

REVIEW

Conventional and alternative allergen immunotherapy: do they work? are they safe?

A. J. FREW

University Medicine, Southampton General Hospital, Southampton, UK

Introduction

Allergen injection immunotherapy has been used to treat allergic disorders since the early decades of this century, when Noon and Freeman at St Mary's Hospital, London, UK first used pollen extracts to treat hay fever [1,2]. Allergen immunotherapy was enthusiastically adopted in North America, where it became the treatment of choice for allergic rhinitis and asthma. In the UK, desensitizing injections were widely used in general practice until 1986 when concerns about their safety led the Committee on Safety of Medicines to set tight constraints on this form of therapy [3]. For historical reasons, hospital-based clinical allergy in the UK has only been available in a limited number of specialist units and most organ-based UK specialists have little training or experience in the diagnosis and treatment of allergies. At the same time, many patients with allergic disorders remain keen to seek specific treatments for their allergies and the relative lack of NHS allergy clinics has led many patients to seek and obtain allergy treatment from practitioners of alternative (complementary) medicine. Concern has been expressed about the efficacy of unconventional allergy treatments and also about the possible risks of withdrawing conventional prophylactic medication such as corticosteroids. A separate but important problem is the differing definitions of allergy used by conventional and alternative practitioners. What then is the evidence for efficacy of conventional and alternative forms of specific desensitization, how safe are they, and if they work, how do they work?

Does allergen immunotherapy work?

Seasonal and perennial allergic rhinitis

The diagnosis of seasonal allergic rhinitis is usually easy to make from the history and specific hypersensitivity can be confirmed by skin testing. In contrast, perennial allergic rhinitis can be much more difficult to diagnose and patients often report a 'continuous cold' without any clear-cut environmental triggers. Many trials of desensitization for

allergic rhinitis have been published since 1914. Most of these were open or uncontrolled, but in this respect the trials were no different to other clinical studies of that era. The treatment strategy appeared logical to patients and doctors, the treatment seemed to work well, and the placebo effect was not well understood. It also appeared to be safe (probably because of the low allergen content of most extracts) and both physicians and patients adopted it without asking the sort of questions that would be required nowadays before the introduction of a new form of therapy.

Medical and public opinion has changed and we no longer assume that treatments are worthwhile simply because they are time-honoured. Moreover, there is no absolute reason why new, purified extracts should be as effective or as safe as older types of extracts. In recent years, there have been several double-blind placebo-controlled trials of partially purified, standardized depot grass pollen extracts in patients with summer hay fever [4-7]. In each of these there were highly significant decreases in overall total symptoms and in the use of rescue medication. Clinical improvement was accompanied by a reduction in immediate conjunctival and nasal sensitivity and a decrease in the cutaneous immediate and late cutaneous reaction to allergen.

Evidence for the efficacy of injection immunotherapy for rhinitis due to other seasonal allergens is less clear-cut. Many patients have received treatment for tree pollen allergy, often as part of a pollen mixture. There are few useful studies of efficacy, partly because most tree-pollen-allergic patients are also allergic to grass pollen. On the other hand, isolated birch pollen allergy is quite common in Scandinavia and specific desensitization has been shown to be effective [8]. Ragweed allergy is a major problem in North America and again immunotherapy has been shown to be effective [9]. However, treatment of other weed pollen allergies (e.g. *Parietaria*) has not been formally evaluated. Autumn rhinitis can be due to allergy to moulds (*Cladosporium*, *Alternaria*, *Aspergillus* spp): biologically standardized extracts of allergenic moulds are not currently available, but immunotherapy with a high quality (non-commercial) *Cladosporium* extract was found to be effective in children [10].

Correspondence: Dr A. J. Frew, University Medicine (Centre Block), Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK.

