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Position Paper on
Allergen Immunotherapy

Report of a BSACI Working Party
January-October 1992

Foreword

Over the last three years, the British Society for Allergy and Clinical Immunology has redoubled its activities in areas of special interest. One area that has engendered considerable controversy in the U.K. and elsewhere over the last few years is the position of allergen immunotherapy, particularly with respect to the risk/benefit ratio. The dramatic events of 1986 when the Committee on Safety of Medicines intervened in the practice of allergen immunotherapy in the U.K., highlighted a need for greater control over this form of treatment. The following seven years have been a rather bleak period for allergen immunotherapy in the U.K., largely due to the small number of hospital-based allergy clinics that are able to provide it under the required stipulation of adequate resuscitation facilities being available and the two-hour waiting period following each treatment, as safeguards against delayed reactions.

Improvements in allergen standardization, and the application of modern tools of molecular biology, cell biology and immunology have not only improved our understanding of the mechanisms of immunotherapy, but have increased the requirement of highly purified and standardized extracts. Moreover, a number of clinical trials conducted over the last three years have pointed to the high efficacy of this form of treatment in certain allergic diseases and have also identified special risk groups such as asthma where immunotherapy is usually contraindicated. Because of these changes and because of our wish to continue to promote good clinical practice within the field of allergy and clinical immunology, we established a Working Party under the able chairmanship of Professor A. B. Kay and secretaryship of Dr A. J. Frew. The Working Party comprised a number of experts in the field of allergy and clinical immunology from the U.K. and consulted widely international experts in this field. In addition, the contributions made by Professor Carol Seymour in the Department of Clinical Biochemistry & Metabolism at St George's Hospital Medical School, London, have proved invaluable in bringing an internal medicine perspective to the document. The resulting deliberations, representing an enormous amount of effort by the Working Party, are presented in this publication.

I hope that this carefully considered document will further provide the basis for improved clinical practice within the field of allergy and clinical immunology, particularly taking into account the conclusions and topics for future study listed at the end of the report. I would like to add my personal thanks to all those who have committed so much time and effort into creating this report, which I believe justly reflects the level of excellence that our Society has achieved over the last few years.

STEPHEN T. HOLGATE

President,

British Society for Allergy & Clinical Immunology

BSACI Position Paper on Allergen Immunotherapy

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Introduction

The use of specific allergen-injection immunotherapy (AII) to treat allergic disorders dates back to the early decades of this century, when Noon and others at St Mary's Hospital, London, pioneered the use of pollen extracts to treat hay fever [Noon 1911; Freeman 1914]. AII was enthusiastically adopted in North America, where it became the treatment of choice for allergic rhinitis and asthma. In the U.K., AII never became as popular, and clinical allergy has largely remained a side-interest of general practitioners and respiratory specialists, in contrast to the U.S.A. and Canada where allergy is a mainstream clinical speciality with its own training programmes and a clearly defined place in patients' minds.

Between 1950 and 1986, allergy injections were widely used in the U.K., especially by general practitioners treating allergic rhinitis. In the U.K., there has been general agreement about the efficacy of AII in seasonal allergic rhinitis but doubt remains about the relative value of AII in asthma or in perennial allergic rhinitis. The fact that AII has not been widely used to treat asthma in the U.K. may perhaps be due to the fact that newer anti-asthma drugs such as salbutamol and beclomethasone became available here 15 years before their appearance on the U.S. market.

In 1986, the Committee on the Safety of Medicines issued a report on fatalities and adverse reactions associated with AII, which appeared to be increasing in frequency and especially dangerous in asthmatic patients. Subsequently the CSM placed stringent restrictions on the practice of AII, and effectively curtailed the administration of AII in general practice [CSM 1986]. In the absence of a system of hospital-based allergy clinics, AII in the U.K. was effectively abolished overnight. Elsewhere in Europe and in North America, allergists noted the CSM report but have continued their practice much as before.

Since 1986, interested groups in the U.K. and elsewhere have sought to ascertain the true risk/benefit ratios of AII and to define more clearly the categories of patients for whom this form of treatment is appropriate. In October 1991, the President of the British Society for Allergy and Clinical Immunology invited Professor A. B. Kay to convene a Working Party to discuss these issues and to prepare a position paper reflecting current expert opinion. A group of experts including allergists, immunologists, clinical pharmacologists, respiratory physicians, general physicians and paediatricians participated in this project and this document is the fruit of their labours.

Where necessary in preparing the report, we have consulted with experts in Europe and North America, but the opinions and viewpoints expressed here are those of the Working Party and are intended to reflect U.K. experience and clinical practice.

AII has been used in a wide variety of allergic conditions but has found its principal use in allergic rhino-conjunctivitis, asthma and hymenoptera-induced anaphylaxis. AII has not been found useful in atopic dermatitis, urticaria and food intolerance and these conditions are not discussed further in the document. The first four chapters of the position paper consider the evidence for efficacy and safety of AII in the treatment of rhinitis, asthma, venom hypersensitivity and drug hypersensitivity. For each condition, the place of immunotherapy in management is reviewed and the specific indications for immunotherapy are outlined. Evaluation of the indications for immunotherapy involves a careful appraisal of both the evidence for efficacy of this form of treatment and the risks of occasional, potentially life-threatening systemic reactions. In subsequent chapters, we review the mechanisms by which immunotherapy may be acting, the current position regarding standardization of allergen extracts, and methods of administering AII. The final chapter addresses adverse reactions to AII and collates all information obtained since 1986 in an attempt to determine the true profile of side-effects and risks associated with AII, and to consider how these complications may best be avoided.

In presenting this report, the Working Party's primary goal has been to optimize the management of patients with severe forms of allergic disease. We have summarized all the available information published since 1986 regarding the efficacy of AII and the pattern of adverse reactions to AII, using strict criteria for acceptability of information. Using these data, we have set out proposals for the selection of patients receiving AII and for the prevention and minimization of side-effects. We conclude that AII does have a place in selected patient groups and that the risk of adverse reactions can be contained by patient selection and the adoption of 'good clinical practices'.

Recent advances in our understanding of the mechanisms of allergic inflammation and immunological tolerance have suggested that a number of alternative approaches to AII may be developed in the medium term. Several of these are in the early stages of development and, although it is too early to make formal judgements, we believe it is likely that improved and possibly safer

forms of specific allergen immunotherapy will be developed in the next decade.

Finally, the members of the Working Party earnestly hope that this report will stimulate research in the field. For example, it is clear that our knowledge of factors contributing to adverse reactions is incomplete. Similarly, the *relative* value of AII in asthma is unknown. AII appears to have some beneficial effect, but has not been formally compared with the best available medical alternatives. Some proponents of AII have claimed that

treating rhinitis by AII may prevent the development of asthma in later life, but again this has never been formally tested. Overall, we believe that the use of AII should be based on properly conducted clinical trials and evaluation. Such trials take time, money and dedication: for the present, we hope that this position paper will stimulate discussion and we would invite comments from any interested parties.

April 1993

CHAPTER 1

Allergen immunotherapy for seasonal and perennial allergic rhinitis

Background

Allergic rhinitis, although frequently trivialized, represents a common and important cause of morbidity. In the U.K., over the past 20 years there has been a four-fold increase in general practitioner consultations for allergic rhinitis. Although this increase may in part be explained by changes in diagnostic fashion and a greater awareness of the condition, the figures represent an undeniable increase in true prevalence [Burr *et al.* 1989; Ninan & Russell 1992].

The mainstay of treatment is allergen avoidance, where possible, and the use of topical and oral anti-allergic drugs. A major advance in recent years has been the use of intranasal corticosteroids with a high topical potency and, at least in conventional doses, a very low potential for systemic side-effects. A further advance has been the introduction of specific histamine H_1 -receptor antagonists with no anti-cholinergic side-effects and a low sedative profile. These measures provide very effective symptom control for the majority of patients. However, there remains a small group of subjects who, despite regular use of the above medication, continue to have troublesome symptoms. It is in this group that AIT retains a place in treatment.

Diagnosis

The diagnosis is based on a careful clinical history supported by documentation of IgE-mediated sensitivity by skin-prick testing. A nasal examination is required to exclude polyps, septal deflection or other structural lesions. Only rarely are target-organ provocation tests required. Although not routinely indicated for specific diagnosis, elevated serum allergen-specific IgE concentrations provide additional supportive evidence prior to consideration of AIT.

Efficacy of allergen immunotherapy

Allergen-injection immunotherapy was initiated in the U.K. over 80 years ago and is still widely practised in Europe, the U.S.A. and elsewhere. The efficacy of AIT in seasonal allergic rhinitis has been confirmed in a number of carefully controlled clinical studies. This is true for grass pollen [Frankland & Augustin 1954; Kerr *et al.* 1963; Varney *et al.* 1991], ragweed pollen [Lichtenstein *et al.* 1971] and birch pollen [Viander & Koivikko 1978].

Selected examples of trials of AIT are shown in Table 1. This table includes only double-blind placebo-controlled studies which evaluated symptoms and medications, or the change in response to provocation tests.

1. Grass pollen: There have been several recent double-blind placebo-controlled trials of partially purified, standardized depot grass pollen extracts in patients with summer hay fever [Bousquet *et al.* 1989, 1990a; Varney *et al.* 1991; Reid *et al.* 1986]. In the study by Varney *et al.*, 40 adult patients with severe seasonal symptoms uncontrolled by conventional anti-allergic treatment (which included topical corticosteroids, disodium cromoglycate and antihistamines) were randomized to receive either a depot grass pollen extract (*Phleum pratense*, Alutard SQ, ALK, Denmark) or matched placebo injections. There was a highly significant decrease in overall total symptoms and a highly significant reduction 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. Efficacy was also confirmed by a reduction in visual analogue symptom scores and in post-seasonal assessments by both the patients and their doctors. In summary, in the face of high seasonal pollen exposure, AIT was effective in reducing both symptoms and requirements for drugs in selected patients with severe symptoms. Clinical improvement was accompanied by a decrease target organ (conjunctival and nasal) and skin sensitivity. Two recent careful studies from France, using a standardized high molecular weight formaldehyde-treated mixed grass pollens extract, similarly demonstrated a marked clinical improvement with reduction in nasal and cutaneous allergen sensitivity in the actively treated group [Bousquet *et al.* 1989, 1990a].

2. Mould allergen: The use of AIT for seasonal mould-induced rhinitis is currently *not* recommended, owing to the lack of commercially available biologically standardized extracts. However, one study which employed a high-quality extract (not commercially available) was effective in children [Dreborg *et al.* 1986]. Thus, at present, mould AIT should only be performed in controlled trials.

3. Perennial allergic rhinitis—house dust mite: Although drug treatment for perennial rhinitis is frequently effective, the use of multiple topical preparations combined with oral preparations throughout the year is inconvenient and patient compliance is often poor. Furthermore, nasal sprays may be ineffective in the presence of marked

Table 1. Selected double-blind placebo-controlled trials of immunotherapy for allergic rhinitis

	Age range (years)	Allergen extract	No in active group	No in placebo group	Response to treatment		
					Symptoms medication scores	Nasal conjunctival tests	Skin test
Grass							
Reid 1986	20-29	Rye grass	9	9	A = 28.1, P = 48.9		
Bousquet 1989	12-46	Formaldehyde allergoid	13	14	Symptoms: Rhinitis A = 20.4, P = 63.5** Conjunctivitis A = 13.3, P = 44.9 Medication: Rhinitis A = 30.5, P = 53.7 Conjunctivitis A = 5.7, P = 40.1**		Reduced**
Bousquet 1990	11-43	Formaldehyde allergoid	A ₁ = 19, A ₂ = 20, P = 18		Symptoms: Rhinitis A ₁ = 57.8***, A ₂ = 63.6***, P = 108.6 Medication: A ₁ = 38.6, A ₂ = 35.3*, P = 44.5	Early response reduced**	Early response reduced**
Varney 1991	19-52	Timothy grass alum-adsorbed depot	A = 21, P = 19		Symptoms: A = 360, P = 928*** Medication: A = 129, P = 627** Visual analogue score: A = 2.2, P = 5.5**	Early response reduced (nasal*** and conjunctival**)	Reduced (early and late phase*** response)
Ragweed							
Lichtenstein 1971	Not given	Ragweed antigens E & K	88 randomized (5 groups)		Reduced**	Early response reduced*	
Brunet 1992	19-56	Ragweed alum precipitated	13	14	Symptoms: A = 4.7, P = 7.5* Medication: A = 0.9, P = 0.7	Early response reduced*	
House dust mite							
Ewan 1988	16-55	<i>D. pteronyssinus</i> aqueous	38 randomized		Visual analogue score: reduced**	Early response reduced*	Early response reduced**
Corrado 1989	17-55	<i>D. pteronyssinus</i> alginate conjugated	66 randomized		Visual analogue score: reduced** (blocking only)	Early response reduced***	
McHugh 1990	17-52	<i>D. pteronyssinus</i> aqueous extract	30	30	Symptoms: A = 16, P = 22.4* Medication: A = 0.19, P = 0.96* Visual analogue score: A = 28.5, P = 38.0*	A = 35.5, P = 52.6*	A = 33.6, P = 46.2*

* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$.A = Active (A₁ = high dose, A₂ = low dose); P = placebo.

nasal obstruction which is a characteristic feature of perennial allergic rhinitis. Up to 30% of patients with perennial allergic rhinitis are uncontrolled by topical corticosteroid therapy [Cockcroft *et al.* 1980]. For these reasons AII may retain a place in treatment for perennial allergic rhinitis due to house dust mite or animals, although it has been less well studied in this regard. Formal evaluation is complicated by the heterogeneous and multifactorial nature of perennial rhinitic symptoms, in which non-allergic factors are frequently involved. In this situation criteria for patient selection assume even greater importance. However, three recent double-blind placebo-controlled trials of adult patients with perennial allergic rhinitis and sensitivity to *Dermatophagoides pteronyssinus* have shown efficacy [Ewan *et al.* 1988a; Corrado *et al.* 1989; McHugh *et al.* 1990]. These studies employed partially purified biologically standardized extracts. One of these studies involved 38 adults and used an aqueous extract: the actively treated group demonstrated a marked reduction in nasal symptoms assessed by visual analogue score and a reduction in nasal and cutaneous immediate allergen sensitivity after three months of treatment. A large number of systemic reactions requiring adrenaline occurred during the induction phase. In retrospect, this rate of adverse reactions is attributable to use of an aqueous extract and an aggressive induction protocol prescribing incremental doses up to the maximal tolerated dose [Ewan *et al.* 1988a]. A more recent study by the same group involving 60 adults with rhinitis has confirmed these findings with reductions in symptoms, medication usage, skin test size and nasal allergen sensitivity. In another double-blind study a standardized extract of *Dermatophagoides pteronyssinus* conjugated to alginate was tested in 66 adults with perennial rhinitis [Corrado *et al.* 1989]. In keeping with previous studies of perennial rhinitis [Blainey *et al.* 1984; D'Souza *et al.* 1973] there was a marked placebo response with improvement in symptoms in both actively treated and placebo-treated patients. Visual analogue score assessments demonstrated a decrease in nasal symptoms of blockage, rhinorrhoea and sneezing in the actively treated group compared with the placebo group, although the differences between the groups were evident only after nine months of treatment and achieved statistical significance only for nasal blockage. There was a significant reduction in nasal symptom diary scores and a non-significant reduction in medication usage in the actively treated group. Nasal provocation testing (assessed by passive anterior rhinomanometry) demonstrated significant reductions in nasal allergen sensitivity at nine months and following fifteen months of treatment. No immediate systemic reactions or anaphylaxis were observed, but delayed reactions (urticaria or worsening of

asthma and rhinitis) were reported in 3% of patients. Thus, both symptomatic benefit and a significant improvement in the nasal response to allergen were demonstrated following hyposensitization with Conjuvac. There were minimal side-effects although superiority over placebo was only apparent after one year of therapy.

