Johns Hopkins conducted a double-blind study of whole body extracts or venom of the implicated insect and compared the results to those with placebo in response to sting challenge [25]. While only 1/18 venom-treated patients experienced a systemic reaction, 7/12 placebo-treated and 7/11 whole body-treated patients had systemic reactions. Venom immunotherapy has since been the standard for treating hymenoptera venom sensitivity. The second practice, termed Rinkle immunotherapy, treated with a dose of extract that was determined by the patient's sensitivity on intradermal testing. This approach, commonly used by otolaryngologic allergists, resulted in a dose of extract that was generally quite low. Again, investigators from Johns Hopkins compared the response to Rinkle and conventional immunotherapy to that of placebo-treated subjects [26]. During the ensuing ragweed season, those subjects who had received either Rinkle dosing or placebo fared the same, while those who had received conventional dosing fared significantly better. Once again, the importance of administering an adequate dose of allergen extract for successful immunotherapy was confirmed.

In 1992, a study was undertaken in which children, allergic to grass and/or birch, with symptoms of allergic rhinitis, but not asthma, were placed on grass and/or birch allergy immunotherapy (AIT) for 3 years. This Preventive Allergy Treatment study then monitored the children over a period of 10 years for the development of asthma. At the conclusion of 3 years of AIT, 2 and 7 years later, the children who received AIT had significantly less asthma than the untreated controls [27].

One last important empirical observation regarding immunotherapy required scientific confirmation. The clinical improvement after a course of immunotherapy appeared to persist for a number of years after stopping, but this was not demonstrated in an adequately controlled study until 1999. Stephen Durham and coworkers discontinued maintenance grass pollen treatment in half of a group who had received immunotherapy for 3 or 4 years [28]. Those no longer receiving active maintenance injections received placebo injections. During the three subsequent grass pollen seasons, there was no significant difference

in symptoms or medication use between the two groups, confirming that immunotherapy could be discontinued after 3 to 4 years with persisting benefit.

Although there were occasional reports or oral and sublingual administration of allergen extracts and briefly enthusiasm for intranasal immunotherapy, subcutaneous immunotherapy dominated the field of AIT for the first 80 years. Subsequently, there has been increasing scientific support for the efficacy and safety of SLIT [22,29]. Initially, SLIT was performed with liquid extracts, but more recently SLIT tablets for grass, ragweed, and house dust mite allergy have been developed and approved by some regulatory agencies. Studies showing efficacy with SLIT have been limited to monotherapy except in two studies where two allergens were administered simultaneously [22].

Noon's concept that hay fever was caused by a toxin in grass pollen to which only some persons were susceptible did not hold up. In 1921, Carl Pausnitz and Heinz Kustner reported that they had transferred skin test reactivity to fish by intradermal injection of serum [30]. This serum factor was henceforth called reagin. In 1935, Robert Cooke reported that immunotherapy induced a blocking antibody [31]. At first, this seemed a likely explanation for the beneficial effect of immunotherapy, but studies repeatedly failed to show a correlation between levels of blocking antibody and clinical response. In the late 1960s, the antibody responsible for reaginic activity was simultaneously discovered in the US by Kimishige and Teruko Ishizaka [32] and in Sweden by Johansson and Bennich [33]. Again, the response of immunoglobulin E (IgE) to immunotherapy did not appear to explain the clinical improvement, since initially specific IgE rose and then declined over several years, long after clinical improvement had been manifest [34].

Richard Evans and Ross Rocklin, at Walter Reed Army Medical Center, reported that immunotherapy suppressed the specific allergen-driven T-cell proliferation [35]. Rocklin, on returning to Tufts Medical Center, published data in 1980, showing that immunotherapy induced antigen-specific suppressor cells [36]. These findings were extended by Jutel in 2003, with the description of allergen-specific regulatory T-cells that secreted interleukin-5 and transforming growth factor-beta [37]. These regulatory T-cells suppressed the T helper cell (Th)1 and Th2 responses and also caused switching from IgE to IgG4 and IgA production. Subsequent studies suggested that the Treg response was not fully sustained. With more prolonged immunotherapy, it waned and instead the dominant immune response became an immune deviation from Th2 to Th1 cytokine responses [38]. The immune response to sublingual appears to be similar to that with subcutaneous immunotherapy [22]. The current understanding of the immune response is summarized in a recent publication [39].

Thus the practice of AIT has evolved over the last century. What will be its future? It may be that allergen extracts will be administered by alternative routes, such as epicutaneously or intralymphatically as is under active investigation. It may be that injection administration will continue, but with recombinant or modified extracts that avoid reactivity with IgE, allowing safer and more efficient administration. For the moment, however, the administration of naturally derived extracts by injection or sublingually is the gold standard by which other approaches must be compared.

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