Perennial allergic rhinitis due to house dust mite is a common clinical problem and can be difficult to treat with allergen avoidance and conventional medication. Current regimes using multiple topical preparations and oral antihistamines throughout the year are often effective but are inconvenient and nasal obstruction can make it difficult for topical sprays to reach the affected mucosa. As a result patients often have to put up with persistent symptoms and this leads to poor patient compliance. Injection immunotherapy can be effective in house dust mite rhinitis although formal evaluation is complicated by the heterogeneous and multifactorial nature of perennial rhinitic symptoms, in which non-allergic factors are frequently involved. Three recent double-blind placebo-controlled trials of adult patients with perennial allergic rhinitis and sensitivity to *Dermatophagoides pteronyssinus* have all shown efficacy [11–13]. In keeping with previous studies of immunotherapy for perennial rhinitis [14–16] there was a marked placebo response, but a greater degree of improvement in the actively treated group compared with the placebo group. In some studies the differences between the groups became clear cut only after 9 months of treatment. Both symptom scores and nasal provocation responses (assessed by passive anterior rhinomanometry) improved at 9 months and following 15 months treatment. The efficacy of injection immunotherapy for perennial rhinitis due to allergy to domestic pets is more difficult to assess in view of the intermittent and variable allergen exposure. No trials have been reported in which injection immunotherapy was given solely for rhinitis due to domestic pets, although studies in patients with cat-induced asthma have demonstrated subjective improvement and a reduction in bronchial sensitivity to allergen as determined by provocation tests [17,18].

To date, only one study has compared the efficacy of specific injection immunotherapy with pharmacological treatment of allergic rhinitis. The efficacy of an aqueous corticosteroid nasal spray and rescue antihistamines for hay fever was compared with allergen injection treatment with Pollinex-R [19]. This study employed a poorly standardized low potency grass pollen extract: immunotherapy was less effective than topical corticosteroids and associated with a number of systemic reactions. Clearly further studies are required using more modern, standardized extracts. A logical approach may be to 'add on' active or placebo injections in a randomized double-blind fashion to standard treatment with topical corticosteroids and antihistamines, in order to assess whether immunotherapy offers any additional benefit over conventional anti-allergic treatment. Similarly, the long-term efficacy of immunotherapy for perennial or seasonal allergic rhinitis is yet to be determined, although in one uncontrolled study,

efficacy was detectable for up to 6 years after discontinuing pollen immunotherapy for seasonal rhinitis [20].

Proponents of immunotherapy point out that allergen injection immunotherapy represents a specific treatment for allergic disease. Unlike conventional pharmacological treatment, immunotherapy may have the potential for long term 'cure' and, possibly, may prevent progression of rhinitis to asthma. In an earlier 15-year follow-up study of pollen immunotherapy in children with allergic rhinitis, the prevalence of asthma at age 16 years was significantly reduced in patients who had received active treatment as compared with placebo-treated patients [21]. This hypothesis urgently needs testing in a long-term randomized trial employing biologically standardized extracts.

Thus, allergen injection immunotherapy is an effective treatment for seasonal allergic rhinitis and for rhinitis due to house dust mite allergy. Although superior to placebo, what clinicians really want to know is whether immunotherapy compares favourably with the best alternative treatment. At present, immunotherapy is recommended in patients with seasonal allergic rhinitis who fail to respond to conventional pharmacological treatment with topical corticosteroids and antihistamines. Injection immunotherapy for perennial allergic rhinitis due to house dust mite allergy is effective, but further studies are required using standardized vaccines in order to monitor safety and identify optimal injection protocols. The role of immunotherapy for allergic rhinitis due to mould allergy or allergy to domestic pets remains unclear and can only be justified as part of a controlled clinical trial.

Allergic asthma

Over the past 70 years, injection immunotherapy has often been used to treat allergic asthma. As with allergic rhinitis, most published reports have been open or poorly controlled and patient numbers were often very small. Among double-blind, placebo-controlled trials of injection immunotherapy in asthma which included at least eight patients in each treatment group, beneficial results have been found in patients with grass pollen asthma [4,5,22] but benefit in house dust mite asthma is less certain. In general, paediatric studies show superior responses to studies in adults [22–25]. Several studies have shown that injection immunotherapy reduces the early asthmatic response to inhaled allergen in cat-sensitive asthmatic patients [16]. The effect of immunotherapy on non-specific bronchial hyperreactivity is less consistent [16,17] and its efficacy in patients who are continually exposed to their cat is unknown. In contrast, injection immunotherapy for dog dander asthma has not been found effective [17].