4. Domestic pets: The efficacy of AII for perennial rhinitis due to allergy to domestic pets is more difficult to assess in view of the intermittent and variable allergen exposure. There are no reported AII trials performed solely for rhinitis due to domestic pets, although several carefully controlled studies in patients with cat-induced asthma have demonstrated a subjective improvement and a reduction in bronchial sensitivity to allergen as determined by provocation tests [Ohman *et al.* 1984; Sundin *et al.* 1986].

AII versus pharmacological therapy

Only one study has compared the efficacy of specific AII 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 [Juniper *et al.* 1990]. In this study, which employed a poorly standardized low-potency extract, AII was less effective than topical corticosteroids and associated with a number of systemic reactions. Clearly further studies are required. A more logical approach may be to 'add on' AII (active or placebo injections in a randomized double-blind fashion) to treatment with topical corticosteroids and antihistamines in order to assess whether AII offers *additional* benefit to conventional anti-allergic treatment.

The long-term efficacy of AII for perennial or seasonal allergic rhinitis is yet to be determined. In one uncontrolled study, efficacy was detectable up to six years after discontinuing AII for seasonal rhinitis [Mosbech & Osterballe 1988].

It must also be acknowledged that allergen-injection immunotherapy represents a specific treatment for allergic disease and, unlike conventional pharmacological treatment, may have the potential for long-term 'cure' and, possibly, the prevention of progression of rhinitis to asthma. In an earlier 15-year follow-up study of AII in children with allergic rhinitis, there was a significantly reduced prevalence of asthma at the age of 16 years in patients who had received active AII as compared with placebo-treated patients [Johnstone *et al.* 1968]. This hypothesis urgently needs testing in a long-term trial employing biologically standardized extracts.

Safety of AII

In the past the use of AII has been criticized on grounds of safety. The use of AII undoubtedly implies a risk of

eliciting severe side-effects and, on occasions, fatalities [Lockey *et al.* 1987]. Following the Committee on Safety of Medicines Report [CSM 1986] the practice of AII in the U.K. has largely ceased outside a few specialist centres. The risk/benefit ratio must be carefully considered in each patient before embarking on AII. Patients with coexistent chronic asthma appear to be at especially high risk of adverse reactions and should be excluded from AII for rhinitis. Safety issues are discussed in detail in Chapters 6, 7 and 8.

Special considerations for AII in children

Review of the literature suggests that AII has a greater beneficial effect in children than in adults. This is most dramatically illustrated in relation to house dust mite AII for patients with asthma [Warner 1981]. The European Academy of Allergology and Clinical Immunology has suggested that it is inappropriate to use AII in children below 5 years of age [Malling 1988]. Such an age cut-off is not justified by any scientific studies, but this is a commonly held view amongst allergists using AII. It is fair to state that children show a greater tendency to spontaneous improvement in allergic disease, although it remains possible that the rate of improvement may be hastened by AII.

The overwhelming majority of trials of AII in childhood have investigated effects on asthma rather than allergic rhino-conjunctivitis. This is mainly because allergic rhino-conjunctivitis tends to be less prominent in childhood than in young adults. In a study of house mite AII for childhood asthma, a significant effect on coexistent rhinitic symptoms was noted [Warner *et al.* 1978]. However, a two-year trial of pollen AII in children failed to find any effect on either seasonal asthma or rhinitis [Hill *et al.* 1982].

The majority of successful trials of AII in childhood have employed house dust mite extracts. The results with pollen allergens have been more variable, with some showing dramatically favourable results [Sadan *et al.* 1969] and some being totally negative [Fontana *et al.* 1966]. There is one published controlled trial of *Cladosporium* therapy in childhood asthma and rhino-conjunctivitis suggesting a favourable effect using a purified standardized extract [Dreborg *et al.* 1986]. However, concerns have been expressed about possible adverse effects of mould AII in childhood; it has been suggested that this form of therapy may induce the production of immune complexes and hence lead to development of immune complex disease [Kad & Ostergaard 1982].

Table 2. Indications and contraindications for AII use in allergic rhinitis

Indications

1. Evidence of IgE-mediated disease in which allergens are considered to be the major triggers
2. Inability to avoid allergen
3. Inadequacy of drug therapy or intolerable side-effects of such treatment
4. Limited spectrum of allergen sensitivities (in general one, or at most two, allergens)
5. Compliance

Contraindications

1. Non-availability of suitable allergen extracts
2. Significant medical or immunological disease
3. Multiple allergies
4. Concurrent treatment with drugs likely to impair possible treatment for anaphylaxis (beta-blockers or other adrenergic blocking drugs)

Adapted from WHO IUIS Report (Thompson *et al.* 1989).

Conclusions and indications for AII in allergic rhinitis

The indications for use of allergen-specific immunotherapy for the treatment of allergic rhinitis and perennial rhinitis are shown in Table 2. The benefits, side-effects, cost and duration of symptomatic treatment must be balanced against those of AII. Thus allergen-injection immunotherapy is an effective treatment for seasonal allergic rhinitis and for rhinitis due to house dust mite allergy.

At present, AII is recommended in patients with seasonal allergic rhinitis who fail to respond to conventional pharmacological treatment with topical corticosteroids and antihistamines. Pollen AII should be commenced well before the pollen season and careful adjustments are required at the start of pollination (discussed further in Chapter 7). Although AII for perennial allergic rhinitis due to house dust mite allergy is effective, further studies using standardized vaccines should be performed in order to monitor safety and identify appropriate AII protocols. AII for allergic rhinitis due to mould allergy or allergy to domestic pets should at present only be performed as part of controlled clinical trials. Treatment of multiple allergies with mixed vaccines is rarely justified because of the lower likelihood of success and the potential for degradation of the mixed extract in storage. In view of the greater potential for adverse side-effects, patients with coexistent chronic perennial asthma should be specifically excluded.

CHAPTER 2

Indications and efficacy of allergen immunotherapy in asthma

Background

Asthma is the commonest chronic disease of young adults and children, and its prevalence appears to be rising in many Western countries, including the U.K. [Burney *et al.* 1990]. The morbidity from asthma is considerable. The presence of asthma may easily be missed by patients and parents; in those patients who are diagnosed asthmatic, treatment is frequently inadequate, often due to insufficient use of prophylactic therapy. Hospital admission rates for asthma, particularly in children, have increased over the last 30 years. Many adult asthmatic patients lose time from work due to asthma. From the mid 1970s there has been a steady increase in the asthma mortality rate [Burney 1986; Anderson *et al.* 1991]. About 2000 patients now die from asthma each year in the U.K., and the majority of these deaths occur in adults. Several studies have identified significant deficiencies in the management of the majority of patients who have died from asthma [British Thoracic Society 1982].

In the light of these findings there would appear to be considerable scope for improving asthma care. In response to these problems, detailed guidelines for the management of chronic and acute asthma in adults have been published recently [British Thoracic Society 1990a, b; International Paediatric Consensus Group 1992; NIH International Consensus Report 1992]. The role of AII in asthma management is, however, controversial. AII is not advocated in the guidelines produced by the British Thoracic Society and National Asthma Campaign [British Thoracic Society 1990a, b], whereas the NIH International Consensus Report on Diagnosis and Management of Asthma [1992] suggests that specific AII may be considered under certain circumstances such as poor control of asthma symptoms despite adequate drug treatment or where allergen avoidance is not possible [NIH International Consensus Report 1992]. In some ways, these differing views reflect existing variations in the use of AII in asthma between different countries. Thus, in the U.K., AII is rarely if ever used to treat asthma, whereas AII is more frequently advocated in other parts of Europe and in the U.S.A.

Asthma in adults

Efficacy

The efficacy of AII in asthma has been assessed in many

trials over the last 40 years [recent studies include Mosbech & Weeke 1986; Ohman 1989; Bousquet *et al.* 1990b]. The results of many of these studies are difficult to interpret owing to the use of poor-quality allergen extracts and to poor study design. Many trials were not placebo controlled, they were either not blinded or were single-blind, and patient numbers were often very small. In this review of recent trials of AII in asthma, studies were only considered if they were double-blind, placebo-controlled, and included at least eight patients in each treatment group.

Grass pollen: Several studies have found that AII has a beneficial effect in patients with grass pollen asthma as assessed by a reduction in asthma symptom and treatment scores (Table 3).

House dust mite: Studies that have examined the effects of AII in asthmatic patients sensitive to house dust mite have produced conflicting results (Table 4). A reduction in the median drug score was reported in studies of asthmatic children [Warner *et al.* 1978; Price *et al.* 1984], whereas no such improvement in asthma control has been convincingly reported in adults.

Animal dander: AII in asthmatic patients sensitive to cats reduces the early asthmatic response to inhaled allergen (Table 5). In one study active treatment delayed the onset of asthmatic symptoms on natural exposure to cats [Ohman *et al.* 1984], and a reduction in symptoms and peak flow recordings was observed following controlled exposure to cats in an exposure chamber, whereas no reduction in non-specific bronchial hyperreactivity was observed. In another study [Sundin *et al.* 1986] a reduction in bronchial sensitivity both to an inhaled cat extract and to histamine was observed following AII. The efficacy of AII in patients who are continually exposed to their cat is unknown. In contrast, AII with a dog extract was unsuccessful [Sundin *et al.* 1986].

Moulds: AII with *Cladosporium* was found to reduce the drug score and early asthmatic response to inhaled allergen [Dreborg *et al.* 1986]. However, there was a high incidence of systemic reactions in the treated group. In a study of a small group of patients sensitive to *Alternaria*, the group receiving AII ($n=13$) showed reductions in nasal and respiratory symptoms compared to the placebo group ($n=11$) [Horst *et al.* 1990]. However, a formal diagnosis of asthma was made in less than 50% of each group (i.e. most of these patients had allergic rhinitis without asthma).

Table 3. Selected double-blind placebo-controlled studies on the effects of AII in grass pollen asthma

Reference	Age range (years)	Allergen extract	No. in active (A) group	No. in placebo (P) group	Response to treatment		
					Symptoms of asthma drug usage	Bronchial challenge to allergen	Skin test response to allergen
Reid <i>et al.</i> 1986	20-39	Standardized	9	9	Reduced (mean symptom treatment score A = 4.7, P = 17.8)		
Bousquet <i>et al.</i> 1989	12-47	Formaldehyde allergoid	18 (64% with asthma)	14 (56% with asthma)	Reduced (mean symptom score A = 4.7, P = 18.1)		Reduced
Bousquet <i>et al.</i> 1990b	11-45	Formaldehyde allergoid	A ₁ : (53% with asthma) A ₂ : (55% with asthma)	18 (50% with asthma)	Reduced (mean symptom score A ₁ = 12.8, A ₂ = 17.4, P = 54.8)		Reduced

Abbreviations: A₁ = low-dose schedule; A₂ = high-dose schedule.

Table 4. Selected double-blind placebo-controlled studies on the effects of AII in asthma patients sensitive to *Dermatophagoides pteronyssinus*

Reference	Age range (years)	Allergen extract	No. in active (A) group	No. in placebo (P) group	Response to treatment		
					Symptoms of asthma drug usage	Bronchial challenge to allergen	Skin test response to allergen
Gaddie <i>et al.</i> 1976	15-68	Tyrosine adsorbed	20	25	No change		No change
Warner <i>et al.</i> 1978	5-14	Tyrosine adsorbed	27	24	Improved (median drug score A = 20, P = 230)	EAR: no change LAR: lost in 50% of A group	
Price <i>et al.</i> 1984	5-15	Tyrosine adsorbed	13	12	Improved (drug score)		
BTA 1979	16-50	Aluminium adjuved	29	17	No change		
Pauli <i>et al.</i> 1984	19-40	Tyrosine adsorbed	9	9	Improved after 6 months but not after 1 year of treatment		
Bousquet <i>et al.</i> 1985	18-42	Standardized	20	10		EAR reduced	Reduced

Abbreviations: EAR = early asthmatic response; LAR = late asthmatic response.

Table 5. Selected double-blind placebo-controlled studies on the effects of AII in cat-induced asthma

Reference	Age range (years)	Allergen extract	No. in active (A) group	No. in placebo (P) group	Response to treatment		
					Symptoms of asthma drug usage	Bronchial challenge to allergen	Skin test response to allergen
Ohman <i>et al.</i> 1984	22-48	Standardized	9	8	Reduced after exposure to cats	EAR reduced	Reduced
Sundin <i>et al.</i> 1986	8-47	Standardized alum-adsorbed	15	17		EAR reduced	
Van Metre <i>et al.</i> 1988	21-52	Standardized	11	11		EAR reduced	Reduced

Abbreviation: EAR = early asthmatic response.

Comparison of AII with other types of treatment for asthma

The effectiveness of specific AII in asthma has not been compared to conventional management with avoidance measures and pharmacological treatment. Without such comparisons it is not possible to assess the risk/benefit ratio of AII with other treatments. Until such studies are undertaken, specific AII in asthma should be regarded as an experimental form of treatment.

Safety

In the U.K. between 1957 and 1986 26 fatal reactions due to AII were reported to the Committee on Safety of Medicines. In 17 of the fatal cases the indication for AII was documented: 16 of these 17 patients were receiving AII to treat asthma [Rawlins *et al.* 1988]. The incidence of systemic reactions in patients receiving AII for asthma has been reported to range from 5 to 35% [Bousquet *et al.* 1990b] (see also Chapter 8).

Indications

On the current published evidence, there are *no* clear clinical indications for specific AII in asthma due to grass pollen, house dust mite, cat or mould allergen sensitivity. Therefore the use of AII to treat asthma should be restricted to research studies only.

Special considerations for the use of AII in childhood asthma

As discussed above, AII for asthma appears to be more beneficial in children than in adults [Warner 1981]. The

group that appears to benefit most is children with seasonal rhino-conjunctivitis with mild coexistent asthma [Paediatric Asthma Consensus Group 1992]. It is not clear why children should have a greater beneficial response as there have been few investigations comparing identical therapy in the different age groups. One study of animal dander AII in adults and children has suggested that children have a greater immunological reactivity with the development of higher levels of IgG and IgG4 antibodies on AII compared with adults. However, this difference in immunological reactivity was not necessarily reflected in either the clinical response or changes in allergen provocation response [Hedlin *et al.* 1986]. It is possible that the difference between children and adults may reflect the greater tendency for spontaneous improvement in allergic disease in childhood, a tendency which may be accelerated by AII.

It has been suggested that AII may modify the natural history of asthma in children, although the only data to support this suggestion come from prolonged open studies using uncharacterized mixed allergen extracts [Rackemann & Edwards 1952; Johnstone & Dutton 1968]. Among other problems, these studies failed to allow for the spontaneous improvement that often occurs in asthmatic patients. There is, therefore, no hard evidence as yet that AII modifies the natural history of allergic disease through childhood and into adult life.

AII attenuates the late asthmatic reaction to allergen inhalation in children [Warner *et al.* 1978]. Subsequent studies have reproduced these findings [Van Bever *et al.* 1988], but few similar observations have been made in adults [Bousquet *et al.* 1990b].

One study has suggested that AII may increase non-specific bronchial hyperreactivity in asthmatic children

(Murray *et al.* 1985). However, this observation has not been confirmed in other studies.

