

Editorial

A century of immunotherapy

Pollen was definitively shown to be the cause of hay fever or as it was known then catarrhus aestivus by Charles Harrison Blackley in 1873. By the beginning of the 20th century the concept had arisen that grass pollen contained a toxin which produced the symptoms. Clemens von Pirquet in 1906 published a paper on the concept of immunity, hypersensitivity and anaphylaxis. He compared horse serum reactions to smallpox vaccination and stated that 'immunity and hypersensitivity can thus be closely related'. He coined the term allergy from 'allos' meaning 'other – an altered state'. Based on this concept that hay fever and infection were rather similar in relation to genesis it followed that an immunisation strategy which had been evolving to prevent infectious disease might work for hay fever. Initial attempts were made to generate an anti-toxin by injecting animals with pollen and using the serum to immunize patients. This was most intensively investigated by William Dunbar in Germany. This proved to be a failure. However, Dr Leonard Noon working in the infectious disease microbiology unit at St Mary's hospital in London pursued this notion by giving injections of pollen extracts to patients with hay fever. He conclusively demonstrated that this would reduce conjunctival reactions to the same extract as that used in the inoculations (1). There is a very sad and poignant last sentence in this paper stating that Dr Noon was handing over the continued observations to his colleague John Freeman during his enforced absence of some months. Sadly he died 2 yr later. However, in September of the same year John Freeman was able to publish further observations on the patients who had received the inoculations as they went through a pollen season. It is remarkable that his publication appeared in September only 2 months after the end of that pollen season (2). Freeman observed a distinct amelioration of symptoms. However, he did qualify this statement by pointing out that 'there is a constant tendency to detect such improvements in adventitious fluctuations in health'. It is a great pity that the huge investment in immunotherapy that

followed these observations did not heed the warning which effectively was describing a placebo response. The toxin anti-toxin theory was eventually disproved when heat labile antibodies known as reagins were identified in 1925 by Coca and Grove (3). It was of course some years before the reagins were identified as being immunoglobulin E (IgE) (4).

The first double-blind placebo-controlled trial of pollen immunotherapy was carried out by Dr William Frankland also from St Mary's hospital and published in 1954 (5). He showed that of the 200 sufferers included in the study 79% on active treatment improved while only 33% on placebo had any improvement. Thereafter, there was a host of published studies demonstrating efficacy of this treatment. It was demonstrated in many studies that a rise in immunoglobulin G antibody to the injected allergen was a fairly consistent finding and it was assumed that this in some way blocked the allergen from accessing IgE. However as is apparent from many publications that have appeared in this journal, the main mechanism by which immunotherapy achieves a moderation of allergic responses is via upregulation of T helper 1 cells and regulatory T cells and down-regulation of T helper 2 responses (6–8).

Another study which investigated the nature of the efficacious response to immunotherapy was conducted by myself. In a trial of house, mite immunotherapy in children with house mite allergic asthma clinical improvement was associated with a diminution or loss of the allergen induced late bronchial reaction (9). The other seminal work was to identify that 3 yr of therapy was associated with a significant carry over effect after cessation of treatment. Thus up to 3 yr after cessation there was a sustained beneficial effect (10).

Successive systematic reviews of specific immunotherapy for asthma have shown that compared with placebo it significantly improves asthma symptoms, medication needs and bronchial hyper-responsiveness when the allergies being treated are to house dust mite, grass or

tree pollen, cat or dog allergen (11). It can therefore be concluded after a century of clinical study that allergen specific immunotherapy is efficacious, has a unique carry over effect after 3 yr of treatment and has benefits for both allergic rhinitis and asthma. There is even a suggestion that administration to children with allergic rhinitis might delay or prevent the onset of asthma (12). Despite these very considerable benefits there remains anxiety that this therapy will have adverse effects which has led guidelines to suggest that it is only recommended for venom anaphylaxis and severe seasonal rhino conjunctivitis. Authoritative asthma guidelines have suggested that while immunotherapy reduces asthma symptoms the size of benefit compared to other therapies is not known (13). Thus if there is to be any further progress in defining the role for immunotherapy in clinical practice, then investigators must over the next decade compare safety and efficacy against conventional pharmacotherapy in well-controlled studies. This will be an important challenge for us to consider addressing.

J. O. Warner

Imperial College, Wright Fleming Institute, Norfolk Place, London W2 1PG

References

1. NOON L. Prophylactic inoculation against hay fever. *Lancet* 1911; i: 1572–3.
2. FREEMAN J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. *Lancet* 1911; II: 814–7.
3. COCA AF, GROVE EF. Studies in hypersensitiveness XIII. A study of the atopic reagins. *J Immunol* 1925: 10: 445.
4. ISHIZAKA K, ISHIZAKA T. Identification of gamma E antibodies as the carrier of reaginic activity. *J Immunol* 1967; 99: 1187.
5. FRANKLAND AW, AUGUSTIN R. Prophylaxis of summer hayfever and asthma: a controlled trial comparing crude grass pollen extracts with the isolated main protein component. *Lancet* 1954; I: 1055.
6. LUE KH, LIN YH, SUN HL, et al. Clinical and immunological effects of sublingual immunotherapy in asthmatic children sensitised to mites: a double blind randomised placebo controlled study. *Pediatr Allergy Immunol* 2006; 17: 408–15.
7. TSAI Y-G, CHIEN J-W, CHEN W-L, et al. Induced apoptosis of Th2 lymphocytes in asthmatic children treated with dermatophagoides pteronyssinus immunotherapy. *Pediatr Allergy Immunol* 2005; 16: 602–8.
8. ANTUNEZ C, MAYORGA C, CORZO JL, JURADO A, et al. Two year follow up of immunological response in mite allergic children treated with sublingual immunotherapy comparison with subcutaneous administration. *Pediatr Allergy Immunol* 2008; 19: 210–8.
9. WARNER JO, PRICE JF, SOOTHILL JF, HEY EN. Controlled trial of hyposensitisation to dermatophagoides pteronyssinus in children with asthma. *Lancet* 1978; ii: 912–5.
10. DURHAM SR, WALKER SM, VARGA E-M, JACOBSON MR, et al. Long term clinical efficacy of grass pollen immunotherapy. *N Engl J Med* 1999; 341: 468–75.
11. ABRAMSON MJ, PUY RM, WEINER JM. Allergen Immunotherapy for Asthma. *Cochrane Library* issue 3, 2001.
12. NIGGEMANN B, JACOBSEN L, DREBORG S, FERDOUSI HA, et al. Five year follow up on the PAT study: specific immunotherapy and long term prevention of asthma in children. *Allergy* 2006; 61: 855–9.
13. BRITISH THORACIC SOCIETY SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK. British guideline on the management of asthma. *Thorax* 2008; 62 (Suppl. 1V): 1–121.