Immunotherapy for asthma due to mould allergy has

been addressed in a small number of studies. Injection immunotherapy with a *Cladosporium* extract reduced drug requirements and blunted the immediate asthmatic response to inhaled allergen but there was a high incidence of systemic reactions in the actively treated group [10]. In a small group of patients with *Alternaria* allergy, the active treatment group showed reductions in both nasal and respiratory symptoms compared with the placebo group [26]. However, less than half of the subjects in each group had asthma—the rest had allergic rhinitis without asthma.

The effectiveness of specific injection immunotherapy in asthma has never been compared with conventional management such as allergen avoidance and drug treatment. Without such comparisons it is not possible to assess the risk/benefit ratio of injection immunotherapy. The British Society for Allergy and Clinical Immunology (BSACI) working party on allergen immunotherapy concluded that until such studies are undertaken, specific injection immunotherapy in asthma should continue to be regarded as an experimental form of treatment [27].

There is, at present, no evidence to support claims that this treatment is different from pharmacotherapy in terms of influencing the evolution of disease. Indeed, the only studies that have investigated withdrawal of therapy have revealed rapid recurrence of asthmatic symptoms [24,28]. With the increase in concern about side-effects and the lack of knowledge of the mechanisms of action of injection immunotherapy, there is little justification for its routine use in childhood asthma. Carefully designed trials are required as a matter of urgency to establish whether injection immunotherapy has any effect in modifying the natural history of asthma in childhood.

Other allergic conditions

Wasp and bee sting allergy are relatively rare but can be severe and even fatal, with an average of four deaths in the UK each year [29]. The efficacy of immunotherapy using pure venom extracts has been shown in several good placebo-controlled trials [30–32] and a history of severe bee or wasp venom-induced systemic reactions with respiratory or cardiovascular symptoms is one of the few absolute indications for allergen immunotherapy. The value of treatment is less certain in patients with milder symptoms such as moderate urticaria, angio-oedema, mild asthma, nausea, light-headedness following stings, even if venom-specific IgE is present.

Allergen immunotherapy has also been tried in a variety of other conditions, but has not been found helpful in non-allergic rhinitis or asthma, atopic dermatitis, chronic urticaria, or hypersensitivity to foods or chemicals [33].

Is allergen immunotherapy safe?

Injection immunotherapy can induce a variety of local and systemic side-effects; these may be either immediate (occurring within minutes) or delayed (occurring up to 12 h after injection). Between 1957 and 1986 the Committee on the Safety of Medicines (CSM) received 357 reports of serious systemic adverse reactions to desensitizing agents. Half of these reports were of anaphylaxis and half of bronchoconstriction [3]. Twenty-six of these reports were of fatal adverse reactions, almost all in patients being desensitized for asthma. The CSM was particularly concerned that the rate of fatalities appeared to be increasing and this led to their decision to place tight controls on the administration of immunotherapy injections. A retrospective survey of US-practice found 46 deaths associated with injection immunotherapy in the same time frame [34]. Since many more American patients are treated each year, this led some to suggest that the UK fatality rate might be due to poor management of complications. Subsequent prospective surveys in the US have shown a higher fatality rate with 19 deaths between 1987 and 1991 [35,36]. A BSACI working party recently reviewed adverse reactions to allergen immunotherapy which have occurred since 1986. From this survey, it emerged that all serious adverse reactions to grass pollen and mite extracts occurred within 30 min of injection, while a small proportion of serious side-effects to venom injections occurred up to 45 min after injection. Anaphylactic reactions were rare but most such reactions started within 5 min of injection with all anaphylactic reactions beginning less than 20 min after injection. Adverse reactions commencing after 60 min were not life-threatening and did not require specific intervention [27].

How does allergen immunotherapy work?