While several trials have demonstrated AIT to be superior to placebo in the treatment of house mite-sensitive asthma, none has compared the risk and benefits with conventional pharmacotherapy. Furthermore, there is 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 symptoms [Bousquet *et al.* 1990; Price *et al.* 1984]. With the increase in concern about side-effects and the lack of knowledge of the mechanisms of action of AIT, there is little justification for its routine use in childhood asthma. Carefully designed trials are required as a matter of urgency to establish whether AIT has any effect in modifying the natural history of asthma in childhood.

Conclusions

AIT is a controversial type of treatment for asthma. There have been few well-controlled studies. In those studies in which a double-blind placebo-controlled study design has been employed, and which have included at least eight patients in each group, a beneficial effect has been found in grass pollen asthma. The clinical efficacy of AIT in adult asthmatic patients sensitive to house dust mite, cats and moulds is less certain, and comparative studies with conventional treatment have not been performed. Further clinical trials are indicated, particularly in mild to moderate childhood asthma. However, on the basis of uncertain efficacy and the potential for serious side-effects, we conclude that AIT is not currently indicated for the treatment of asthma.

CHAPTER 3

Hymenoptera hypersensitivity

Background and exposure risks

In the U.K., hymenoptera venom allergy is usually caused by stings from the honey bee (*Apis mellifera*) or the wasp (*Vespula* spp.). The vast majority of U.K. patients with bee venom allergy are beekeepers and their relatives or neighbours; they have close contact with bees and are thus at high risk of being stung [Ewan 1984, 1985; Ewan *et al.* 1993]. Most beekeepers experience frequent stings (in some cases, hundreds of stings each season). In contrast, wasp venom allergy usually occurs in patients who have been stung infrequently, often at long intervals (over many years). There are a small number of patients at high risk of repeated wasp stings (e.g. fruit-farm or bakery workers) and this risk factor needs to be noted when considering whether venom immunotherapy is indicated as part of their management.

Clinical features

Hypersensitivity reactions to hymenoptera stings may be either local or generalized. Local reactions are excessively large local swellings at the site of a sting and may persist for several days. Generalized reactions are remote to the site of the sting; they are often rapid in onset and vary in severity from mild rashes to life-threatening anaphylactic shock. Common features include erythema, urticaria, angioedema, laryngeal oedema, bronchospasm or hypotension. Less often patients may develop rhinitis, vomiting, diarrhoea, retrosternal pain, fits or visual disturbances. Vasovagal symptoms commonly follow stings, leading to light-headedness, fainting, incontinence and loss of consciousness. It can be difficult to distinguish these symptoms from those of true anaphylaxis.

There is a high spontaneous cure rate as shown in studies of the natural history of venom allergy and in the placebo-treated groups of controlled trials of venom immunotherapy. Patients who have previously had a generalized reaction do not necessarily have similar reactions to subsequent stings. In a venom immunotherapy trial 40% of the placebo group had no reaction to a challenge sting, despite a history of previous generalized reactions [Hunt *et al.* 1978]. In other studies of hymenoptera allergy, sting-challenge tests elicited generalized reactions in 20% of those with a history of mild systemic reactions [Blaauw & Smithuis 1985; van der Zwan 1991] and in 34-51% of those with a history of severe systemic reactions [Blaauw & Smithuis 1985; van der Zwan 1991]. Of those with a history of a large local reaction, only about 40% go on to develop systemic reactions to sting

challenges [Graft *et al.* 1984; Mauriello 1984]. A smaller degree of spontaneous improvement was observed in a study of the natural history of generalized reactions, among adults with previous generalized reactions, field stings elicited a further generalized reaction in 74% of wasp-allergic patients and 80% of bee-allergic patients [Ewan 1984]. However, it is important to recognize that some of these subsequent generalized reactions were less severe; Settipane and Chafee [1979] studied patients who had had a generalized reaction to a bee sting and were subsequently re-stung; 44.5% had an improved grade of reaction.

Efficacy

It is well established that venom immunotherapy using pure venom extracts is highly effective [Hunt *et al.* 1978; Muller *et al.* 1979]. The first controlled trial of AIT using venom extracts found that treatment with pure venom had a 95% success rate, compared to an improvement rate of 40% in the placebo-treated group; treatment with extract of whole body of bee or wasp, as performed for the previous 50 years, was no better than placebo [Hunt *et al.* 1978]. Since then several other studies have confirmed the efficacy of pure venom, which seems more effective in wasp hypersensitivity than in bee venom allergy (Table 6). A variety of treatment regimes have been tried; a maintenance dose of 100 µg of pure venom (initially 4-weekly, then 6-weekly) seems to protect the majority of patients, although higher doses may be required for some bee venom-allergic patients.

The high efficacy of venom immunotherapy might suggest that all patients with hymenoptera venom allergy and a history of generalized reactions should be treated. However, before commencing treatment it is necessary to assess the risk/benefit ratio and to consider both the incidence of side-effects and the spontaneous cure rate. Side-effects from venom immunotherapy are common, and include immediate hypersensitivity reactions of varying degrees of severity, including anaphylaxis. In various different trials, systemic adverse reactions have been reported in from 5 to 40% of individuals [Müller 1990]. In a prospective study in the U.K. an even higher rate of systemic reactions was observed, affecting 23% of all wasp venom injections and 10% of bee venom injections, although many of these were extremely mild [Ewan & Stewart 1992]. In most studies, systemic adverse reactions seem to occur more commonly with bee venom than with

Table 6. Efficacy of venom immunotherapy, assessed by response to sting challenge

Author	Insect	Sting challenge (no. of patients)	Generalized reaction (no. of patients)
Gillman <i>et al.</i> 1980	Bee	18	4 (22%)
Müller 1990	Bee	148	34 (23%)
Hunt <i>et al.</i> 1978*	Bee and wasp	18	1 (5%)
Golden <i>et al.</i> 1981	Wasp	147	4 (3%)
Mosbech <i>et al.</i> 1986	Wasp	19	0
Müller 1990	Wasp	57	5 (9%)

* Only 7/12 (58%) in placebo-treated group had generalized reactions to sting challenge.

wasp venom. It is important to note that large local reactions to venom injections occur at some time in most patients, usually during the induction phase of treatment.

Selection of patients for venom immunotherapy

Diagnosis

The diagnosis of insect-sting allergy is primarily based on a history of allergic reaction following a sting. It is therefore important to obtain a full history, including details of type and severity of reaction, and for each reaction, the rapidity of onset, number of stings causing a reaction, treatment required and response to therapy. Frequency of stings, intervals between stings and the number of stings not causing reactions must also be recorded for it is only then that an accurate picture of the natural history and severity of reactions can be obtained.

The demonstration of specific IgE antibody either to bee or to wasp venom can be assessed either by a skin test with pure venom extract (usually by intradermal method), or by measuring serum-specific IgE antibodies (usually by RAST). Intradermal skin tests are more reliable than RAST. Because of the considerable spontaneous remission rate, it has been argued that all patients being considered for VIT should undergo provocation tests, either by injecting the appropriate venom subcutaneously or by giving a sting in hospital, to confirm that they are truly hypersensitive before embarking on VIT [Müller 1990]. This is a controversial issue and the majority of allergists in Europe do not carry out these provocation tests.

Risk of further stings

In assessing the risk/benefit ratio of venom immunotherapy, it is important to consider the likelihood of future exposure. This can be estimated from the number and frequency of previous stings, but other factors also

need to be considered, including current lifestyle, geographical location, and specific risk factors for stings (e.g. beekeeper, baker, greengrocer, etc.). It is quite common for wasp-allergic patients to have been stung only a few times at long intervals. The physician has to decide whether or not to embark on immunotherapy, with a definite risk of inducing an allergic reaction during treatment, when the patient may not be stung again for many years; moreover, by the time the next sting occurs, the patient may no longer be reactive to venom or the beneficial effects of immunotherapy may have worn off.

Indications

General indications

The general indications for venom immunotherapy are summarized in Table 7. These are to be viewed as guidelines and, before deciding on immunotherapy, the risk/benefit ratio must be assessed for each patient, taking into account the factors discussed above. It is, however, difficult to be dogmatic, since the great problem with insect-sting allergy is that it is not possible to predict the severity of the reaction to the next sting. Whatever the nature of the reaction, it is essential to confirm the presence of venom-specific IgE before starting venom immunotherapy. Patients with a history of severe venom-induced systemic reactions accompanied by respiratory and cardiovascular symptoms should be given venom immunotherapy. Venom immunotherapy is not usually indicated for moderate reactions in patients with a low risk of future stings but venom immunotherapy should be considered for patients with repeated moderate systemic reactions and/or a high risk of further stings. Mild systemic reactions, such as erythema, urticaria or angioedema not involving the respiratory tract do not require venom immunotherapy. There is a considerable variation in venom immunotherapy practice in Europe, where some allergists use it to treat all patients presenting with

Table 7. Indications for venom immunotherapy

Type of reaction	Venom-specific IgE*	Venom immunotherapy
1. Severe systemic (respiratory and/or cardiovascular symptoms)†	Positive	Yes
2. Moderate systemic (urticaria, angioedema, mild asthma, nausea, light-headedness, etc.)	Positive	Depends on frequency of reactions, likelihood of future exposure and access to medical services
3. Mild systemic (erythema, urticaria, angioedema)	Positive	No
4. Large local	Positive	No
5. Any form of reaction	Negative	No

* Shown by skin test and/or as venom-specific serum IgE.

† Includes severe dyspnoea due to laryngeal oedema, asthma, marked hypotension, collapse or loss of consciousness.

systemic reactions, even if these only involve cutaneous symptoms. In the U.K. it is considered that treating such patients with venom immunotherapy exposes them to unnecessary risk for uncertain and limited gain. At present there is no evidence to suggest that venom immunotherapy is indicated in the treatment of large local reactions or unusual systemic reactions such as vasculitis or fever.

Another factor to consider is the accessibility of medical help: venom immunotherapy might be indicated for a patient living in a remote part of the country far away from a doctor or hospital, whereas for a patient with a similar history living in a city it might be more appropriate to recommend drug therapy for a reaction, should it occur. Thus the decision to embark on a course of venom immunotherapy requires consideration of the risk of exposure, the patient's circumstances and the severity of reactions to previous stings.

Special circumstances

There are a number of special circumstances which affect the general principles stated above.

Children: Spontaneous improvement is more common in children than in adults [Schubert *et al.* 1983, Valentine *et al.* 1990]. Thus children should not normally be given venom immunotherapy [Ford & Davison 1987]. One exceptional situation is beekeepers' children who have had repeated severe systemic reactions, although it would probably be more appropriate to remove the bees!

Elderly patients: Elderly patients tend to have more severe reactions and a greater rate of fatality from hymenoptera stings. However, they also have a higher rate of adverse reactions to immunotherapy and respond less well to

adrenaline. All of these are probably due to coexisting cardiovascular disease. Except in the case of beekeepers, the risk of further stings in the elderly is probably lower than for the general population, and thus venom immunotherapy is not usually indicated.

Beta-blocker therapy: Beta-blocking agents alter the physiological response to adrenaline, leading to unopposed alpha-receptor stimulation which may result in an overshoot in blood pressure. Beta-blockers should be discontinued, and alternative therapy established, before venom immunotherapy is commenced.

Pregnancy: It is clear that venom immunotherapy should *not* be started during pregnancy, but there is a lack of consensus as to whether a patient already receiving venom immunotherapy should continue this during pregnancy. In the U.S.A. pregnancy is not regarded as a contraindication to maintenance treatment. In the U.K. there is less experience of giving immunotherapy in pregnancy, and therefore this Working Party concluded that it was generally *inadvisable* to continue venom immunotherapy injections during pregnancy since there is a risk, albeit small, of inducing an anaphylactic reaction with each maintenance injection. In some individuals, circumstances may make it desirable to continue immunotherapy during pregnancy, but each such decision must be carefully considered and justified on an individual basis. If immunotherapy is recommenced after delivery, special care must be taken to start again with the lowest dose of venom, otherwise severe systemic reactions may occur on reintroducing venom immunotherapy (this is a general precaution which applies in all patients who restart immunotherapy after a prolonged break from treatment).

CHAPTER 4

Drug hypersensitivity

Background

Adverse reactions to drugs are common in clinical practice. It has been estimated that approximately one-third of hospitalized patients will suffer an adverse reaction to one or more drugs during their stay in hospital [Miller & Greenblatt 1976]. Only a small proportion of these (approximately 10%) will be caused by immunological mechanisms. Data on the incidence of drug reactions in an outpatient population are less complete. Reactions that are severe enough to cause or contribute to hospitalization probably occur at a rate of about 0.3 to 3.7% of total hospital admissions [Caranosos *et al.* 1974; McKenzie *et al.* 1976; Miller 1974]. The higher the molecular weight of the drug (such as insulin), the more likely it will give rise to allergy. Low molecular weight drugs (such as penicillin and its metabolites) may cause allergic reactions by acting as haptens: in this case, the immunological response is directed against the carrier protein-hapten complex. However, drugs and their metabolites vary in reactivity. The term 'reactivity' is used to describe the type or strength of the bond between drug and carrier; the higher the bonding affinity *in vitro*, the more likely it is to induce an allergic reaction. Covalent bonds are more likely to produce an immunogenic carrier-hapten combination.

Allergic reactions to drugs do not generally occur on first exposure, but may occur with prolonged administration. However, cross-reactivity between drugs is common, and a patient may be allergic to all drugs of similar category even though exposure to each drug has not occurred. Only a very small dose or quantity of drug is required to produce an allergic reaction, and in this respect allergic reactions resemble idiosyncratic reactions. This clearly distinguishes allergic drug reactions from drug overdose or dose-related side-effects. The critical distinguishing feature is whether the immune system is involved.

Drug allergy is very different from the type of hypersensitivity states described earlier in this position paper. In many instances reactions to drugs occur without the mechanism being clearly defined, or where the true nature of the allergic response is unclear. It is important to distinguish reactions such as acute urticaria following oral anti-inflammatory drugs, which are due to the effects of the drug directly on mast cell mediator release. For these reasons, only broad recommendations can be provided in this chapter. Although allergic adverse reactions to intravenous anaesthetic and neuromuscular blocking drugs are well recognized [Association of Anaes-

thetists 1990], desensitization has not been recommended in this type of intolerance because alternative anaesthetic regimens are available. Specifically this section will discuss penicillin and insulin hypersensitivity as examples of IgE-mediated allergic responses, and reactions to non-steroidal anti-inflammatory drugs since it may be necessary to desensitize patients requiring these agents for the treatment of chronic rheumatic disorders.

It should be noted that drugs, in contrast to many of the other allergens discussed in this report, can readily be avoided since there is such a wide choice of alternative therapies. *The single most important feature in the management of a patient with drug allergies is to avoid using the drug.* Thus with drugs, the issue of desensitization only arises if it is essential to use a drug to which the patient is allergic, in a clinical setting where there is no alternative therapy.

Penicillin allergy

An allergic reaction to penicillin or its derivatives occurs in 1-10% of treated patients [Parker 1975]. Most of these are minor skin rashes and are a nuisance but not life-threatening. Anaphylactic reactions to penicillins occur most frequently in the 40-49 year age group and when the drug is given parenterally. Penicillin hypersensitivity declines with time; the greater the interval since a previous reaction, the less likely the sensitivity is to exist; and atopy is not a predisposing factor. The major immunological determinant is the penicilloyl group, the main metabolic product from penicillin [Parker *et al.* 1962]; a number of minor determinants are produced by metabolism through other pathways [Saxon *et al.* 1987].

