One hundred years of allergen immunotherapy: Time to ring the changes

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One hundred years have passed since Noon1 made his original observation that prophylactic inoculation with grass pollen extract in patients with hay fever resulted in effective desensitization, as shown by a decrease in immediate conjunctival sensitivity to grass pollen. Interestingly, in this centenary year of immunotherapy, despite many advances, we continue to use whole allergen extracts administered through the subcutaneous route as usual practice.

The observation by Prausnitz and Küstner1 that a serum factor ("reagin") could transfer immediate allergen sensitivity as shown by means of skin testing was followed by the observation by Cooke et al3 that serum obtained after pollen immunotherapy could confer "immunity as well as hypersensitivity" (Table I). These seminal observations long preceded the discovery of IgE antibody as "reagin" by Ishizaka et al4 and Johansson and Bennich5 and the concept of allergen-specific IgG "blocking antibodies"6 with functional activity that remains popular today. The suppressive influence of ragweed injection immunotherapy on allergic inflammation in target organs was shown by Creicco et al7 Passalacqua et al8 similarly demonstrated decreased local eosinophilia and associated adhesion molecule expression during sublingual immunotherapy, Warner et al9 and Rak et al10 observed decreases in allergen-induced late asthmatic responses and associated bronchial inflammation, respectively, in children and adults.

Table I. One hundred years of allergen immunotherapy

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Milestone</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Noon1</td>
<td>First grass pollen subcutaneous immunotherapy trial</td>
<td>1911</td>
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<tr>
<td>Prausnitz and Küstner2</td>
<td>Passive serum transfer of immediate skin prick test reactivity &quot;reagin&quot;</td>
<td>1921</td>
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<tr>
<td>Freeman21</td>
<td>First grass pollen rush immunotherapy trial</td>
<td>1930</td>
</tr>
<tr>
<td>Cooke et al3</td>
<td>Concept of serum blocking antibodies</td>
<td>1935</td>
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Frankland and Augustin22
First double-blind, placebo-controlled, subcutaneous grass pollen immunotherapy trial
1954

Lowell and Franklin24
Grass pollen effective in multimellergen mix subcutaneous immunotherapy
1965

Ishizaka et al44 and Johansson and Bennich5
Discovery of IgE antibody
1966

Johnstone and Dutton27
Long-term benefits of subcutaneous immunotherapy in children
1968

Hunt et al31
Efficacy of Hymenoptera venom vs whole-body extract subcutaneous immunotherapy
1978

Wamer et al10
Suppression of late asthmatic responses after mite immunotherapy
1978

Rocklin et al12
Role of antigen-specific suppressor T cells in immunotherapy
1980

Gleich et al6
Early increase in IgE level after ragweed subcutaneous immunotherapy, blunting of seasonal IgE
1982

Scadding and Brostoff55
First double-blind trial of sublingual immunotherapy
1986

Creticos et al8
Inhibition of allergic inflammation in the target organ after ragweed immunotherapy
1989

Rak et al11
Inhibition of late asthmatic responses after birch immunotherapy in adults
1991

Norman et al73
First T-cell peptide subcutaneous immunotherapy trial in patients with cat allergy
1994

Akdis et al13
Role of IL-10 and regulatory T cells in venom immunotherapy
1998

Passalacqua et al49
House dust mite allergoid sublingual immunotherapy
1998

Durham et al68
Long-term clinical efficacy of grass pollen subcutaneous immunotherapy
1999

Niederberger et al90
First trial of recombinant allergen subcutaneous immunotherapy in patients with birch allergy
2004

Creticos et al76
Ragweed Toll-like receptor 9 agonist subcutaneous immunotherapy
2008

Jacobsen28
Prevention of asthma after pollen subcutaneous immunotherapy in children (the PAT study)
2007

Durham et al70
Long-term clinical efficacy of ragweed sublingual immunotherapy
2010

The link between altered T-cell responses and immunotherapy was first highlighted by Rocklin et al.12 who identified peripheral antigen-specific T suppressor cells after successful desensitization. Evidence for the critical role of regulatory T cells and IL-10 was highlighted by Akdis et al.13, 14 as well as Yamanaka et al.15 whereas the concept of a more delayed in-time downregulation of allergen-specific CD4 T H2 responses in favor of T H1 responses in the periphery and in the specific organ has developed in parallel.16, 17, 18, 19 It remains unclear to what extent it is either altered memory T-cell responses, altered B-cell responses, or both that are responsible for the long-lived antigen-specific tolerance that characterizes successful allergen immunotherapy. This is in contrast to the short-lived symptomatic relief obtained with antiallergic drugs, such as antihistamines, or topical or oral corticosteroid treatment.