The mechanism by which allergen immunotherapy exerts its beneficial effect is still largely unclear. A variety of immunological changes have been described during and after courses of immunotherapy but it remains uncertain which (if any) of these is responsible for relief of symptoms. For many years, allergen immunotherapy was thought to work by inducing the production of allergen-specific IgG antibodies ('blocking antibodies') which could intercept and neutralize allergen before it could bind to cell-surface IgE [13,37–40]. Although allergen-specific IgG is certainly induced, clinical improvement usually precedes the rise in IgG and there is no correlation between the degree of improvement and the titre of 'blocking antibody' [13]. In any event it is difficult to see how allergen-specific IgG could intercept the allergen in disorders where allergen contact occurs at mucosal surfaces and sensitized mast cells

are closer to the allergen than the IgG molecules, which are largely in the plasma and interstitial tissue fluid. In the longer term there is altered regulation of IgE synthesis [13,39] leading to reduced total and allergen-specific IgE as well as attenuation of the usual rise in allergen-specific IgE that occurs in the pollen season. Again the onset of clinical improvement occurs well before changes in the plasma IgE concentrations. More recent work has suggested that immunotherapy alters T-cell cytokine profiles in the cells recruited following allergen exposure [41]. In allergic subjects, intradermal challenge with allergen extracts induces infiltration with activated eosinophils and T-cells expressing TH-2-pattern cytokines (IL-3, IL-4, IL-5 and GM-CSF) [42,43]. Conventional injection immunotherapy given over a 9-month-period reduced both the immediate and late-phase skin responses to allergen as well as improving clinical symptoms. When biopsies were taken from skin sites challenged 24 h previously with allergen, these showed a significant decrease in eosinophil infiltration and a shift in cytokine expression towards a TH-1-like pattern of cytokine expression [41].

Although altered T-cell reactivity is a plausible explanation for the mechanism of desensitization for airborne inhaled allergens, different mechanisms may apply in hymenoptera venom desensitization. In particular, the evidence for protective IgG antibodies is more persuasive [40]. Further support for this theory comes from passive immunization studies in which transfer of hyperimmune IgG fractions protected against anaphylaxis [32,44]. Nevertheless, it is worth noting that in 'rush immunotherapy' schedules [32], patients can be desensitized to venom over 1–5 days, without any associated changes in specific IgG or IgE titres. It has been suggested that rush desensitization may work in a different manner from conventional immunotherapy: rush protocols may cause direct desensitisation of basophils by progressive, partial degranulation with the increasing doses of venom, so that the patients' basophils eventually become unresponsive. This might then allow the high maintenance dose to be given without triggering anaphylaxis. Formal proof of this hypothesis is lacking and there is certainly a higher rate of adverse reactions with this type of desensitization protocol [45].

Homoeopathy and other non-conventional treatments of allergic disease

A significant number of practitioners of alternative (complementary) medicine have an active interest in the diagnosis and treatment of allergy. There are two distinct areas of divergence from mainstream clinical allergy. The first and less controversial area is the use of alternative forms of treatment for patients in whom the diagnosis of allergic

disease is not disputed. The second area, and the one which causes most argument, concerns the definition of allergic disease itself and the tests used to confirm a diagnosis of allergy.

Homoeopathy is a well-established form of alternative medicine and is based on the principle of treating disease by giving minute quantities of substance(s) that cause disease or symptoms of disease. Although this may sound superficially similar to injection immunotherapy, the quantities of allergen given are much smaller, and in some instances the degree of dilution used means that the medication probably does not contain any active material whatsoever. Homoeopathy is widely used as an alternative to conventional treatment for a variety of disorders including allergies. A recent review of published reports cited over 100 separate trials of homoeopathic treatment [46]. Many of these reports were small case series and few were adequately controlled. Three studies of homoeopathy for hay fever were judged to have adequate methodology with double blinding and a placebo arm. In the best designed of these studies, which was double-blind and placebo-controlled, the investigators concluded that a 10^{60} -fold dilution of grass pollen extract was effective in controlling hay fever symptoms [47] although even in this study there were methodological weaknesses [48].

Despite years of use, there is as yet no adequate scientific basis to explain how homeopathy might exert any beneficial effect which is distinct from the placebo-effect observed with virtually all forms of allergy treatment. Indeed, the dilution principle used to manufacture some homoeopathic vaccines should ensure that not one molecule of the original pollen remains in an extract since the dilution factor (up to 10^{60}) vastly exceeds Avogadro's number (6×10^{27}). Claims have been made that agitation of the mixture during dilution (succussion) may impart an 'immunological memory' to the water molecules. In 1988 a report published in *Nature* suggested that human basophils could be triggered by ultra-dilute anti-IgE which was prepared by succussion but not by anti-IgE prepared in an identical dilution series but not succussed [49]. Initial scepticism from the mainstream scientific community has been strengthened by a recent report refuting the observation [50].