Diagnosis

The specific IgE antibody which develops following penicillin therapy is usually directed against the major and/or the minor determinant antigens. Antibody against the major determinant is most common, but severe anaphylactic reactions are usually due to IgE directed towards minor determinants. Skin-prick testing has been used to diagnose penicillin allergy, using either a derivative of the major determinant, benzylpenicilloyl polylysine (PPL) or the minor determinants including benzylpenicillin itself [DeSwarte 1986; Green *et al.* 1977; Warrington *et al.* 1978]. A classical weal and flare reaction after 15 minutes is a positive response and suggests the presence of specific IgE. A multi-centre cooperative study of almost 3000 patients has assessed the usefulness of skin

tests to penicillin-G and PPL in the assessment of penicillin hypersensitivity [Green *et al.* 1977]: 19% of 1718 patients with a history of penicillin allergy had a positive skin test to either or both agents, and 7% of 1229 of patients with no such history had positive responses. Among patients with a history of penicillin allergy where a detailed history was available, positive skin tests were noted in 46% with a history of anaphylaxis, 17% with a history of urticaria or angioneurotic oedema, and 7% with a history of a maculopapular reaction. PPL generally gave higher reaction rates than penicillin-G, but both skin tests were needed to elicit the maximum number of patients reacting. When formally challenged with penicillin, 67% of patients with a history of adverse reaction and a positive skin test developed an allergic reaction. Only 3% of the patients with a negative skin test had a reaction to challenge and only a quarter of these (0.75% of total with negative skin tests) had early reactions which might possibly have been mediated by IgE. In a more recent study, skin tests for penicillin-G, penicilloic acid and PPL were performed on 740 subjects with suspected penicillin allergy [Sullivan *et al.* 1981]. Approximately 95% of these patients had histories of apparent allergic reactions to beta-lactam antibiotics and 63% were skin-test positive. The prevalence of positive skin tests was related to the time elapsed between clinical reactions and skin testing. Seven to 12 months after reactions, 93% tested positive while 22% were positive 10 years or more after reactions. Testing with PPL, penicilloic acid and penicillin-G detected 76.3%, 55.3% and 57.1%, respectively, of the patients with positive reactions. Thus a positive skin-test reaction to penicillin is not necessarily an accurate predictor of the development of a hypersensitivity reaction to subsequent exposure.

Almost all beta-lactam antibiotics show some cross-sensitization. The newest beta-lactam antibiotics seldom cause clinical problems [Petz 1978]. Eight percent of patients with a history of penicillin allergy reacted to cephalosporins, whereas 1.9% of individuals with no history of penicillin allergy experienced a reaction when given cephalosporin. Thus the penicillin-allergic patient appears four times more likely to experience an allergic reaction to cephalosporins than the non-penicillin allergic patient. This compares with the 30-70% chance of reacting to a re-administration of a penicillin derivative in a penicillin-allergic patient [Petz 1971; Thoburn *et al.* 1966; Moellering & Swartz 1976].

Efficacy of desensitization to penicillin

Stark *et al.* [1987] reported efficacy and safety of penicillin desensitization in 24 adults and two children with serious infections that required treatment with a beta-lactam

drug. Onset and gradual worsening of wheezing led to abandonment of desensitization in one subject, but the remaining 25 patients were successfully desensitized. Thus penicillin desensitization can be useful and is a safe approach.

Penicillin desensitization uses very small, increasing doses of the drug, but its precise mechanism of action is as yet unknown. As a result of the desensitization process, positive direct and passive transfer skin tests diminish or become negative [Sullivan 1982; Sullivan *et al.* 1982; Brown *et al.* 1982; Naclerio *et al.* 1983].

Various routes of penicillin desensitization have been proposed which include oral, subcutaneous, intramuscular and intravenous. Regardless of the route or method chosen for the procedure, the basic principles remain the same, and are outlined in Tables 8 and 9. Initially, small doses of the drug are given; at 15-minute intervals thereafter the dose is usually doubled, with continuation of this process until the full therapeutic dose of the drug is given by the optimal route. Desensitization should not be undertaken under cover of antihistamines or steroids, since these drugs may mask the subsequent reaction during the procedure.

It is imperative to perform this procedure in a setting where resuscitation facilities are immediately available, and it should only be performed by a physician experienced in this technique. A systemic reaction during desensitization is treated in the usual way as for anaphylaxis (see Chapters 5 and 8). It is also important to inform patients that they may become sensitive to penicillin again when the therapy is discontinued. Patients who had an allergic reaction during treatment, or who have positive skin tests, are warned against taking penicillin in the future without prior testing. They should be advised to obtain medical identification tags stating that they are allergic to penicillin.

Indications

The theoretical indication for penicillin desensitization is the necessity to use antibiotic therapy in bacterial infections in which there is no other alternative except penicillin. In practice the clinical setting would have to be that of a life-threatening infection, such as septicaemia and bacterial endocarditis, for which no alternative antibiotic treatment was possible. In practice this situation hardly ever arises.

Insulin allergy

Over the last ten years, the incidence of allergic reactions to insulin has declined, due to improved purification of commercial insulin preparations.

Table 8. Oral desensitization protocol

Step*	Phenoxymethyl penicillin			Dose		Cumulative dosage	
	Units ml	mg ml	Amount ml	Units	mg	Units	mg
1	1000	0.6	0.1	100	0.06	100	0.06
2	1000	0.6	0.2	200	0.12	300	0.18
3	1000	0.6	0.4	400	0.24	700	0.42
4	1000	0.6	0.8	800	0.48	1500	0.9
5	1000	0.6	1.6	1600	0.96	3100	1.86
6	1000	0.6	3.2	3200	1.92	6300	3.78
7	1000	0.6	6.4	6400	3.84	12,700	7.62
8	10,000	6	1.2	12,000	7.2	24,700	14.82
9	10,000	6	2.4	24,000	14.4	48,700	29.22
10	10,000	6	4.8	48,000	28.8	96,700	58.02
11	80,000	48	1.0	80,000	48	176,700	106.02
12	80,000	48	2.0	160,000	96	336,700	202.02
13	80,000	48	4.0	320,000	192	656,700	394.02
14	80,000	48	8.0	640,000	384	1,296,700	778.02
Observe patients for 30 minutes							
Change to benzylpenicillin G (intravenous)							
15	500,000		0.25	125,000			
16	500,000		0.50	250,000			
17	500,000		1.0	500,000			
18	500,000		2.25	1,125,000			

* Interval between steps = 15 minutes.

Indications

Allergic reactions to insulin occur in a number of patients after a lapse in treatment, and the first decision to be made is whether alternative therapy would be effective. If not, desensitization should be considered. Local reactions to insulin are rarely of clinical significance, since they are only mild and transient. Thus desensitization should only be considered with systemic reactions.

Desensitization employs subcutaneous injections. If desensitization is initiated within 24 hours of an insulin-allergic reaction, the initial desensitizing dose should be one-sixth to one-third of the dose producing the reaction. The dose is then increased by five units per day. If more than 24 hours have elapsed since the reaction, a serial-dilution intradermal skin-test titration should be performed. If the patient is sensitive to pork or beef insulin, they should be transferred to human insulin. Desensitization should only be performed if the patient shows allergy to human insulin. The initial dose is the highest concentration to which the patient appears to demonstrate a skin reaction, as determined by skin-test titrations.

A possible desensitization schedule for patients treated

24 hours or more after their last insulin injection is shown in Table 10. This method is used in non-emergency situations. In more urgent situations, injections may be given every 30 minutes. A doctor must be present during the entire procedure. Successful desensitization usually permits the re-institution of insulin. Occasionally, patients cannot tolerate the necessary total daily dose of insulin as a single dose; such patients should be given divided doses. Skin-test titrations during desensitization show progressively diminishing cutaneous sensitivity, and skin tests may become negative after successful desensitization.

Aspirin intolerance

Aspirin sensitivity can cause rhinitis, asthma and urticaria and is thought to be due to an altered pharmacological response to the drug and not to an IgE-mediated allergy. It is covered here because it was specifically mentioned in the CSM report [1986] and patients can be successfully desensitized. Aspirin-sensitive patients will

Table 9. Parenteral desensitization protocol

Step*	Concentration of β -lactam drug (mg/ml)	Amount (ml) subcutaneous	Dose (mg)	Cumulative dosage (mg)
1	0.1	0.10	0.01	0.01
2	0.1	0.20	0.02	0.03
3	0.1	0.40	0.04	0.07
4	0.1	0.80	0.80	0.15
5	1	0.15	0.15	0.30
6	1	0.30	0.3	0.60
7	1	0.60	0.6	1.2
8	10	0.10	1	2.2
9	10	0.20	2	4.2
10	10	0.40	4	8.2
11	10	0.80	8	16.2
12	100	0.15	15	31.2
13	100	0.30	30	61.2
14	100	0.60	60	121.2
15	1000	0.10	100	221.2
16	1000	0.20	200	421.2
17	1000	0.40	400	821.2
18	1000	0.50	500	1321.2
Observe patient for 30 minutes				
19	1000	Intravenous	0.5 g	1821.2
20	1000	Intravenous	1.5 g	3321.2

* Interval between steps = 15 minutes.

often react to other drugs and foods containing salicylates and to other non-steroidal anti-inflammatory drugs (NSAIDs). Most aspirin-sensitive respiratory patients can be successfully desensitized to aspirin and other NSAIDs.

Efficacy

Desensitization of patients with aspirin-sensitive rhinosinusitis has been shown to clear hypertrophic rhinitis in three-quarters of the patients [Lumry *et al.* 1983]. A double-blind cross-over study has compared three months of aspirin desensitization to three months of placebo treatment in 25 asthmatic patients with severe aspirin sensitivity and disease of the upper and lower respiratory tracts [Stevenson *et al.* 1984]. Approximately two-thirds of the aspirin-sensitive asthmatic patients experienced a reduction in nasal symptoms and were able to decrease their use of topical corticosteroids compared with the three months when they received placebo. The severity of asthma also decreased in approximately half of the patients.

Aspirin desensitization is time consuming and expensive. The risk of a patient developing a severe asthma

attack during the treatment period is real, and aspirin desensitization is therefore best conducted in centres where resuscitation facilities are immediately available.

The efficacy of aspirin desensitization in patients with chronic urticaria and aspirin sensitivity is far less clear. Experience from the Scripps Clinic and Research Foundation suggests that aspirin desensitization is unhelpful in patients with urticaria. Asad reported that six out of eight aspirin-sensitive patients with urticaria and angioedema reacted to aspirin and could then be desensitized to aspirin [Asad *et al.* 1984]. However, most of the patients had predominantly respiratory symptoms when challenged with aspirin. Further work is needed to determine whether aspirin-sensitive urticaria responds to desensitization.

Indications

The indications for aspirin desensitization are severe rhino-sinusitis in an aspirin-intolerant patient where conventional medication (anti-histamines, nasal topical corticosteroids) has failed. In addition, desensitization to non-steroidal anti-inflammatory drugs should be con-

Table 10. Insulin desensitization schedule in a patient seen more than 24 hours after the reaction*

Day	Time	Dose (units insulin)	Route of administration
1	8.00 a.m.	0.00001	Intradermal
	12.00 noon	0.0001	Intradermal
	5.00 p.m.	0.001	Intradermal
	10.00 p.m.	0.001	Intradermal
2	8.00 a.m.	0.01	Intradermal
	12.00 noon	0.1	Intradermal
	5.00 p.m.	1.0	Subcutaneous
	10.00 p.m.	1.0	Subcutaneous
3†	8.00 a.m.	2.0	Subcutaneous
	12.00 noon	4.0	Subcutaneous
	5.00 p.m.	8.0	Subcutaneous
4‡	8.00 a.m.	10.0	Subcutaneous
	12.00 noon	12.0	Subcutaneous
	5.00 p.m.	14.0	Subcutaneous
5	8.00 a.m.	18.0	Subcutaneous
6	8.00 a.m.	25.0	Subcutaneous
7	8.00 a.m.	30.0	Subcutaneous

* The schedule should be flexible and adjusted if local or systemic reactions occur. Initial doses are given with crystalline (regular) insulin and are based on skin-test titrations.

† Consideration to changing to an intermediate insulin such as NPH insulin (isophane insulin) should be given on Day 3.

‡ Hypoglycaemic precautions are necessary by Day 4 or Day 5.

sidered in any clinical situation where the drugs are needed to treat a pathological entity (e.g. rheumatoid arthritis) in patients who are intolerant to these drugs.

Special considerations for treatment of drug hypersensitivity in children

Children commonly have skin rashes in association with viral infections. Concurrent treatment may precipitate urticaria (especially in infectious mononucleosis). In addition, the family and attending physician may suspect that normal viral rash was due to antibiotic hypersensitivity. The vast majority of such children do not, in fact, have any subsequent reaction to the offending antibiotic on formal investigation [Bierman *et al.* 1969; McKenzie *et al.* 1976; Whyte & Greenan 1977; Graff-Lonnevig *et al.* 1988]. Since alternative antibiotics are usually available, it is rarely necessary to consider desensitizing children to antibiotics. Exceptions would include children with rheumatic fever or cystic fibrosis, in whom it may be essential to use penicillin rather than any other antibiotic.

Conclusions

Adverse reactions to drugs are common but the mechanisms of such reactions vary and are in many cases poorly understood. Desensitization is occasionally used in the treatment of drug allergy, but more work in this area is clearly needed.

CHAPTER 5

Mechanism of allergen immunotherapy

The mechanism by which allergen immunotherapy exerts its beneficial effect is unclear. A variety of immunological changes have been described but it remains uncertain which (if any) of these is responsible for relief of symptoms. In this review of possible mechanisms of AIT, the current position for inhaled allergens and for venom is discussed separately, since it is conceivable that different mechanisms may operate in response to allergen challenge across mucosal surfaces and through the skin.

Inhaled allergens

It is generally accepted that immunotherapy is clinically effective for pollen-induced and for house dust mite-induced rhinitis, providing that appropriate extracts are used. In addition to a reduction in symptoms and/or drug consumption, it is usually possible to demonstrate reduced sensitivity to allergen in the target organ, using nasal or conjunctival provocation tests.

Antibody responses

Specific IgE. Specific IgE concentrations increase during the first 3 months of conventional AIT, and slowly decline to pre-treatment levels by 12 months [Hedlin *et al.* 1990; McHugh *et al.* 1990]. In the long term, specific IgE levels gradually decline [Frostad *et al.* 1983] but it is rare for specific IgE to disappear completely. In most studies the majority of the clinical benefit has already occurred by 3 months, so specific IgE levels *per se* do not seem to be related to the mechanism of AIT. It is possible that local changes in IgE regulation, production in the target organ or regional lymph nodes are not reflected in serum IgE concentrations. Alternatively, there may be functional changes in IgE that are not reflected by measurement of total specific IgE. *In vitro* studies have suggested that IgE is functionally heterogeneous and that allergen-specific IgE molecules are of two types, those that react with histamine-releasing factors (IgE⁺) and the remainder which do not (IgE⁻) [Lichtenstein 1988]. The production of IgE⁺ molecules would lead to increased mediator release from basophils, thought to be important in the late-phase reaction. It has been postulated that AIT may work through the redirection of IgE production towards IgE⁻, but as yet there are no hard data to support this theory. Circumstantial support for this hypothesis comes from a study of *Cladosporium* AIT in which histamine release from basophils decreased during the early phase of treatment, despite an increase in cell-bound IgE [Malling & Stahl-Skov 1988].