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Clinical developments

Frankland25 summarizes clinical developments in immunotherapy over the past 100 years. After the death of Leonard Noon from tuberculosis the same year as his seminal publication, his colleague John Freeman extended observations on pollen immunotherapy to include documentation of seasonal symptoms and the introduction of modified immunotherapy protocols, including the first rush protocol in 1928.21 The first double-blind controlled trial of pollen immunotherapy was published by Frankland and Augustin22 in 1954 and established a firm scientific foundation for the further development of allergen immunotherapy. Frankland was a founding member of the British Allergy Society, and in his 99th year, he remains very active within the allergy community in the United Kingdom.

The practice in the United States of multiple-allergen immunotherapy is in contrast to the usual practice in Europe.23 The elegant study of Lowell and Franklin24 in 1964 was the first to clearly demonstrate that a single allergen (ragweed) in a multimellergen mixture was effective in reducing seasonal allergic symptoms. Norman and Lichtenstein25 were the first to demonstrate the allergen specificity of ragweed immunotherapy. The results of one double-blind placebo-controlled trial of multimellergen immunotherapy in children was disappointing.26 Further controlled trials with a more inclusive mix of relevant allergens in defined allergic populations are required. Johnstone and Dutton27 first highlighted the possibility that immunotherapy in children conferred long-term benefits. This concept is supported by a more recent randomized controlled trial of 3 years of pollen injection immunotherapy in children with hay fever in whom a 2- to 3-fold reduction in the risk of
progression from rhinitis to asthma was observed that persisted for up to 7 years after discontinuation of treatment. The corticosteroid dose in asthmatic children has also been reported to be reduced on immunotherapy. The duration of immunotherapy (3 vs 5 years) needed for optimal clinical improvement, however, is not established. Hunt et al demonstrated the efficacy of purified venom over insect whole-body extract and placebo in patients with anaphylaxis to the stings of Hymenoptera.

Guidelines

The World Health Organization position paper published in 1998 made recommendations regarding major allergen content for the efficacy of immunotherapy. A major advance since 1980 has been attempts to standardize the allergen content of extracts for both diagnosis and Immunotherapy in terms of both biological potency and content of major allergens. Several dose-response studies calculated on the basis of major allergen content have confirmed the dose dependency of immunotherapy in both phase II provocation studies and phase III trials. The CREATE project, under the guidance of van Ree and Chapman et al, has resulted in the availability of several standardized allergens and laboratory assays for measurement of allergen content that should facilitate more effective standardization of extracts. Doceo recommendations for US practitioners are given in the practice parameters published in this issue. Continued effective cooperation among academia, industry, and regulatory agencies is necessary for further progress.

After the World Health Organization report, the Cochrane Collaboration has provided rigorous scientific evaluation and expanded the evidence base in favor of immunotherapy, although the limitations of meta-analysis in terms of the heterogeneity of included studies and the possibility of positive publication bias are acknowledged. Recent advances include the Grades of Recommendation, Assessment, Development and Evaluation approach, which focuses more critically on actual clinical value and cost-effectiveness. The availability of standardized allergen extracts has permitted dose-response studies that have informed more definitive phase III trials. The World Allergy Organization has provided guidelines to optimize clinical trial design, and the GA2LEN collaboration has provided advice on proper reporting according to the Consolidated Standards of Reporting Trials criteria. These issues are discussed in the article by Calderon et al. The recent "big trials" have clearly defined the value of both subcutaneous and sublingual immunotherapy in adults and children with seasonal pollinosis, including identification of optimal doses and the optimal preseasonal duration of sublingual immunotherapy.

In this issue Cox et al provide a comprehensive third update to their practice parameters for immunotherapy. Highlights include an algorithm for the key decision points for the use of immunotherapy and a new classification and grading of systemic reactions that should facilitate a more accurate and standardized method for reporting side effects. Controversial issues, such as circumstances in which concomitant use of β-blockers might be reasonable and whether to recommend a prophylactic antiallergic agent to patients undergoing immunotherapy, are carefully considered. Hankin and Lockey discuss patient adherence to immunotherapy. Sadly, the main conclusion is the lack of data in contrast to studies evaluating compliance with pharmacologic treatment. Hankin and Lockey highlight several simple approaches that could be pursued, and this must surely represent an opportunity for professional organizations to support studies to evaluate adherence to improve patient selection for immunotherapy and outcomes. Lockey and Hankin review the limited data available from the United States and elsewhere concerning the economic costs of immunotherapy. Although acknowledging the methodologic shortcomings of these studies and the need for more robust data, they conclude that subcutaneous immunotherapy is associated with significant health care savings, with one study showing up to an 80% reduction in health costs at 3 years after completion of treatment.