Other forms of specific anti-allergy treatment have been performed with varying degrees of success. Two forms of sublingual desensitization have been publicized. High dose sublingual immunotherapy uses much larger amounts of allergen than are used in conventional (injection) immunotherapy [51]. Allergens administered by this route may have some topical action on mucosal surfaces but it seems likely that most of the material will undergo proteolytic degradation in the stomach and intestines. Whether any of this allergenic material actually enters the body in an

antigenically recognizable form is quite unknown. Low-dose sublingual immunotherapy is essentially a variant of homoeopathy. Adherents claim efficacy but few controlled evaluations have been conducted [52]. Again formal comparison with conventional treatments are still required.

Enzyme-potentiated desensitization (EPD) involves co-administration of very small amounts of allergens with the enzyme beta-glucuronidase. The theory is that the enzyme facilitates access to the immune system and thereby achieves greater efficacy than would be possible with the same dose of allergen given alone. EPD is claimed to be effective in allergic rhinitis [53], ulcerative colitis [54] and in childhood hyperactivity [55]. These reports lack sufficient detail for objective evaluation and formal comparisons with conventional forms of therapy will be needed before the relative efficacy and value of EPD can be determined [57].

Provocation-neutralization therapy is an extension of the provocation-neutralization diagnostic technique used by clinical ecologists (practitioners of environmental medicine) [58]. In this technique, progressively higher doses of a test substance are administered intradermally or sublingually until the subject shows a response. This dose is then termed the 'provocation dose'. The dose of test substance is then adjusted (up or down) until the response disappears. This dose is the 'neutralization dose' and is then used for treatment. Although some practitioners test and treat for specific allergy, to recognized allergens, others use a combination of phenol, ethanol and formaldehyde to test and treat for 'sensitivity' to unrelated chemicals, the controversial 'multiple chemical hypersensitivity syndrome'. By conventional diagnostic criteria, these patients do not have allergy, in that conventional tests for specific IgE are negative. However, the alternative allergist often employs additional diagnostic methods to determine whether the patient's symptoms are attributable to commensal or environmental agents. These include provocation-neutralization testing, leucocytotoxic tests, lymphocyte subset counts, hair analysis, applied kinesiology, Vega (black box) testing or auriculo-cardiac reflexology [58].

If positive, the patients may be told that they are 'allergic' to one or more agents (usually multiple agents are implicated). Sometimes a more general label of 'environmental illness' is applied. Once diagnosed as allergic, management commonly takes the form of allergen avoidance through restriction diets, physical isolation etc. Desensitization may be performed by a variety of techniques among which the provocation-neutralization technique is perhaps the most widely used. In the absence of an agreed definition of illness or any objective criteria to assess improvement, it is impossible to judge whether the treatment is effective or not. A 1989 review of the published

literature on provocation-neutralization by the American College of Physicians found no evidence of efficacy [57] and formal evaluation by non-ecologists did not provide any evidence that the technique was superior to placebo [59].

Future developments

Recent advances in our understanding of the mechanisms of allergic inflammation and immunological tolerance have suggested a number of alternative approaches to allergen immunotherapy. Over the past 6 years commercial efforts have centred on devising better means of quality control and standardization [60] with the aim of providing the practising allergist with vaccines of known and predictable properties. With the increasing recognition of the importance of T-cells in allergy and inflammation [61], two new lines of investigation have opened up: the first of these explores the dependence of IgE production upon the elaboration of a number of chemical messengers (cytokines) which variously promote or inhibit production of IgE antibodies [62]. The second approach is to study the sites on allergen molecules (epitopes) which are recognized by T-cells but do not bind IgE [63]. Having found suitable epitopes, the aim is to prepare peptide vaccines which will switch off allergen-specific T-cells but which will not cause histamine release or anaphylaxis, since they will not be recognized by IgE bound to mast cells or basophils [64]. Through these approaches it is likely that improved and safer forms of allergen immunotherapy will be developed in the next decade.