Specific IgG. Allergen-specific IgG levels also increase during effective immunotherapy. In patients with allergic rhinitis and asthma, baseline levels of specific IgG are low. In a clinically effective trial of *D. pteronyssinus* AIT for rhinitis, specific IgG levels, measured by ELISA, increased sharply in the first 3 months of AIT in parallel with clinical improvement [McHugh *et al.* 1990]. Similar changes in specific IgG have been observed after pollen AIT [Sadan *et al.* 1969; Ortolani *et al.* 1984; Bousquet *et al.* 1988]. The 'blocking antibody' theory suggests that the efficacy of AIT depends on changing the balance between 'harmful' IgE antibodies and 'protective' IgG antibodies [Creticos *et al.* 1984]. This theory was supported by a study of ragweed AIT, in which the IgG:IgE binding ratio increased after treatment and correlated significantly with a fall in symptom score while the IgG antibody binding of ragweed antigen E also increased but did not correlate with symptoms [Zeiss *et al.* 1977].

IgG subclasses. Considerable attention has been devoted to the role of IgG subclasses, particularly IgG1 and IgG4, in relation to clinical outcome. With occasional exceptions, most patients fail to make an IgG2 or IgG3 response during AIT. Several studies with different allergens (house dust mite, cat and grass pollen) have shown that a rise in IgG4 is associated with improvement [Devey *et al.* 1976; Van der Giessen *et al.* 1976; Nakagawa *et al.* 1983, 1987; Hedlin *et al.* 1986; McHugh *et al.* 1990]. Another study, however, suggested that a rise in IgG4 is associated with treatment failure [Djurup & Malling 1987]. A detailed study of antibody changes during effective *D. pteronyssinus* AIT found that specific IgG and IgG1 concentrations increased over the first 3 months of treatment and then remained elevated without further change for 12 months, while the specific IgG4 level increased steadily over the 12 months [McHugh *et al.* 1990]. The IgG:IgE ratio increased and there was a subclass switch from IgG1 to IgG4. In this study there was no elevation in specific IgG, IgG1 or IgG4 in the groups treated with placebo or with a conventional but clinically ineffective house dust mite extract. There was a highly significant correlation between clinical efficacy and the rise in IgG, IgG1 and IgG4, the association being most marked with IgG4. Conversely, low IgG antibody responses were associated with failure. While these observations are compatible with the hypothesis that IgG subclasses may modulate antigen-IgE interactions, this response might simply be the expected immune response to repeated immunization with a potent antigen [Aalberse

et al. 1983] and need not be causally related to the mechanism of AII. Thus potent and effective extracts can be clearly shown to elicit an IgG response but it remains uncertain whether this response is relevant to the beneficial effects of AII in allergic disease.

Local antibodies. Allergen-specific IgA and IgG antibodies are detectable in nasal secretions and appear to be produced locally. Although there is a small increase in specific IgG in nasal secretions after AII, this is much less than the increase in serum IgG [Platts-Mills 1979]. There are no data showing correlations between antibody levels in secretions and clinical efficacy.

Skin-prick and allergen inhalation tests

The immediate and late-phase skin-test responses to allergen are reduced after AII [Bousquet *et al.* 1988; Ewan *et al.* 1988a; Varney *et al.* 1991]. The mechanism of this effect is not certain. In a comparison of parameters used to assess allergen AII, changes in the immediate skin-test response did not correlate well with other parameters of efficacy such as symptom scores or drug scores [McHugh & Ewan 1992].

In children the most consistent effect of immunotherapy on allergen challenge has been the attenuation of the late-asthmatic reaction to allergen inhalation [Warner *et al.* 1978; van Bever *et al.* 1988]. Few similar studies have been performed in adults [Bousquet *et al.* 1990b].

Cellular effects and cytokines

The above studies illustrate the poor correlation between clinical response to AII and changes in IgE and IgG antibody. For this reason, attention has recently focused on the influence of AII on the cellular arm of the immune response, on the recruitment of cells to allergic tissue sites and on the pattern of mediators that these cells produce. For example, ragweed AII resulted in inhibition of both the early- and late-phase nasal responses to allergen challenge [Furin *et al.* 1991]. This was accompanied by a decrease in antigen-induced eosinophil migration into the nasal mucosa, as determined by nasal lavage. Similarly, AII in birch pollen-sensitive patients reduced seasonal increases in bronchial responsiveness, in the number of eosinophils, and in BAL concentrations of eosinophil cationic protein [Rak *et al.* 1988]. In patients with perennial allergic rhinitis and house dust mite allergy, there was a reduction in mast cell numbers in nasal epithelial scrapings following treatment [Otsuka *et al.* 1990]. Mite AII also results in a reduction in serum neutrophil chemotactic activity (an activity associated with mast cell degranulation) [McHugh *et al.* 1989].

AII in ragweed-sensitive hay fever patients resulted in decreased immediate nasal pollen sensitivity and a decrease in mast cell basophil-associated mediators including histamine and TAME esterase [Creticos *et al.* 1985]. Recent studies have emphasized the importance of T-lymphocyte recruitment and activation during human allergic responses. AII has been shown to suppress allergen-induced T-cell proliferative responses [Rocklin *et al.* 1980] and to induce an increase in circulating numbers of allergen-specific CD8⁺ lymphocytes [Nagaya *et al.* 1985]. Mosmann and colleagues, based on *in vitro* studies of murine T-cells, have distinguished two types of CD4⁺ T-lymphocyte, which differ in the profile of cytokines they produce. T_H1-type cells produce predominantly interferon-gamma and IL-2, while T_H2-type cells produce IL-4 and IL-5; both subsets produce IL-3 and GM-CSF [Mosmann *et al.* 1986]. Wierenga and colleagues found that antigen-specific T-lymphocyte clones from human atopic donors produced T_H2-type cytokines in response to common aeroallergens including pollens and house dust mite [Wierenga *et al.* 1990]. In contrast, *B. pertussis*-stimulated T-lymphocytes produced T_H1-type cytokines—namely IL-2 and interferon-gamma. Recent studies have confirmed a similar dichotomy in human skin reactions: allergen-induced cutaneous responses are associated with T-lymphocyte infiltration and activation as well as tissue eosinophilia [Frew & Kay 1988]. Using *in situ* hybridization, it has been possible to show preferential expression of mRNA for T_H2-type cytokines, particularly IL-4 and IL-5 during these late-phase cutaneous reactions [Kay *et al.* 1991]. When such reactions were induced in a group of subjects participating in a placebo-controlled trial of grass pollen immunotherapy [Varney *et al.* 1991], clinical improvement was accompanied by a decrease in the size of the macroscopic late-phase skin response. Analysis of skin biopsies obtained 24 hours after intradermal challenge revealed a significant reduction in the numbers of infiltrating T-lymphocytes and a trend for a reduction in the number of activated eosinophils. *In situ* hybridization studies demonstrated T_H2-type cytokine mRNA responses in the biopsies from both active and placebo-treated groups. In contrast, significant hybridization for IL-2 and interferon-gamma was only observed in the actively treated group. These findings suggest that inhibition of the late response following AII is associated with the suppression of allergen-induced T-cell recruitment and the appearance of T_H1-type cytokine expression [Varney *et al.* 1993]. These results support the view that AII may be working through induction of T-cell tolerance, comparable to that observed during induction of immune tolerance *in vitro* [O'Hehir *et al.* 1991].

Taken together, the above data suggest that AII

inhibits effector cell mechanisms at allergic inflammatory sites following both natural and experimental allergen challenge. Mast cell and eosinophil mechanisms seem to be particularly targeted but induction of T-cell tolerance may be the primary event with consequent effects on local IgE or mast cell activity and inhibition of tissue eosinophilia. An important goal for future vaccine development may be the production of 'non-stimulatory peptides' which can modify suppress T-lymphocyte responses while avoiding the risk of systemic adverse reactions and anaphylaxis which result from mast cell activation.

Venom

The mechanism of venom immunotherapy (VIT) is also controversial. Early studies showed a marked elevation in the concentration of venom-specific IgG in patients treated with venom extracts [Sobotka *et al.* 1976; Lichtenstein *et al.* 1979]. In a study using a lower dose IT regime, which resulted in more treatment failures, the level of venom-specific IgG was the only parameter that distinguished successful and unsuccessful treatment outcomes [Golden *et al.* 1982]. In keeping with this, adverse reactions to IT were found to occur more often in patients with lower IgG levels [Lichtenstein *et al.* 1979]. Since the IgG response was associated with protection from stings, therapeutic targets were recommended, namely that a two-fold increase in specific IgG or a critical level of IgG against anti-honey bee-phospholipase A2 or against wasp venom should be attained during AIT [Lichtenstein *et al.* 1979].

This hypothesis was further supported by the observation that bee-allergic subjects no longer reacted to sting challenge if they were infused with hyperimmune serum from beekeepers [Lesso *et al.* 1978]. Infusion of hyperimmune beekeeper gammaglobulin has also been successfully used to allow continuation of bee venom AIT in patients who would otherwise have had to stop because of allergic reactions to treatment [Müller *et al.* 1986; Bousquet *et al.* 1987].

Despite these observations, systemic reactions can still occur in patients on VIT with venom-specific IgG levels well above the 'protective' level, while some patients with low levels of IgG can nonetheless tolerate a sting challenge [Müller *et al.* 1989]. Other studies in untreated patients have shown no correlation between concentrations of venom-specific IgG, IgG1 or IgG4 and the response to a provocation sting [Blaauw & Smithuis 1985; Kampelmacher & van der Zwan 1987]. Thus the correlation observed after treatment probably reflects parallel effects induced by IT and not a causal relationship.

In reporting studies where IgG did not correlate with protection, a variety of explanations have been put

forward to explain the discrepancy. It has been suggested that the subclass response might be important and that IgG4 antibodies were associated with protection from stings [Urbanek *et al.* 1986]. Alternatively, there might be a lack of IgG to a particular venom component: patients vary in the venom antigens to which they make IgE or IgG antibodies [Kemeny *et al.* 1983] although in this particular study failure of IgG to confer protection was not associated with lack of IgG to any known antigen. Differences between successfully and unsuccessfully desensitized patients in the affinity of their specific IgG is another suggestion [Devey *et al.* 1989].

Recent work suggests that IgG responses in bee and wasp venom allergy are different, reflecting the different degree of exposure to stings. In a study of patients with systemic reactions to stings, wasp venom patients were found to present with low wasp venom IgG levels, while bee patients (most of whom have been stung frequently) present with significantly higher bee venom IgG levels [Ewan *et al.* 1993a]. In the wasp-allergic patients, specific IgG levels rose with VIT, whereas there was either no change or only a small further rise in specific IgG in the bee group. This difference between bee and wasp venom allergy has not been taken into account in earlier studies assessing the role of IgG in protection, and in many of these studies bee and wasp patients were considered as a single group and wasp patients predominated. This might lead to confounding in correlation analysis of clinical and IgG responses. Alternatively elevated specific IgG concentrations may relate to the degree of allergen exposure and be unrelated to the development or lack of development of tolerance to the allergen.

No correlation has been found between the level of venom-specific IgG and the severity of the last systemic reaction [Ewan *et al.* 1993a] or between level of venom-specific IgG and the outcome of sting challenge, in either untreated patients [Blaauw & Smithuis 1985; Kampelmacher & van der Zwan 1987] or patients treated by VIT [Müller *et al.* 1989]. If protection from stings is indeed IgG-mediated, then the relevant immune response must be more complex, and not adequately reflected by measurement of total venom-specific IgG.

The phenomenon of rush induction of immunotherapy also raises questions about the protective role of IgG. In rush induction of VIT, the normal (3-month) initial course of AIT is condensed into 1-5 days [Nataf *et al.* 1984], and a highly sensitive patient with serious generalized reactions to stings can be rendered unresponsive to venom (i.e. able to tolerate a dose of venom equivalent to about two stings) in as little as 6 hours. Not surprisingly, there is no change in specific IgG or IgE levels during rush induction [Ewan *et al.* 1993b] but specific IgG levels begin to rise 2-3 weeks later. IgG therefore appears to have no

role in the mechanism of rush AIT, which may involve pharmacological rather than immunological processes. It has been argued that rush induction may work by depleting mast cell mediators (repeatedly but subclinically after incremental doses of venom) so that the patient is incapable of responding to larger doses. Against this theory, however, patients can develop anaphylactic reactions to the highest dose despite having had no reaction up to and including the penultimate dose, equivalent to 1-66 stings [Ewan *et al.* 1993b].

Summary

In summary, the clinical and *in vitro* correlates of successful immunotherapy are as follows:

Early

- increase in allergen-specific IgE
- increase of allergen-specific IgG and IgG4 over 3 months

Late

- attenuation of seasonal rise in allergen-specific IgE
- gradual decline in allergen-specific IgE to pre-treatment values
- gradual increase of allergen-specific IgG4 over 12 months
- attenuation of early- and late-phase asthmatic responses
- attenuation of early- and late-phase responses in the skin and nose
- attenuation of allergen-induced eosinophil and CD4⁺ T-cell recruitment
- shift of cytokine expression at cutaneous allergen-exposed sites towards a T_H1-like pattern
- increased expression of CD25 (IL-2 receptor and HLA-DR) at cutaneous allergen-challenged sites.

CHAPTER 6

Allergen standardization

Introduction

The need for standardization of allergen extracts has been recognized since the early days of allergen immunotherapy. Early attempts to achieve consistency relied on crude weight:volume ratios or estimation of protein nitrogen content. Failure to achieve consistent batch potency led to problems in both diagnostic and therapeutic use. Very rapidly, it became clear that accurate diagnosis of allergy and the safe treatment of patients by AIT could only occur if allergen extracts with consistent potency and composition were used.

Allergen extracts

Allergen extracts are complex mixtures of proteins. The precise number of components varies depending on the allergen source and on the extraction process. Multiple antigens have been identified in animal dander extracts (10-20 separate antigens), dust mite extracts (20-40 antigens) and pollen extracts (20-50 antigens) [Lowenstein 1983; Lind *et al.* 1984; Lowenstein & Marsh 1981]. Crossed immunoelectrophoresis or immunoblot techniques can be used to determine which components of an extract bind IgE. Any antigen which stimulates an IgE response and binds IgE is termed an *allergen*, while antigens which bind IgE from more than 50% of patients are usually regarded as *major allergens*. Potentially, all the antigenic components recognized by animal antisera may be allergens in humans. However, in practice, between 25% and 50% of the proteins in any allergen extract are allergens, and one to three proteins will be major allergens [Lowenstein *et al.* 1987].

Protein extraction is a simple technique, but it is much more complex to derive extracts which contain all relevant allergenic determinants and which have consistent composition from batch to batch. The final composition of an allergen extract depends on many factors, including the nature of the source material; how it is handled prior to extraction; the consistency of the extraction process; degradation during extraction; depletion of some components during purification (by dialysis, ultrafiltration, etc.); degradation in storage (especially important if allergens are mixed) [Dreborg 1992]. Each of these factors can affect both the relative composition of the final extract and the allergenicity of the individual components.

