

REVIEW

Hundred years of allergen immunotherapy

A. J. Frew

Department of Allergy and Respiratory Medicine, Brighton and Sussex Medical School, Brighton, UK

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Summary

Allergic rhinitis was almost unknown until the early 19th century, but within 100 years it was described as a modern epidemic. Pollen was identified as the likely cause of hayfever and although the nature and mechanisms of the sensitivity remained obscure, it was speculated that hayfever might be caused by a toxin in pollen. Vaccination schedules were developed to treat this, but later it became clear that an antibody was responsible. The first clinical trials of specific immunotherapy (SIT) were published in 1911 and 1914 and were followed by several similar papers from the United States. The use of skin prick tests and new allergen extraction techniques accelerated the development of SIT, which became a widespread practice, especially in the United States. Formal controlled clinical trials were reported in 1953 (United Kingdom) and in 1965 (United States). Since then, many controlled clinical trials have confirmed the efficacy of SIT, and although some concerns have arisen around safety, SIT remains a valid option for treating allergic disease. Recent developments include the introduction of sublingual immunotherapy, and clinical trials of recombinant and peptide vaccines. Future developments should increase efficacy and safety, but the biggest challenge to the wider use of SIT is probably economic, as patients and healthcare providers become increasingly critical of all forms of allergy treatments.

Correspondence:

Anthony J. Frew, Department of Respiratory Medicine, Royal Sussex County Hospital, Brighton BN2 5BE, UK.
E-mail: anthony.frew@bsuh.nhs.uk

Introduction

The medical history of allergic disorders is relatively recent. Although asthma had been described in antiquity, its allergic features were not clearly identified until modern times, and allergic rhinitis (AR) was almost unknown until the early 19th century. The first medical description of AR is probably that of Bostock, who reported his own personal condition in 1819 at a meeting of his local Medico-Chirurgical Society. In his report, Bostock commented that his case presented 'an example of an unusual train of symptoms about the beginning or middle of June every year' [1]. Bostock set about finding other cases, and over the next 10 years he identified 27 similar cases 'in all England'. By the end of the 19th century, hayfever had become a much more common problem and contemporary accounts talk about it as a modern epidemic. Pollen was identified as the likely cause of hayfever by Wyman and Blackley [2, 3], working independently in the United States and United Kingdom. However, the nature and mechanisms of the sensitivity would remain obscure for many decades.

Around this time, there was great interest in the development of vaccines for infectious diseases, led by the

efforts of Koch and Pasteur. Although not addressing allergic conditions, these experiments laid the theoretical framework that would lead to specific immunotherapy (SIT). For example, the ability to generate a protective response (antigenicity) could be dissociated from the ability to cause damage (virulence), either by attenuation of the bacterial strain or by heat treatment to kill the organism. The discovery of diphtheria toxin, and development of the science of passive immunization, led Dunbar and others to speculate that hayfever might be caused by a toxin present in pollen grains. 'Pollatin', an anti-pollen antibody raised in rabbits and horses, was claimed to offer benefit [4], but could not be replicated by others. Attempts to actively immunize against grass pollen were dropped because of severe reactions.

Anaphylaxis was analysed and then formally described in 1902 by Portier and Richet. This phenomenon helped to explain some of the earlier contradictory features of AR and attempts to treat it by immunization. After noting that the lung changes in asthma were similar to those found in guinea-pigs suffering from anaphylaxis, Meltzer suggested that asthma might be due to a form of anaphylaxis [5]. When experimental incremental immunization protocols were developed, which would protect sensitized

guinea-pigs from anaphylaxis [6], the scene was set for the possibility of using incremental dosage therapy to treat asthma and hayfever.