Conclusions

Noon and Freeman's original idea was to induce immunity against the harmful components of pollen [1,2]. Although conceptually incorrect, their clinical discovery sparked a major medical industry which, in the spirit of the times, relied on clinical observation for evidence of efficacy. Modern medicine demands more formal evaluation and it is comforting to find in clinical trials that injection immunotherapy does have measurable clinical effects, in addition to clearly demonstrable placebo effects. Some evidence of efficacy has been also adduced for non-conventional 'alternative' forms of allergy treatment. For both conventional and alternative therapies, further comparisons with best non-desensitizing medical management are still required.

Understanding how immunotherapy works remains something of an enigma. Early theories about blocking antibodies have not withstood scientific scrutiny and current views favour a direct effect on allergen-reactive T-lymphocyte subsets. Future developments in immunotherapy are likely to hinge on a better understanding of the

mechanisms of immunological tolerance and suppression, while current commercial efforts are directed to providing purer, better standardized allergen extracts which offer more accurate dosage while minimizing the potential for side-effects. With this convergence of science and clinical practice, we can safely conclude that conventional allergen immunotherapy does indeed have a good scientific basis.

References

- Noon L. Prophylactic vaccination against hay fever. *Lancet* 1911; 1:1572.
- Freeman J. Vaccination against hay fever: report of results during the first three years. *Lancet* 1914; 1:1178.
- Committee on the Safety of Medicines. CSM update: Desensitizing vaccines. *Br Med J* 1986; 293:948.
- Bousquet J, Maasch HJ, Hejjaoui A et al. Double-blind placebo-controlled immunotherapy with mixed grass pollen allergoids. III. Efficacy and safety of unfractionated and high molecular weight preparations in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol* 1989; 84:546-56.
- Bousquet J, Hejjaoui A, Soussana M, Michel FB. Double-blind placebo-controlled immunotherapy with mixed grass pollen allergoids. IV. Comparison of the safety of two dosages of a high molecular weight allergoid. *J Allergy Clin Immunol* 1990; 85:490-7.
- Varney VA, Gaga M, Frew AJ et al. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by anti-allergic drugs. *Br Med J* 1991; 302:265-9.
- Reid MJ, Moss RB, Yao-Pi Hsa et al. Seasonal asthma in northern California. Allergic causes and efficacy of immunotherapy. *J Allergy Clin Immunol* 1986; 78:590-600. Also cited as 1013.
- Viander M, Koivikko A. The seasonal symptoms of hyposensitized and untreated hayfever patients in relation to birch pollen counts: correlations with nasal sensitivity, prick tests and RAST. *Clin Allergy* 1978; 8:387-96.
- Lichtenstein LM, Norman PS, Winkenwerder WL. A single year of immunotherapy for ragweed hayfever: immunologic and clinical studies. *Ann Intern Med* 1971; 75:663-71.
- Dreborg S, Agrell B, Foucard T et al. A double-blind, multicenter immunotherapy trial in children using a purified and standardized *Cladosporium herbarum* preparation. I. Clinical results. *Allergy* 1986; 41:131-40.
- Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. *Clin Allergy* 1988; 18:501-8.
- Corrado OJ, Pastorello E, Ollier S et al. A double-blind study of hyposensitization with an alginate conjugated extract of *D. pteronyssinus* 'Conjuvac' in patients with perennial rhinitis. *Allergy* 1989; 44:108-15.
- McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of *D. pteronyssinus* in allergic rhinitis comparing clinical outcome with changes in antigen-specific IgE, IgG and IgG subclasses. *J Allergy Clin Immunol* 1990; 86:521-32.
- D'Souza MF, Pepys J, Wells ID et al. Hyposensitization with *Dermatophagoides pteronyssinus* in house dust allergy. A controlled study of clinical and immunological effects. *Clin Allergy* 1973; 3:177-93.
- Blainey AD, Phillips MJ, Ollier S, Davies RJ. Hyposensitization with a tyrosine adsorbed extract of *Dermatophagoides pteronyssinus* in adults with perennial rhinitis. *Allergy* 1984; 39:521-8.
- Bousquet J, Calvayrac P, Guérin B et al. Immunotherapy with standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of immunotherapy. *J Allergy Clin Immunol* 1985; 76:734-44.
- Ohman JL, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. *J Allergy Clin Immunol* 1984; 74:230-9.
- Hedlin G, Graff-Lonnevig V, Heilborn H et al. Immunotherapy with cat and dog dander extracts. II. In vivo and in vitro immunological effects observed in a 1 year double blind placebo study. *J Allergy Clin Immunol* 1986; 77:488-96.
- Juniper EF, Kline PA, Ramsdale EH, Hargreave FE. Comparison of the efficacy and side effects of aqueous steroid nasal spray (budesonide) and allergen-injection immunotherapy (Pollinex-R) in the treatment of seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1990; 85:606-11.
- Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988; 43:523-9.
- Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children. A 14 year study. *Pediatrics* 1968; 42:793.
- Bousquet J, Calvayrac P, Guérin B et al. Immunotherapy with standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of immunotherapy. *J Allergy Clin Immunol* 1985; 76:734-44.
- Warner JO, Price JF, Soothill JF, Hey EN. Controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with asthma. *Lancet* 1978; 2:912-15.
- Price JF, Warner JO, Hey EN, Tuner MW, Soothill JF. A controlled trial of hyposensitization with tyrosine-adsorbed *Dermatophagoides pteronyssinus* antigen in childhood asthma. In vivo aspects. *Clin Allergy* 1984; 14:209-19.
- van Bever HP, Stevens WJ. Effect of hyposensitization upon immediate and late asthmatic reaction and upon histamine reactivity in patients allergic to house dust mite (*D. pteronyssinus*). *Eur Respir J* 1992; 5:318-22.
- Horst M, Hejjaoui A, Horst V, Michel F-B, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. *J Allergy Clin Immunol* 1990; 85:460-72.
- BSACI Working Party on Allergen Immunotherapy. Position paper. *Clin Exp Allergy* 1993; 23(S3):1-44.
- Bousquet J, Hejjaoui A, Michel FB. Specific immunotherapy in asthma. *J Allergy Clin Immunol* 1990; 86:292-305.
- Ewan PW. Allergy to insect stings: a review. *J Roy Soc Med* 1985; 78:234-9.