Goals of allergen standardization

For diagnostic testing, the aim is to produce an extract which will elicit positive skin tests in all subjects with

clinical hypersensitivity to that allergen. Ideally, skin-test extracts should contain all potentially allergenic components and all IgE-binding epitopes should be intact. Similar considerations apply to allergen extracts used for serological (e.g. RAST) testing. For therapeutic use, the goal is to produce an extract which is clinically efficacious and has a low incidence of adverse reactions. Despite many years of investigation, the precise mechanisms of successful AIT are still unresolved (see Chapter 5). In practice, purified extracts have been shown to have some degree of clinical efficacy even though they contain an incomplete or restricted range of components [Fwan *et al.* 1988a]. Adverse reactions to vaccines are largely due to recognition of allergenic determinants by cell-bound IgE, but reactions can also occur to the non-allergenic protein components. Chemically modified allergens can have reduced IgE-binding properties but still retain clinical efficacy and immune potency [Bousquet *et al.* 1989]. Whether purified or standardized, such modified or incomplete extracts would be inappropriate as diagnostic agents.

Allergen standardization

Simple weight:volume ratios and protein nitrogen values are poor indicators of allergen content [Baer *et al.* 1970]. Commercial house dust mite extracts with identical protein nitrogen content can vary by several thousand-fold in their content of a major house dust mite allergen (*Der p 1*) [Chapman *et al.* 1987]. Protein nitrogen values are particularly vulnerable to variability in the efficiency of extraction processes and offer no guarantee of the level of allergenicity [Baer *et al.* 1970]. Failure to understand this led to a significant number of adverse reactions when physicians changed over from non-standardized to standardized extracts [Lockey *et al.* 1987; CSM 1986], since highly purified and standardized extracts could have identical protein nitrogen content to old unstandardized extracts, but were sometimes found to be 100 to 10,000 times more potent in biological terms. Standardization of allergen extracts requires development of specific allergen standards which can then be compared with new batches in assays of potency and composition. Allergen extracts can be standardized in two different ways: assays of potency and assays of individual allergenic components.

Standardization by assays of potency

Allergenic potency can be measured *in vivo* by quantitative skin testing or *in vitro* by RAST inhibition, EI ISA inhibition or basophil histamine release assays [Dreborg

& Frew 1993]. All these methods rely on the ability of human IgE to bind the allergen and depend on the qualitative and quantitative IgE composition of the sera from the selected patients: results will therefore vary depending on patient selection criteria as well as the assay methodology. When extracts are similar in composition, it is fairly straightforward to establish their relative potencies. When extracts differ substantially in composition, it can be difficult to obtain parallel dose-response curves, and this limits the validity of comparisons of potency. Within one company's products, composition is usually quite consistent and batch-to-batch consistency can be assured by comparison with an in-house standard using RAST inhibition [Dreborg & Frew 1993]. Currently, standardization by skin tests is usually performed only for the initial batch as RAST inhibition is reproducible and much less time-consuming.

It should be noted that since allergic individuals vary in the intensity and pattern of their IgE response, standardized extracts from different sources will not necessarily induce identical sized wheals in *individual* allergic subjects, even though these extracts will give similar average skin-test responses when tested in *groups* of allergic subjects. This is especially true for extracts that contain several different allergenic components.

Biological standardization

There is general agreement regarding the need to standardize the potency of allergen extracts and to minimize batch-to-batch variation. There is, however, some controversy regarding the best way of expressing the potency of extracts of different allergens. In the past each manufacturer devised their own system of units. In recent years it has been argued that the potency of allergen extracts should be expressed in terms of their ability to induce skin-test responses in a group of subjects sensitive to that allergen [Turkeltaub 1989; Dreborg 1989a]. In other words, animal dander extracts, pollen extracts, dust extracts, etc. should all be labelled with the same system of units, and an extract of 100,000 biologically relevant units per millilitre should elicit the same sized reaction in populations of patients who are respectively sensitive to each of the allergens under test. This concept is called 'biological standardization'.

There are two main methods of biological standardization: in the Nordic method, skin-prick tests are performed on selected patients referred to a University Hospital outpatient allergy clinic and the allergen potency is related to the wheal size induced by histamine [Dreborg 1989b]. In the American method, intracutaneous skin tests are performed on a subgroup of available patients who are highly sensitive to the test allergen. Extracts are compared

in terms of their ability to induce a mean erythema diameter sum of 50 mm, and are not related to histamine [Turkeltaub 1989]. Due to their different selection criteria and technical requirements, these methods give similar, but not identical relative potencies. Comparison between the two systems is further complicated by the fact that European extracts are usually dialysed to remove low molecular weight substances, whereas American extracts are not [Dreborg & Frew 1993]. Biological standardization provides an approximate equivalence of extracts from the same or different allergen source in terms of their average reaction size. This approach confers enhanced safety and efficacy as the units will predict *in vivo* allergenicity. However, biological standardization does not address either the relative composition of the extracts or the efficacy of extracts in therapeutic use. Extracts with identical biological activity in skin tests can have quite different compositions, so biological standardization is not a guarantee of batch-to-batch consistency, nor does it eliminate variation between the products of different manufacturers.

Biological standardization has several theoretical advantages, but recent events in the U.S.A. have demonstrated an unforeseen problem. Following their introduction into clinical practice, several biologically standardized cat fur extracts labelled as 100,000 allergy units/ml (AU/ml) were shown to have a true activity closer to 10,000 AU/ml. Regulatory authorities and clinicians are now extremely concerned about this inconsistency. The FDA has proposed relabelling all extracts to preserve the definition of the AU while some manufacturers and clinicians believe that this relabelling may lead to dosage errors.

Standardization by determination of major allergen content

The major allergen content (MAC) of an extract can be determined by a variety of methods using polyclonal or monoclonal antibodies. These methods depend on appropriate selection of the major allergen but are independent of variation in patients' sera and patient selection criteria [Platts-Mills & Chapman 1991].

A number of International Standards (IS) have been prepared under the auspices of the IUIS [WHO 1978; Helm *et al.* 1984; Ford *et al.* 1985; Norman 1988; Nedergaard-Larsen *et al.* 1988]. These can be used as references to determine content of individual allergen components, but are not licensed for use *in vivo* [Yunginger *et al.* 1988]. Because the composition of the IS and a new extract may differ, the strength in IU/ml of a new extract can vary depending on which component is used for comparison. This is relevant for extracts which contain more than one major allergen (i.e. the majority of

extracts currently available for diagnostic and therapeutic use). It has been suggested that determination of MAC would be a better means of calibrating allergen extracts [Platts-Mills & Chapman 1991], but there is a potential drawback in that MAC determination does not take into account the influence of other major or minor allergens which may be important in causing symptoms in some people. If these other allergens are omitted from the final preparation, the extract may be ineffective in treatment and give false negatives in diagnostic testing; if other allergens are present in excess, standardization by MAC could underestimate biological potency, and lead to an excessive rate of adverse reactions.

In limited analyses, MAC has been shown to vary up to four-fold between biologically standardized pollen extracts [Dreborg & Einarsson 1992; Lowenstein *et al.* 1991], and by several thousand-fold in commercial dust mite and dog dander extracts [Chapman *et al.* 1987; Schou *et al.* 1991]. Thus MAC determination is not a direct replacement for *in vitro* standardization of extract potency. However, composite measurement of several major allergens has been used successfully for ragweed and cat extracts in the U.S.A.

Current labelling of commercial extracts

Although several manufacturers have adopted biological standardization and the Nordic BU for labelling diagnostic materials, there is less agreement about the optimum unit to be used for therapeutic extracts. Some authorities consider that therapeutic extracts should also be standardized by their biological potency, while others believe that there should be a separate system of 'therapeutic units', based on the top maintenance dose (e.g. all maintenance doses would be defined arbitrarily as 10,000 TU (treatment units), with lower concentrations and induction doses expressed as fractions of the maintenance dose. The major drawback to BS methods is that while unmodified extracts can be readily standardized by potency, subsequent modifications may render the extract hypo-allergenic without affecting efficacy to the same extent. Assays of MAC may be similarly affected by chemical modification of epitopes. At present most manufacturers use company-specific units to label their therapeutic extracts, and discussions about the introduction of a single internationally accepted therapeutic unit are ongoing.

Mixtures of allergens

In the past, patients with multiple sensitivities were often treated with mixtures of allergen extracts. These mixtures

were prepared sometimes commercially and at other times by the allergist as an individualized mixture. In general the efficacy of such mixtures is less than the efficacy of single allergen extracts in mono-allergic patients. In addition, mixing allergens can lead to progressive degradation of one or more of the allergenic components with unpredictable consequences to the composition and safety of the mixture [Dreborg 1992].

Modified extracts and peptide epitopes

Most efforts in allergen standardization have been directed towards conventional allergenic extracts, where manufacturers attempt to reproduce extracts of high allergenicity as consistently as possible in terms of the balance and content of the relevant allergenic components, and the overall allergenic potency. Such attributes are suitable for extracts used in diagnosis, but are not necessarily ideal for therapeutic preparations, which should have minimal side-effects (i.e. generalized allergic reactions, toxicity or large local reactions). Ideally, therapeutic materials should have markedly reduced allergenic activity (relative to the native extract), while retaining (or improving) therapeutic efficacy. The simplest approach has been to prepare alum-precipitated extracts, in which the macromolecular components of the extract are adsorbed onto alumina gel, which serves as an adjuvant to enhance the antibody response. Other adjuvants with similar properties have also been used. The adsorbed allergens are released slowly and thus their effect is spread over a longer time, reducing the likelihood of generalized allergic reactions. In general, the approach to standardizing these extracts has been to analyse the allergen extract before alum-adsorption, and then to check for low allergenicity of the fluid phase (e.g. using RAST inhibition).

Chemically modified allergens (allergoids) [Marsh *et al.* 1970, 1981] with greatly reduced allergenicity are now in widespread use in Europe; in most cases these extracts also incorporate an adjuvant such as alumina gel. The native extracts used to prepare allergoids are first standardized by RAST inhibition and/or analysis of allergen content and are then modified under highly controlled conditions that are designed to assure lot-to-lot consistency [Maasch & Marsh 1987]. The resultant allergoids are analysed for residual allergenicity by RAST inhibition; consistent reduction of allergenic activity is important to ensure product safety, since allergoids are routinely used in more aggressive dosage regimes than conventional allergen extracts. Further standardization of the allergoid may include analysis of the molecular weight profile by gel filtration HPLC.

In the case of peptide allergen-epitope products currently under development, no specified standardization procedure has yet been recommended. Should any of these products prove to be clinically efficacious, standardization should be relatively straightforward since they are likely to be low molecular weight compounds that can readily be analysed by standard peptide analytical methodology such as reverse-phase HPLC.

Future trends in allergen research and standardization

Since 1986 there has been rapid growth in the volume of information concerning all types of allergens. The expansion of allergen research has been facilitated by technological improvements in protein and DNA sequencing. A large number of major allergens have now been described and many have been sequenced at the protein and/or cDNA levels [Chua *et al.* 1988; Ansari *et al.* 1989a; Ansari *et al.* 1989b; Breiteneder *et al.* 1989; Silvanovich *et al.* 1991; Griffith *et al.* 1992]. Progress has also been made in the analysis of allergenic epitopes using cloned human T-cells [Perez *et al.* 1990; Rogers *et al.* 1991; O'Hehir *et al.* 1987; O'Hehir *et al.* 1988; Huang *et al.* 1991]. These technical improvements have made it easier to determine major and minor allergen content of allergen extracts and may in future allow manufacturers greater control in preparation of extracts with defined composition.

In the long term, improved understanding of the

mechanisms of successful AIT should allow the development of modified or semi-synthetic vaccines which retain the T-cell epitopes necessary to induce tolerance, but no longer carry the IgE-binding epitopes responsible for inducing adverse reactions.

Conclusions

The primary goal of manufacturers, clinicians and regulatory authorities alike is to ensure the safe and effective diagnosis and treatment of clinical allergy. For the present, this goal is best achieved by four measures:

1. Skin testing and AIT should be performed with biologically standardized extracts, the potency of which has been determined by *in vivo* methods in relevant patient groups.
2. To minimize the risk of confusion and dosage error, extracts should be clearly labelled, in a single system of units.
3. To minimize degradation in storage and consequent loss of potency, allergen extracts should be stored appropriately and should not be mixed.
4. Unless there are good reasons for doing otherwise, clinicians should not switch from the products of one company to those of another during a course of treatment.

CHAPTER 7

Methods of administration

This chapter contains an overview of the practice of immunotherapy. More detailed information on these aspects of injection immunotherapy can be found in the EAACI position paper on immunotherapy [Malling & Weeke 1993].

Selection of preparations

There are three main types of extracts: aqueous, depot and modified preparations. Aqueous allergen preparations are more easily standardized. Their main disadvantage is that, because of their rapid absorption, they have a much greater frequency of systemic side-effects than depot preparations [Ewan 1989]. Aqueous extracts are widely used in North America but in Europe their use is largely restricted to venom immunotherapy, and for rush or clustered AIT schedules.

In depot preparations, the allergen is bound to a carrier, e.g. absorbed onto aluminium hydroxide, from which it is slowly released. Depot extracts produce fewer adverse reactions than aqueous extracts [Ewan *et al.* 1988b; Malling *et al.* 1992]. They are widely used in Europe, particularly for inhaled allergens. Standardization of depot preparations is more difficult than for aqueous preparations [see Chapter 6].

Chemically modified preparations include methoxy-polyethylene glycol (mPEG) modified extracts and allergoids (formaldehyde or glutaraldehyde modified extracts). The rationale of modifying extracts is to reduce allergenicity (ability to induce IgE-mediated reactions) but retain immunogenicity (ability to stimulate the appropriate protective immune response) [Dreborg 1989a]. However, despite some successful clinical trials [Bousquet *et al.* 1988, 1989, 1990a], these extracts have not yet established themselves in routine clinical use.

It is generally believed that better purification and standardization of allergen extracts will reduce the risks of adverse reaction without reducing efficacy, although conclusive evidence to support this view has been hard to obtain. The use of depot or chemically modified allergen extracts may substantially improve the benefit:risk ratio by degrading IgE-binding epitopes, while retaining the antigenic properties relevant to desensitization. In the future, novel vaccines consisting of immunodominant T-cell peptide epitopes may become available as an alternative to conventional extracts [Soloway *et al.* 1991; Rothbard & Gefter 1991]. Such preparations would again be immunogenic but not allergenic since the IgE-binding epitopes would not be present.

The use of whole-body extracts of stinging insects,

allergen extracts prepared from foods, feathers, synthetic materials, bacterial extracts, gums and glues, enzymes or occupational allergens cannot be justified on scientific grounds. These vaccines are either unstandardized or of unproven efficacy. The use of vaccines prepared from multiple allergens is not recommended as the individual components can adversely affect each other and evidence for the efficacy of multiple allergen AIT is lacking.

Dose schedules

Parenteral route (subcutaneous injections)

1. CONVENTIONAL REGIMES

Various regimes are used, which follow a general scheme summarized below.

Initial or induction course. Injections are given weekly or twice weekly, starting with a very low dose of allergen and gradually increasing to reach the maintenance dose after about 3 months. The lower doses are sometimes given in two or three divided doses, at half-hour intervals.

Maintenance treatment. The maintenance dose is repeated, usually monthly, for a variable period. Commonly maintenance treatment is given for 3 years but this duration is arbitrary, and current trends are towards longer periods of maintenance therapy.

Choosing a maintenance dose. This partly depends on the allergen extract, but in general efficacy seems to be related to the maximum dose that can be tolerated. This means that there is often a narrow 'window' between achieving efficacy and inducing unacceptable side-effects. Many allergists, especially in North America, 'push' the dose of allergen until they reach a dose which induces large local reactions. This practice cannot be wholeheartedly recommended, but it does emphasize a fundamental difficulty in practising allergen immunotherapy successfully, since apparent improvement with low doses of allergen probably represents no more than a placebo effect. For venoms, the maximum dose is usually 100 µg of purified material. For comparability between different regimens, it is important that the potency of allergen extracts is expressed in terms of their biological activity. Many older preparations are still widely used but are uncharacterized and unstandardized in terms of biological activity.