At this time, St Mary's Hospital London was one of the high places of medical science. The pathology department led by Almroth Wright attracted clinicians and scientists interested in the prevention and cure of disease by immunization. Leonard Noon came to St Mary's in 1910, having previously worked at the Pasteur Institute. Here, he met John Freeman and together they developed the first effective immunotherapy protocol, whose centenary we are now celebrating. In accordance with the beliefs of the time, Noon thought that hayfever was caused by a soluble toxin contained within the pollen of grasses, and noted that some patients recovered from this affliction – a phenomenon he attributed to the development of an active immunity against the toxin. Noon acknowledged the efforts of Dunbar to achieve passive immunity against pollen, but noted that this was difficult and laborious, as well as being unable to achieve a permanent cure. Noon's intention was therefore to achieve active immunity against the toxin, using an incremental dosage regime that might get around the problems encountered with earlier forms of active immunization. Noon calibrated extracts in terms of pollen weight/volume and the injections were given as a course of weekly injections before the pollen season. In his seminal paper, published in the *Lancet* in 1911, Noon reported clinical efficacy, as judged by the patient's reported symptoms, as well as noting several aspects of SIT that remain valid today [7]. These included

- an initial increased in sensitivity, followed by progressive tolerance of allergen (judged by conjunctival provocation tests) and
- systemic reactions if the dose is increased too rapidly or if dosage intervals are too short.

Noon concluded that the sensitivity of hayfever patients could be reduced by at least 100-fold but it was not clear whether this immunity would be sufficient to carry the patient through a whole season without experiencing their usual annual attacks of hayfever.

Sadly, Noon died from tuberculosis shortly after publication of his paper, and hence never saw the impact of his work. In 1914, Freeman [8] published the results of the first 3 years of SIT. Importantly, this paper is the first to report persistent benefit after cessation of SIT – only one year's follow-up had been possible by this date, but the concept of a long-term benefit had been demonstrated. Europe had other priorities in 1914, and although it is interesting to speculate whether SIT might have captured the imagination if the Great War had not broken out, the eventual outcome was that allergy and SIT remained minor academic interests in the United Kingdom and elsewhere in Europe until the 1950s.

Around the time of Freeman's 1914 paper, various reports of SIT started to appear in the US medical literature [9–11]. At this distance, it is not clear whether these other clinical studies were truly independent, but within a very short time, immunotherapy acquired a momentum of its own in the United States, and much of the next phase of development flowed from these early clinical adopters. At a 1915 meeting of the New York Academy of Medicine, Robert Cooke described favourable results in 140 patients [12], and over the next 15 years, a whole clinical science and enterprise grew up. It rapidly became clear that the mechanism of allergic sensitivity was immunological hypersensitivity and not because of toxins. The use of skin prick tests led to identification of a wider range of agents that seemed to be capable of inducing allergic reactions. In turn, the development of new methods of extracting allergenic components from foods and environment provided extracts both for diagnostic testing and for treatment. During this phase of the historical development of SIT, both physicians and patients showed an uncritical willingness to accept favourable reports of efficacy. Dosage regimes were rather arbitrary and there was no perceived need to demonstrate the validity or efficacy of any given therapy.

Looking back, one wonders at the way SIT was adopted, but several factors will have contributed to this, including the lack of alternative effective treatments, and the evangelical work of Cooke, Coca and others who educated the early cadres of allergists and stimulated the establishment of hospital clinics for allergy throughout the United States, leading in turn to the training of the allergy specialists who set up shop in towns and cities across America. House dust mite was identified as a cause of allergy in 1921 [13], leading to the widespread adoption of house dust extracts for treatment for rhinitis and asthma [14]. Only much later was it realized how many people are sensitized without being symptomatic.

Freeman articulated a doctrine of prophylactic thorough desensitization and argued that abolition of skin prick test reactivity should be the end goal of treatment. However, during the 1920s, it was noted that clinically successful SIT could be achieved without abolition of skin sensitivity [15–17], and Cooke therefore proposed that the treatment should be called hyposensitization rather than desensitization [15]. In 1931, a joint committee of the Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions was established to consider how best to standardize extracts and treatment schedules. Although it failed in these objectives, the joint committee did manage to develop a system of accreditation for training programmes in allergy [18]. For some years to come, allergen extract standardization remained based on the protein nitrogen content of the extract, although technical aspects of allergen preparation were enhanced by the optimization by Coca, in 1923, of

reagents for allergen extraction. By 1935, Cooke and colleagues had identified a protective factor in serum, which was induced by SIT. The protection appeared to be transferable by blood transfusion, in that ragweed-sensitive recipients were protected after receiving blood from donors who had been treated for their ragweed allergy [19]. This finding led to the concept of 'blocking antibodies' [19], whose significance has only recently been understood. Cooke and Loveless showed that similar antibodies could be induced in non-allergic subjects who were injected with ragweed extracts, and that these antibodies could block passive transfer of cutaneous reactivity to allergen [20].