- 30 Müller U, Thurnheer U, Patrizzi R, Spiess RHR. Immunotherapy in bee sting hypersensitivity. Bee venom versus whole body extract. *Allergy* 1979; 34:369-78.
- 31 Gillman SA, Cummins LH, Kozak PP, Hoffman DR. Venom immunotherapy: comparison of 'rush' vs 'conventional' schedules. *Ann Allergy* 1980; 45:351-4.
- 32 Bousquet J, Fontez A, Aznar R, Robinet-Levy M, Michel FB. Combination of passive and active immunisation in honey bee venom immunotherapy. *J Allergy Clin Immunol* 1987; 79:947-54.
- 33 Malling HJ, Weeke B. Revised EAACI position paper on Immunotherapy. *Allergy* 1993; 48:S14.
- 34 Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. *J Allergy Clin Immunol* 1987; 79:660-7.
- 35 Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TAE. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 1993; 92:6-15.
- 36 Reid MJ, Lockey RF, Turkeltaub P, Platts-Mills TAE, Lehrer SB. Fatalities from Immunotherapy 1990-91. *J Allergy Clin Immunol* 1992; 89:Abst 823.
- 37 Sadan N, Rhyne MB, Mellits ED et al. Immunotherapy for pollinosis in children. Investigation of the immunologic basis of clinical improvement. *N Engl J Med* 1969; 280:623-7.
- 38 Sobotka AK, Valentine MD, Ishizaka K, Lichtenstein LM. Measurement of IgG blocking antibodies: development and application of a radioimmunoassay. *J Immunol* 1976; 117:84-90.
- 39 Zeiss CR, Metzger WJ, Levitz D. Quantitative relationship between IgE antibody and blocking antibodies specific for antigen E in patients given immunotherapy with ragweed antigen E. *Clin Exp Immunol* 1977; 28:250-5.
- 40 Golden DBK, Meyers DA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical relevance of the venom-specific IgG antibody level during immunotherapy. *J Allergy Clin Immunol* 1982; 69:489-93.
- 41 Varney VA, Hamid QA, Gaga M et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. *J Clin Invest* 1993; 87:623.
- 42 Frew AJ, Kay AB. The relationship between infiltrating CD4+ lymphocytes, activated eosinophils and the magnitude of the allergen-induced late phase cutaneous reaction in man. *J Immunol* 1988; 141:4158-64.
- 43 Kay AB, Ying S, Varney V et al. Messenger RNA expression of the cytokine gene cluster, IL-3, IL-4, IL-5 and GM-CSF in allergen-induced late-phase cutaneous reactions in atopic subjects. *J Exp Med* 1991; 173:775-8.
- 44 Lessof MH, Kagey-Sobotka A, Lichtenstein LM. Effects of passive antibody in bee venom anaphylaxis. *J Hopk Med J* 1978; 142:1-7.
- 45 Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol* 1990; 85:473-9.
- 46 Kleijnen, J. Knipschild P, ter Riet G. Clinical trials of homeopathy. *Br Med J* 1991; 302:316-23.
- 47 Reilly DT, Taylor MA, McSharry C, Aitchison T. Is homeopathy a placebo response? Controlled trial of homeopathic potency with pollen in hayfever as model. *Lancet* 1986; ii:881-6.
- 48 Frew AJ, Corrigan CJ, Kay AB. Homeopathy and hay fever. *Clin Exp Allergy* 1991; 21:751-2.
- 49 Davenas E, Beauvais F, Amara J et al. Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature* 1988; 333:816-8.
- 50 Hirst SJ, Hayes NA, Burrridge J, Pearce FL, Foreman JC. Human basophil degranulation is not triggered by very dilute antiserum against human IgE. *Nature* 1993; 366:525-7.
- 51 Taudorf E, Laursen LC, Lanner A et al. Oral immunotherapy in birch pollen hay fever. *J Allergy Clin Immunol* 1987; 80:153-61.
- 52 Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy* 1986; 67:263-71.
- 53 Fell P, Brostoff J. A single dose desensitisation for summer hay fever. *Eur J Clin Pharmacol* 1990; 38:77-9.
- 54 McEwen, LM. A double-blind controlled trial of enzyme-potentiated desensitisation for the treatment of ulcerative colitis. *Clin Ecology* 1987; 5:47-51.
- 55 Egger J, Stolla, A, McEwen LM. Controlled trial of hyposensitisation in children with food-induced hyperkinetic syndrome. *Lancet* 1992; 339:1150-3.
- 56 Kay AB, Frew AJ, Warner JO, Lessof MH. Hyposensitisation for food-induced hyperkinetic syndrome. *Lancet* 1993; 341:114-15.
- 57 American College of Physicians. Position paper: clinical ecology. *Ann Intern Med* 1989; 111:168-78.
- 58 Royal College of Physicians. Allergy: Conventional and alternative concepts. RCP London 1992. Also published in *Clin Exp Allergy* 1992; 22(S3):1-44.
- 59 Jewett DL, Fein G, Greenberg MH. A double blind study of symptom provocation to determine food sensitivity. *N Engl J Med* 1990; 323:429-33.
- 60 Dreborg S, Frew AJ. Revised EAACI Position paper on Allergen Standardization and Skin Tests. *Allergy* 1993; 48(S14):49-82.
- 61 Corrigan CJ, Kay AB. T cells and eosinophils in the pathogenesis of asthma. *Immunology Today* 1992; 13:501-7.
- 62 Purkerson J, Isakson P. A two signal model for regulation of immunoglobulin isotype switching. *FASEB J* 1992; 6:3245-52.
- 63 O'Hehir RE, Young DB, Kay AB, Lamb JR. Cloned human T lymphocytes reactive with *Dermatophagoides farinae* (house dust mite): a comparison of T- and B-cell antigen recognition. *Immunology* 1987; 62:635-40.
- 64 O'Hehir RE, Busch R, Rothbard JB, Lamb JR. An in vitro model of peptide-mediated immunomodulation of the human T-cell response to *Dermatophagoides* spp. (house dust mite). *J Allergy Clin Immunol* 1991; 87:1120-7.

Copyright of Clinical & Experimental Allergy is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.