Seasonal versus year-round administration. In the past, pollen AIT was usually administered in the 3 months

before the onset of the pollen season. However, it is now usual to give monthly pollen AII throughout the year, and in this way a higher cumulative dose can be achieved. Induction courses should always be started out of season in order to minimize the risk of adverse systemic reactions – pollen sensitivity is increased due to natural grass pollen exposure in the pollen season.

2. RUSH SCHEDULES

Conventional regimes are very time-consuming for patients and medical staff, and a number of shortened regimes have been studied. In rush induction, the initial course is condensed into a very short period, usually a few days. Patients need to be admitted to hospital and the incidence of adverse reactions is significantly greater than for conventional regimes [Hejjaoui *et al.* 1992]. For venom AII, induction can be achieved in one day (ultra-rush); this regime is better tolerated for wasp venom than bee venom [Ewan *et al.* 1992b]. There are also cluster or semi-rush regimes, in which patients attend at weekly intervals and receive several injections at each visit, spaced out over the day. In this way, the maintenance dose can be reached in about 4 weeks.

Other forms of specific immunotherapy

Over the years, a number of investigators have tried to desensitize allergic patients by the oral or inhaled routes. Although some successes have been claimed [Scadding & Brostoff 1986; Taudorf *et al.* 1987], these remain controversial forms of therapy, which should be regarded as experimental for the time being. Studies showing benefit have usually involved administration of very high doses of allergen in enteric-coated tablets. The ideal dose is not known, nor the frequency of administration. The doses used have been 200–4000 times higher than with conventional subcutaneous AII. Problems in defining the dose of allergen and understanding the mechanism of action of oral AII include variable degradation of allergen by gastrointestinal enzymes, unknown or variable absorption of allergen, and the uncertain short- and long-term results of stimulating the local immune response in the gut mucosa. Oral immunotherapy has a low incidence of adverse effects but further properly controlled studies will be needed to evaluate efficacy.

It is important not to confuse AII with certain unconventional and unproven forms of 'allergy treatment' which also involve the administration of putative allergens by various different routes. Neutralization therapy, an extension of the provocation-neutralization testing procedure used by clinical ecologists, involves treatment by intracutaneous, subcutaneous or sublingual routes (usually self-administered). Unstandardized mixtures of

various substances are used to treat so-called environmental illness or 'total allergy syndrome' – disease entities which are not recognized by conventional medicine.

Enzyme potentiated desensitization (EPD) is another form of unproven therapy and consists of injections of minute doses of allergens and other substances, mixed with the enzyme beta-glucuronidase. EPD is claimed to be of benefit in a wide range of allergic and non-allergic diseases but these claims are not supported by convincing trials using objective end-points [RCP 1992].

Administration and safety monitoring

It is important that staff (doctors and nurses) are trained to administer allergens correctly, to identify early signs of adverse reactions and to institute appropriate treatments for side-effects. We recommend that injections should be given in a clinic, normally in hospital, where facilities for the treatment of anaphylaxis and general resuscitation equipment are readily available. Ideally, the same allergist or his/her staff should administer the AII injections until the maintenance dose is reached. Maintenance therapy may then be continued by the allergist or by a physician in another hospital (closer to the patient's home) provided that there is very close collaboration between the physician treating the patient and the allergist. The involvement of other physicians is suboptimal but is sometimes necessary because of the relatively small number of allergists in the U.K. – otherwise patients would have to make frequent long journeys, rendering AII impracticable for many patients who might benefit from AII. Ideally such physicians should only take over management once the patient is well-established on an initial course without a history of serious adverse reactions.

We recommend that all patients receiving AII should be educated in the likely side-effects and the way that these should be managed. Patient knowledge should be reinforced and checked regularly and patients should be encouraged to seek medical attention if they develop delayed side-effects.

Before each injection

At each clinic visit, patients should be reviewed by a doctor with experience in AII, who should document any recent infection, intercurrent illness, current medication, recent exacerbations of allergies including asthma, and any recent exposure to allergen, e.g. stings or exposure to large quantities of house dust or pollen. The patient should be asked if there was any delayed reaction to the last allergen injection, and details of its nature, timing and treatment should be recorded. If any of these risk factors are present, the doctor must consider either omitting the injection or modifying the dose to be given (see Table 11).

Table 11. Indications for adjustment of dosage

Event	Action
Systemic reaction to previous injection	Reduce next dose by two to four dose steps, depending on the severity of reaction. For life-threatening reactions, review indications for AII
Delayed large local reactions > 8 cm diameter	No increment or reduce dose
Information from history taken before each injection	
Recent respiratory infection (in last week)	Reduce dose or omit†
Exacerbation of asthma*	Reduce dose or omit†
Asymptomatic fall in usual peak flow rate	Reduce dose or omit†
Exacerbation of other allergic disease	Reduce dose or omit†
Increased exposure to allergen e.g. insect sting, pollen season, animal contact	Reduce dose or omit†
Intercurrent illness	No increment or reduce or omit dose†
Increased interval between injections	No increment or reduce dose
Changing to a new batch of allergen	Reduce dose to previous dose on induction schedule or to half dose on maintenance schedule

* NB: AII is not recommended in asthmatic patients in the U.K.

† The magnitude of the dose reduction depends on the severity of the adverse reaction. Safety is the principal consideration – if in doubt, reduce or omit the dose.

In the U.K., AII is not currently recommended for patients with asthma. However, peak expiratory flow rate should be measured before injection in all patients with a history of asthma, however mild, even if symptoms have been present only in the past or only in particular seasons. Prior to authorizing the injection, the physician should check that all drugs likely to be needed to treat reactions are immediately available.

Pre-medication (prophylactic drugs). The routine administration of 'prophylactic' oral antihistamines is not recommended, since this may mask minor systemic reactions, and possibly lead to a more serious reaction on a subsequent injection, which might have been prevented modified by anticipation and modification of the dose schedule. However, patients with repeated very large local reactions may be helped by pre-treatment with oral antihistamines and non-steroidal anti-inflammatory drugs.

Administration of allergen injection

The dosage schedule should be kept in each patient's case notes, together with a record of each dose given and the time and site of each injection. It is essential to check the preparation, batch, strength and dose with another member of team. One-millilitre graduated syringes should be used for accuracy and the injection should be given

slowly subcutaneously, first drawing back to avoid intravenous injection. The recommended site for injection is the lateral aspect of the upper arm.

After injection

Patients are asked to alert the doctor/nurse at the onset of the slightest adverse symptom. This is important as systemic reactions are usually easy to reverse, provided that they are treated promptly. Patients should be checked regularly, and asked about specific symptoms. The injection site should be monitored for signs of any local reaction. At present in the U.K., in order to comply with recommendations from the Committee on Safety of Medicine [1986], patients must remain under medical supervision for 2 hours after the injection. (See 'Prevention of adverse reactions' below and Chapter 8 for further details.)

After leaving hospital

Patients must be educated regarding possible reactions, including delayed local or urticarial reactions, and what treatment may be needed. It is important that there is good communication between the specialist and the general practitioner who may be called to treat a delayed reaction. All AII patients with a history of asthma should be instructed to carry a beta-2 agonist inhaler. Patients

who have previously developed large delayed local reactions should be given a supply of antihistamine tablets and all AII patients should be given a telephone number for rapid access to their specialist.

Adjustment of dosage

The manufacturer's dose schedule for each extract should be regarded only as a guideline, and frequently the schedule will have to be modified in the light of events occurring during the course of treatment. These decisions are difficult, unless the doctor is experienced in immunotherapy. Rigid or inappropriate adherence to the dose schedule carries the risk of inducing serious allergic reactions. Indications for dosage adjustment are summarized in Table 11.

Anti-allergic drugs

All anti-allergic drugs should be continued when immunotherapy is commenced, but these drugs can be reduced as evidence of clinical improvement appears.

Prevention of adverse reactions

Dosage and timing. A proportion of side-effects and deaths from AII have been attributed to errors in dosage and timing. Care should therefore be taken to ensure that patients receive the correct dose of the correct allergen at the correct time. As with other drugs, dosage instructions should be checked carefully by two people and injections given in an unhurried manner. However, it is noteworthy that adverse reactions can be induced by low as well as high doses of allergen [Thompson *et al.* 1989]. In patients with high sensitivity it is advisable to commence the course of treatment at a reduced starting dose.

Patient selection. Patients should be excluded from immunotherapy if they have risk factors that render them more likely to experience side-effects, less able to recover from anaphylaxis, or less able to respond to treatment for adverse reactions. According to the 1992 EAACI position paper [Malling & Weeke 1993], immunotherapy is absolutely contraindicated in the following groups of patients:

- Those with concurrent cardiac, immunopathological or malignant disease.
- Those who are unable to respond normally to adrenaline or other beta-agonists, e.g. patients receiving monoamine oxidase inhibitors or beta-blockers. NB: beta-blockers do not appear to increase the incidence of adverse reactions but hinder the treatment of anaphylaxis or asthma if they do develop [Executive Committee AAA&I 1989; Hepner *et al.* 1990].

- Patients who are, for whatever reason, considered insufficiently willing or motivated to attend regularly or complete the course of treatment.

Immunotherapy is not currently recommended for:

- Children under 5 years of age (guideline, no hard evidence).
- Pregnant women (in special circumstances it may be appropriate to continue VIT maintenance but a course of AII should not be started during pregnancy).
- Patients with a history of chronic perennial asthma, who have an FEV₁ or PEF consistently less than 85% predicted.
- Patients with severe dermatitis.

Observation after injection. Patients must be watched carefully, particularly during the first 10 minutes after allergen injection, since most serious reactions will occur early. An important general principle is to treat anaphylaxis quickly, as this increases the likelihood of prompt resolution. At present patients must be detained for 2 hours to comply with the 1986 CSM recommendation [CSM 1986]. A review of all available recent U.K. data indicates that reactions commencing after 30 minutes are not life-threatening and rarely require specific intervention (see Chapter 8 on adverse reactions).

Treatment of adverse reactions

All physicians who administer parenteral drugs should know and practise an 'anaphylaxis drill'. This drill should be written down as a standard procedure and should be known by all staff involved in the treatment area. Prompt treatment is the single most important factor in the successful treatment of serious systemic side-effects.

Local side-effects. Some degree of immediate local swelling occurs in almost all patients, and requires either no treatment or oral antihistamines. More severe local reactions are usually of late onset and may be helped by oral antihistamines with or without the addition of a non-steroidal anti-inflammatory drug. These drugs are more effective when given prior to injection, and should be used prophylactically in patients who experience repeated large local reactions.

Systemic side-effects.

Mild systemic reactions. Rhinitis, erythema, urticaria, or mild localized angioedema not involving the respiratory tract usually only requires treatment with antihistamines.

Moderate systemic reactions. Treatment will depend on the nature and severity of the reaction. Mild asthma

may be treated with inhaled beta-2 agonists. Mild angioedema, nausea, light-headedness or sensations of tightness in the throat without respiratory difficulty may require hydrocortisone, intramuscular or oral antihistamines.

Severe systemic reactions (laryngeal oedema and respiratory distress). Severe cases are treated as for anaphylaxis. Prompt treatment with adrenaline is the single most important measure. Inhaled adrenaline (up to 20 puffs of a Medihaler-epi) may be given additionally, particularly for upper airway obstruction.

Treatment of generalized anaphylaxis. The suggested management is to give 0.5 mg adrenaline immediately by subcutaneous or intramuscular route, to be repeated within 5 minutes if there is no response. Oxygen should be administered and an intravenous cannula inserted. Intra-

muscular corticosteroids and antihistamines should then be given. The blood pressure should be checked frequently and if hypotension is present, plasma expanders should be given. A tourniquet should be applied to the limb above the allergen injection site, and further local adrenaline (0.3 mg) should be given to the injection site to promote vasoconstriction and delay further absorption of allergen. Detailed advice on the treatment of anaphylaxis can be found elsewhere [e.g. BNF, Ilesof 1989, Bochner 1991, Fisher 1992]. The most important principle is that adrenaline must always be given and should be repeated if the patient fails to improve. Other drugs can then be added as required (e.g. glucocorticoids, anti-histamines, nebulized beta-2 agonists, oxygen and intravenous fluids).

CHAPTER 8

Adverse reactions to allergen immunotherapy

Clinical nature of side-effects

Allergen-injection immunotherapy can induce a variety of local and systemic side-effects. Such adverse reactions can be further classified as either immediate (occurring within minutes) or delayed (occurring up to 12 hours after injection). Local immediate reactions are IgE mast cell-mediated and present as weals and erythema at the skin injection site, usually within 30 minutes or so after the injection. These reactions are relatively common: on their own they are not serious, but they may alert the physician to an impending immediate systemic reaction. Local delayed reactions occur as swelling and erythema at the injection site within a few hours of injection. They may be but are not always preceded by immediate local reactions, are an inconvenience to the patient, but are not a serious side-effect and do not predict the development of systemic side-effects. Systemic reactions (defined as reactions remote to the injection site) are usually rapid in onset (i.e. within a few minutes) and may be either organ-specific (e.g. rhinitis, asthma, irritation of the throat) or generalized (e.g. skin reactions such as urticaria, itching, flushing, angioedema, etc. or, most seriously, generalized anaphylaxis). Generalized anaphylaxis can be fatal; it is characterized clinically by hypotension, laryngeal oedema with dyspnoea and cyanosis, bronchospasm, nausea, vomiting and diarrhoea. However, presentation can vary, with either cardiovascular or respiratory symptoms dominating the clinical picture. Systemic delayed reactions are much less frequent than systemic immediate reactions and present as urticaria, rhinitis or excessive tiredness following injection. In patients with pre-existing asthma there may also be exacerbation of asthma. When bronchospasm occurs as a delayed reaction, it is never accompanied by other features of generalized anaphylaxis (i.e. hypotension, laryngospasm, nausea, vomiting and diarrhoea do not occur as delayed reactions).

Prevalence of adverse reactions to AII

In the 29-year period from 1957 to 1986 the CSM received 357 reports of serious systemic adverse reactions (anaphylaxis or bronchospasm) to desensitizing agents in the U.K. [Committee on the Safety of Medicines 1986]: 53% of these cases involved anaphylaxis and 47% bronchospasm; 93% of these reactions occurred during the induction phase of treatment. The median time from injection to onset of reaction was 10 minutes, with 76% commencing within 30 minutes of injection; 15% of reported reactions started between 30 and 120 minutes

after injection, and 8% between 2 and 36 hours after treatment. Separate figures for anaphylaxis and bronchospasm in this data set are not available [Rawlins *et al.* 1987]. During the same period, a total of 1,459,273 courses of treatment were administered in the U.K., giving a rate of one reported case of severe adverse reaction per 4088 courses. The data available to the CSM indicated that, depending on the allergen preparation used, the incidence of anaphylaxis or bronchospasm ranged from 1 in 63 to 1 in 32,495 treatment courses. However, there was no statistical evidence to suggest that any particular allergen preparation was more or less likely than another to induce adverse reactions.

Since the CSM report, several U.K. centres have set out to accumulate new data on the pattern and prevalence of systemic adverse reactions to AII. A survey of BSACI members in February 1992 revealed that half of the U.K. physician members of the society (27/60) were currently treating patients by AII, and 10 were prospectively collecting data on adverse reactions.