In the early 1950s, the true benefit of SIT came under scrutiny, and a number of controlled clinical trials were set up. In retrospect, it is perhaps surprising how unscientific medicine was in those days, and although immunotherapy has received much criticism for its empirical origins, much the same point could be made about a whole range of medical practice. Perhaps, the most farsighted of the early clinical trials was that conducted by Frankland and Augustin, who were working with Freeman at St Mary's in London. They performed a controlled study comparing crude pollen extract with the isolated main protein component. They also included a placebo arm (phenolized saline) and an ultrafiltrate that had been shown to contain little or no allergenic activity. Both of the active treatments were found to be much more effective than the ultrafiltrate or the placebo [21]. Perhaps, because the title of the article suggested a comparison between two active materials, without mentioning the placebo arm, this article did not receive the attention it deserved. For another decade, allergists in the United States and Europe continued with their anecdotal practice until 1965 when Lowell and Franklin [22] published their landmark study in the United States. This double-blind controlled study looked at withdrawal of ragweed from the multiple allergen extracts that were prescribed to multi-sensitized patients, and showed that those receiving ragweed had fewer symptoms and required less rescue medication than those who were deprived of ragweed. This study had the key advantage of an active control, in that placebo patients had local reactions to their injections, because they were being treated for unrelated allergies. As well as demonstrating the allergen specificity of SIT, this trial brought to an end the era of anecdote and unsupported clinical claims, and heralded a new era in the scientific evaluation of studies of the effectiveness of immunotherapy. The other seminal study reported around this time was performed in children with asthma. In this period, when clinical trials were conducted differently, well before the days of ethics committees, Johnstone and Dutton randomized all children attending their clinic between August 1953 and January 1955, to one of four treatments. Neither the subjects nor their parents were

aware of the treatment being given. Compared with those who received placebo or very dilute allergens, those treated with the two higher doses of SIT were much more likely to lose their asthma after 4 years, and among those in whom asthma persisted, the likelihood of having severe disease was much lower in those who had received active treatment [23]. Although such a study could not be conducted today, the data are useful in confirming the dose-response of SIT, and its potential for reducing the duration and severity of asthma.

Since then, many controlled clinical trials have been performed, and their effects have been summarized in meta-analysis. The efficacy of SIT for different conditions is reviewed elsewhere in this series: from the historical perspective, the main question is whether we should be restricting analyses to well-defined types of SIT used in modern trial designs, or whether we should continue to include data from the early trials. On a number of grounds, not least the heterogeneity of the vaccines, and the variability of the study period and outcome measures, it is probably now appropriate to consign most pre-1986 clinical trials to the history books, and to focus on the outcomes of large-scale studies, conducted according to modern technical standards.

With the discovery of IgE, clinical and scientific allergy moved onto a new plane. At last it was possible to measure the antibodies that were responsible for the phenomena that had been described over a century earlier. And with this understanding, there was an acceleration of studies addressing the mechanisms of allergic disease and also the mechanisms underpinning successful SIT. The clear demonstration that SIT attenuated the late-phase of the allergic response [24] refocused attention on other aspects of the immune response, and over time it became clear that cell-mediated immunity was an important element in the expression of allergic disease and its treatment. Several groups tried to improve the effectiveness of vaccination programmes by using adjuvants [25] or depot preparations [26] to boost the effect of the allergen extract. Alongside this, various modifications were made to vaccines, to reduce their ability to bind to IgE while retaining their ability to stimulate a cellular response. Among these was the development of inactivated allergoids, proteins that were denatured with aldehydes to reduce their ability to bind IgE while retaining their antigenicity [27]. New methods were also developed to characterize and standardize allergen extracts, allowing better control of the allergenic content of proprietary allergen vaccines. During this period, investigators in Baltimore showed that there was no relationship between the production of allergen-specific IgG antibodies and the efficacy of ragweed immunotherapy [28]. This work would pave the way for future studies of the role of T cells in SIT.