Sublingual immunotherapy

After the first double-blind trial in mite-sensitive adults, sublingual immunotherapy has emerged as an effective alternative to the subcutaneous route and is widely practiced in Europe, although at present to a lesser extent in the United States. Unlike subcutaneous immunotherapy, sublingual immunotherapy might act primarily through its effects on oral Langerhans cells. Several published definitive trials of grass pollen tablets have confirmed their efficacy, safety, and tolerability in both adults and children. The sublingual route appears safe and has broadened the availability of immunotherapy to include self-administration, although continued vigilance after registration of products in Europe is ongoing and a proper standardized reporting system for side effects of sublingual immunotherapy is required. The repertoire of large sublingual studies needs to be extended to include seasonal allergens other than grass and also perennial allergens, including mites, molds, cockroach, and animal dander. If safety and tolerability continue to be acceptable, this should allow a broadening of the evaluations from rhinitis to include asthma, eczema, and food allergies. In the case of food allergies, there have also been several studies suggesting a beneficial effect of oral immunotherapy, but further studies are required to establish the safety and efficacy of this approach, particularly in patients with peanut allergy. It is noteworthy that unlike the Lowel and Franklin study of subcutaneous immunotherapy reported above, grass pollen sublingual immunotherapy was ineffective when administered as part of a multiallergen mix, which questions the likely value of multiallergen sublingual immunotherapy in contrast to the single-allergen approach favored in Europe. There is a need to evaluate more patient-centered outcomes and cost-effectiveness of the sublingual approach, as addressed by Canonica and Passalaqua in their article.

Long-term benefits

The demonstration of clinical and immunologic tolerance to seasonal pollens (persistance of benefit for several years after
discontinuation of immunotherapy) and the possibility that pollen immunotherapy might reduce progression to asthma\(^{26}\) and prevent new sensitizations\(^{69}\) are reviewed by Canonica and Passalacqua.\(^{67}\) These observations raise the question of whether immunotherapy should be introduced earlier in the course of allergic disease, as suggested in the recent World Allergy Organization position paper, rather than to be restricted to those patients who do not respond to the usual antiallergic drugs or those who experience unacceptable side effects of pharmacotherapy. One recent large double-blind trial of grass pollen tablets has confirmed long-term remission after 3 years of immunotherapy.\(^{70}\) A recent open, partially randomized study of mid

immunotherapy suggested that 4 rather than 3 years of sublingual immunotherapy might be optimal for long-term tolerance.\(^{71}\) Further large, double-blind, randomized trials are needed to rigorously test the preventive effects of immunotherapy on the development of new sensitizations and disease progression before firm recommendations can be made.

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Novel approaches and future directions

Casale and Stokes\(^{72}\) herein review novel approaches to immunotherapy, commencing with the use of subcutaneous allergen in combination with anti-IgE treatment. Other approaches summarized include peptide immunotherapy that uses short, linear T-cell epitopes that retain immunogenicity while losing the potential to cross link IgE and induce anaphylaxis.\(^{73},\) 74 Allergoids are an alternative attempt to reduce allergenicity,\(^{75}\) whereas adjuvants such as CpG-containing bacterial DNA fragments\(^{76}\) and bacterial cell wall LPSs (MPL)\(^{77}\) combined with allergen have been shown to be effective in inducing immune deviation and suppressing symptoms. The recent successful development of recombinant wild-type\(^{76},\) 78 and modified\(^{80}\) allergens holds promise in terms of optimal standardization and the potential for personalized immunotherapy tailored to individual IgE sensitivities.\(^{81}\) The use of intra-lymph node injections of allergen\(^{82}\) and, more recently, of allergen-containing patches for transdermal use\(^{83}\) have stimulated great interest.

The jewel in the crown of allergen immunotherapy is its ability to induce long-term tolerance (ie, clinical efficacy after its discontinuation). The demonstration that both the subcutaneous and sublingual routes might induce tolerance should broaden the indications for immunotherapy in the future.\(^{55}\) Novel approaches, including the sublingual route, that achieve tolerance effectively,\(^{84},\) 85 safely, and in a more convenient and cost-effective manner require enthusiastic support and further development rather than a continued reliance on the current traditional subcutaneous immunotherapy with its acknowledged limitations. The progress made in these past 100 years of immunotherapy combined with new technologic and scientific advances on the horizon portend dramatic changes for the next 100 years (Fig 1).

![Figure 1](https://example.com/image1)

Figure 1. January 2011 cover image.

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