All this progress was rudely interrupted in 1986, when concerns were suddenly raised in the United Kingdom about the safety of desensitization. Looking back a quarter

of a century, we can see how the various elements came together: improved and therefore stronger vaccines were being used in an ever wider group of patients, without proper facilities to deal with complications. We now know that most of the serious and fatal events occurred in people with asthma rather than in those with rhinitis, but the response of the regulatory authorities to a cluster of fatalities was quick and decisive: they effectively banned SIT except in clinics that were familiar with its use and had appropriate resuscitation facilities to deal with any adverse events [29]. The net result was to severely reduce the amount of SIT occurring in the United Kingdom, and to raise concerns everywhere else. In the United States, the American Academy of Allergy and Immunology asked its members to report any serious adverse events, and over the next few years a picture emerged of occasional catastrophic events in patients with relatively mild illness. Despite exhortations for care, fatal events continued to be reported to the end of the century [30, 31].

Despite the Committee on Safety of Medicines injunction, or perhaps because of it, UK researchers have continued to study the mechanisms and practice of SIT. Varney et al. [32] provided evidence of the efficacy of injection SIT in hayfever because of grass pollen during the first season of therapy, and this has been further confirmed in a larger study, which also demonstrated a dose-response [33]. A long-term study of the patients from the earlier of these two studies has shown the durability of SIT when given for 3–4 years [34]. Critical evaluation of all the available data by meta-analysis has confirmed the beneficial effect of injection SIT for several different allergens [35] while identifying significant heterogeneity in the various clinical trials, which in turn has led to calls for greater standardization of clinical trial design [36].

But perhaps the most lasting legacy of the 1986 debacle was a renewed interest in alternative routes of administration. Oral and sublingual administration of allergen extracts had been tried during the first half of the 20th century, but subsequently fell into disrepute. Since 1986, there has been a revival of interest in sublingual immunotherapy (SLIT). The precise mechanisms by which sublingual SIT works remain unclear but a substantial body of evidence has now accumulated from well-conducted

clinical trials, indicating that SLIT can procure reductions in symptom scores and rescue medication usage in patients' seasonal allergic rhinitis that are comparable with what can be achieved by injection SIT [37]. It remains uncertain whether this can be improved by continuing for several years, and how long the benefit lasts for. Local side-effects are common, but usually well tolerated. Systemic side-effects were relatively rare, and much less serious than those encountered with injection SIT. For perennial allergens, less clinical trial data are available [38], and there are only limited data in children, although recent studies have been encouraging [39, 40]. SLIT is now being used routinely in some parts of Europe (especially Italy and France), and is gradually spreading to Northern Europe and the United States. Overall, the introduction of SLIT seems likely to widen the scope of SIT and to allow an expansion of the number of patients able to receive therapy [41]. The relative efficacy of SLIT and injection SIT has not been determined and only limited data are available from published comparative studies [42, 43] or from comparing meta-analyses [27, 34].

Conclusions

SIT developed from a desire to inoculate patients with hayfever against a supposed toxin in pollen. Although the underlying concept has proved false, SIT remains in use over a century later, and is clinically effective in patients with rhinitis or asthma whose symptoms are clearly driven by allergic triggers. Initial uncritical enthusiasm has been replaced by more rigorous clinical trials data. Perhaps surprisingly, we are still unsure exactly how SIT works, but it is now widely believed that SIT induces regulatory T cells that are capable of damping the response to allergen exposure in sensitized subjects [44]. Concerns about safety in the mid-1980s led to improvements in safety, and also to the adoption of the sublingual route for SIT. The next century of SIT may see the development of vaccines that are better standardized or the use of recombinant allergens, both of which should improve the safety profile of SIT, but the basic concept of SIT remains valid as it enters its second century.

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