Detailed information was made available to the Working Party by seven of these clinicians (Table 12). Dr Stokes (Brook Hospital Allergy Clinic) has treated 41 patients with grass pollen extracts, two with wasp venom and one with house dust mite extract. Blood pressure and pulse were carefully monitored and no systemic reactions were detected from 549 injections.

Dr Frankland (London) has treated 164 patients with 1364 injections since 1986. Three systemic reactions were observed from these injections: two of these systemic reactions were minor urticarial rashes in visiting American patients who had had a longer than usual interval between injections. The third systemic reaction was also relatively mild, an asthmatic episode occurring 5 hours after injection and not even requiring ventolin in a patient receiving AII for allergic asthma, who received an abnormally high initial induction dose (chosen in order to accelerate induction before the start of the pollen season).

Drs Wilson and Dixon (Liverpool) have given 919 courses of grass pollen AII (initially with Allpyral and subsequently with Alutard and Allergovit preparations) since 1986. In total this represents 8102 injections which induced local reactions on 125 occasions, 166 minor systemic reactions (urticaria, rhinitis and mild wheeze) and 20 severe systemic reactions requiring treatment. All the severe systemic reactions began within 30 minutes of injection and responded rapidly to treatment. None required admission to hospital. Two episodes of mild wheeze began between 30 and 60 minutes while the other

164 mild/moderate reactions also started within 30 minutes.

Dr Durham at the Royal Brompton Hospital Allergy Clinic has followed 50 patients treated with grass pollen AIT and 11 patients with hymenoptera AIT. These patients had 39 large local reactions, five delayed mild systemic reactions and seven immediate systemic reactions from a total of 3167 injections (1387 induction and 1785 maintenance injections). The systemic reactions occurred exclusively during the induction phase of AIT. The seven immediate systemic reactions comprised five cases of itching and flushing, one case of mild 'chest tightness' and one case of hypotension and bradycardia. All seven episodes commenced within 10 minutes of injection and responded rapidly to administration of subcutaneous adrenaline.

In a clinical trial of an aqueous *D. pteronyssinus* extract Dr Ewan (Cambridge) reported a high rate of systemic reactions [126 systemic reactions in 541 injections (23%) in 27 patients]. Only ten of these 126 (8%) reactions were serious and required treatment with adrenaline; all ten of these severe systemic reactions began within a few minutes of injection. This study concluded that the aqueous preparation was unsuitable for clinical use [Ewan *et al.* 1988b]. Depot preparations of house dust mite extracts were equally efficacious and did not induce any serious systemic reactions. Sixty minor systemic reactions occurred in the 916 injections (6%) given to the 40 patients in two depot studies [McHugh *et al.* 1990]. These minor reactions would mostly have been overlooked if this had not been a prospective study. In the depot trial, mild bronchospasm was the most frequent symptom, occurring in 18/23 (78%) immediate reactions and in 5/17 (29%) delayed minor systemic reactions (onset after >2 hours), but these asthmatic reactions occurred almost exclusively in subjects who were already known to be asthmatic [Ewan *et al.* 1988a; Ewan *et al.* 1988b].

Professor Lee (Guy's Hospital) provided data on 2363 VIT injections given between March 1986 and March 1992. A total of 61 systemic reactions were recorded in this period: 79% (48/61) of these systemic reactions occurred during the induction phase and 21% (13/61) during maintenance treatment. Most of the systemic reactions (47/61) occurred in the first half-hour after injection, with 7/61 becoming apparent within the second half-hour (30–60 minutes). One patient developed mild chest discomfort after 70 minutes. The remaining six systemic reactions were also minor, occurring between 2 and 8 hours after injection and taking the form of rhinitis, itching, skin rashes, hoarseness or chest tightness.

Dr Ewan reported similar experiences with hymenoptera venom immunotherapy, with three anaphylactic

reactions in 727 injections given to 26 patients. All three of these reactions began within 20 minutes of injection. Three moderately severe systemic reactions occurred, requiring antihistamines but not adrenaline (onset 5.5 and 25 minutes after injection). Two episodes of extreme lethargy occurred for which parenteral treatment was given: these commenced 50 and 75 minutes after injection. Eighty minor immediate systemic reactions were recorded and there were 40 delayed reactions (all but two taking the form of mild lethargy without objective signs). Just one patient developed new adverse symptoms between 60 and 120 minutes, and these took the form of marked lethargy without any objective signs [Ewan & Stewart 1993].

Dr P. Fitzharris (St Mary's Hospital, London) provided information on 12 patients treated for hymenoptera sensitivity with either conventional or modified rush desensitization protocols. In over 300 clinic visits, representing approximately 600 injections, only one systemic reaction was observed. This was a mild subjective reaction 55 minutes after an induction injection; the patient reported a feeling of flushing accompanied by pallor but no change in pulse or blood pressure.

In addition to these U.K. centres, several European and North American centres have recently published their experience with systemic reactions induced by IT. The Montpellier group reported that the incidence of systemic side-effects varies according to dosage schedule, with 'rush immunotherapy' more likely to induce systemic reactions than conventional induction regimes [Hejjaoui *et al.* 1990]. This group has also provided detailed information on the timing of systemic reactions in 1152 mite-allergic and 176 pollen-allergic patients receiving IT. Both house dust mite and grass pollen AIT induced a similar pattern of systemic reactions, with a slight tendency for pollen-induced reactions to occur earlier than mite extract-induced reactions. Three-quarters of all cases of anaphylaxis started within 10 minutes of injection and none began after 20 minutes. Onset of bronchospasm peaked between 5 and 15 minutes, while episodes of urticaria mostly started between 10 and 20 minutes after injection. In none of their cases did bronchospasm or urticaria start more than 45 minutes after injection [Hejjaoui *et al.* 1990; Hejjaoui *et al.* 1992] (see Table 13).

The Copenhagen group recently presented their experience with 100 patients who received a total of 2823 injections in three different induction regimes [Malling & Bjornsten 1992]. Systemic reactions occurred with 5.3%–6.4% of injections, depending on the treatment regime. No cases of anaphylaxis occurred. Significant systemic reactions were only seen with aqueous extracts, and never when depot preparations were used. On the other hand, depot preparations were associated with an increased

Table 12. Summary of new adverse reaction data collected in the U.K. since 1986

Centre	Allergen	No. of courses	No. of injections	Local	Adverse reactions		
					Severe	Moderate	Mild
Durham (Brompton)	GP	50	3167	39	1	6	5
Durham (Brompton)	HV	11	447	10	0	0	3
Ewan (Cambridge)	HDM (aq)	27	541	nr	10	116	(mostly mild)
Ewan (Cambridge)	HDM (dep)	40	916	nr	0	0	60
Ewan (Cambridge)	HV	26	727	nr	3	5	120 (mostly lethargy)
Fitzharris (St Mary's)	HV	12	600	nr	0	0	1
Frankland (London)	Mainly GP	164	1364	nr	0	0	3
Lee (Guy's)	HV		2363	nr	4	21	36
Stokes (Brook)	Mainly GP	44	549	nr	0	0	nr
Wilson & Dixon (Liverpool)	GP	919	8102	125	20	110	56

Abbreviations: HDM = house dust mite; HV = hymenoptera venom; GP = grass pollen; nr = not recorded.

NB: Definitions of mild/moderate/severe reactions vary between centres. Operational definitions used for above table were:

Severe: anaphylaxis or other systemic reaction requiring immediate treatment.

Moderate: urticaria and/or wheeze, possibly requiring specific treatment.

Mild: other systemic reactions: mild rash, rhinitis, nausea, malaise, lethargy, etc. not requiring treatment.

incidence of minor systemic reactions. The incidence of systemic reactions was greater when the injection was given by an inexperienced team member and with larger doses of allergen (these factors may be related): 171 out of 172 systemic reactions started within 30 minutes, with the remaining systemic reaction starting 35 minutes after injection.

A report of 139 patients receiving AII for venom or inhalant allergy in Israel highlights the importance of asthma as a risk factor for adverse reactions, with 40% of asthmatics experiencing systemic reactions at some point during their course of AII compared with 13% of non-asthmatics receiving similar courses of AII [Tamir *et al.* 1992].

Table 13. Pattern of systemic side-effects to AII

Adverse reaction	Timing	Peak onset
Immediate		
Anaphylaxis	0-20 mins	5-10 mins
Bronchospasm	2-45 mins	5-15 mins
Acute urticaria	5-45 mins	10-20 mins
Delayed		
Rhinitis	90-240 mins	
Urticaria	120-480 mins	
Lethargy	Rare variable onset	

Fatalities

Between 1957 and 1986 the CSM was informed of 26 fatalities resulting from anaphylaxis or bronchospasm after administration of allergen preparations in the U.K. The indication for AII was stated to be asthma (i.e. not rhinitis) in 16 of the 17 for whom this information was available. From these data and other reports it is clear that asthmatics are particularly at risk for fatal adverse reactions to AII. Eleven of the CSM deaths were reported after 1980 and five in the 18 months running up to the end of the survey. In the U.S.A., 46 deaths associated with AII or skin testing were reported in a 42-year period up to 1986 (collected and summarized by Lockey *et al.* [1987]). The denominator (number of treatment courses) for these 46 fatalities is unknown but the fact that these were published cases makes the data likely to be an underestimate of the true incidence. Subsequently the American Academy of Allergy & Immunology (AAAAI) has conducted two questionnaire surveys in the U.S. which have revealed higher fatality rates, with nine deaths reported between 1987 and 1989 and 10 deaths in 1990-91 [Reid *et al.* 1990, 1992]. At least 16 of these 19 deaths were in patients with asthma (asthma status was unknown for the other three cases). Asthma was the immediate cause of death in 11/12 and anaphylactic shock in 1/12 inadequate clinical information was supplied in the other seven cases. Most of these asthmatics were clinically unstable or steroid-dependent. Accidental overdosage was thought to

be a factor in 5/19 cases, but otherwise there was no clear association with any particular extract, or with induction rather than maintenance therapy. The onset of symptoms was within 20 minutes in all cases for which data were supplied (onset was unknown in seven cases). The AAAI has recommended caution in assessing patients before AII but continues to regard asthma as an indication for AII [Norman & van Metre 1990; Executive Committee AAA&I 1990].

Prevention of adverse reactions

Appropriate patient selection is vital in order to maximize the benefit:risk ratio. A proportion of side-effects and deaths are claimed to be due to errors in dosage and timing. Care should therefore be taken to ensure that patients receive the correct allergen at the correct dose and time. Detailed instructions for patient selection and safe administration of allergen extracts are given in Chapters 1, 4 and 7.

Observation time

The evidence accumulated since 1986 indicates that the vast majority of serious systemic reactions start early, usually within a few minutes. Almost all reported serious systemic reactions have started within 30 minutes but some less serious systemic reactions have commenced up to 45 minutes after injection. Adverse reactions commencing between 30 and 60 minutes occurred only with hymenoptera venom AII and none were reported in patients receiving pollen AII. Symptoms developing in this window included urticaria, rhinitis, nausea, perioral

paraesthesiae, coughing or lethargy but there were no cases of anaphylaxis.

Based on these data it seems that if *anaphylaxis* is going to occur, it will start rapidly (within 5–10 minutes of injection) and will virtually never begin later than 20 minutes after injection. Delayed reactions (starting after 60 minutes) are unusual and take the form of rhinitis, itching and skin rashes (usually urticaria). In fact, most delayed reactions start more than 2 hours after injection and do not require specific treatment. Thus, 30 minutes of observation should detect all cases of AII-induced anaphylaxis but would miss some cases of bronchospasm and acute urticaria. Most North American and European allergists regard 30 minutes of observation as adequate. The WHO IUIS report [Thompson *et al.* 1989] concurred and stated that there is no convincing evidence that a longer waiting period alters the fatality rate. However, recent U.K. experience (cited above) suggests that a small proportion of systemic side-effects requiring treatment will develop between 30 and 45 minutes after injection. Reactions commencing after 60 minutes are relatively mild and rarely require specific treatment or intervention. Therefore, this BSACI working party recommends that, provided patients are correctly selected for desensitization, *an observation period of 60 minutes* after injections is sufficient to detect all systemic reactions requiring treatment. In addition, patients showing any sign of systemic adverse reaction should be detained beyond 60 minutes to ensure resolution of the reaction before discharge from the clinic. These recommendations will need to be reviewed and amended in 2–3 years to reflect new data.

CHAPTER 9

Conclusions and topics for future study

This report has summarized all the available information published since 1986 regarding the efficacy of IT and the pattern of adverse reactions to IT, using strict criteria for acceptability of information. Using these data, we have set out proposals for the selection of patients receiving IT and for the prevention and minimization of side-effects. We conclude that IT does have a place in selected patient groups and that the risk of adverse reactions can be contained by patient selection and the adoption of 'good clinical practices'.

Recommendations

1. Specific allergen-injection immunotherapy should be used on a routine basis only in (a) patients with seasonal allergic rhinitis (hay fever), who have failed to respond adequately to anti-allergic drugs, and (b) wasp and bee venom hypersensitivity.
2. Specific allergen immunotherapy should be administered only in hospitals, or in specialized clinics. Adrenaline should always be immediately available and there should be easy access to resuscitative facilities. Attendant staff should be trained in resuscitative techniques.
3. Patients should be kept under close supervision for the first 60 minutes after each injection. This period should be extended if the patient has any generalized symptoms, however mild, at the end of the observation period.
4. Severe or generalized delayed reactions should be recorded and reported to the CSM, with accurate details of timing, treatment and response.
5. Specific allergen immunotherapy is not recommended in chronic asthma. Also, at the present time, immunotherapy should not be used for the treatment of mild asthma unless part of a carefully controlled research project. Immunotherapy is not recommended in non-allergic rhinitis, non-allergic asthma, atopic dermatitis, chronic urticaria, food hypersensitivity, drug and chemical hypersensitivities.
6. The use of allergen immunotherapy in children requires specialist assessment. Immunotherapy can be helpful but as childhood allergic disease shows a natural tendency towards improvement, appropriate patient selection is of paramount importance.
7. Whole-body extracts of stinging insects, allergen extracts prepared from foods, feathers, synthetic materials, bacterial extracts, gums and glues, enzymes and occupational allergens should not be used. Vaccines prepared from multiple allergens are not recommended.
8. Extracts prepared from mould spores, animal danders, or house dust mites (*Dermatophagoides* spp.) are also not recommended for routine use at present. Physicians using these preparations on a 'named patient' basis should continue to keep close supervision for 2 hours after each injection.
9. All allergy extracts (for skin testing as well as intermediate products intended for immunotherapy) should be biologically standardized.
10. These recommendations should be regularly revised and modified, as necessary, in the light of new information.

Recent advances in our understanding of the mechanisms of allergic inflammation and immunological tolerance have suggested that a number of alternative approaches to IT may be developed in the medium term. Several of these are in the early stages of development and, although it is too early to make formal judgements, we believe it is likely that improved and possibly safer forms of immunotherapy will be developed in the next decade. These new treatments will require formal evaluation and comparison with both conventional immunotherapy and conventional medical management with drugs.

It remains vital to ascertain the true risk/benefit ratios of current forms of IT and to define more clearly the categories of patients for whom this form of treatment is appropriate. All members of the Working Party earnestly hope that this report will stimulate research in the field. Important topics for future research include the following topics—other subjects for research will doubtless suggest themselves and this list is by no means meant to be exhaustive!

1. The *relative* value of AII in asthma as compared with best conventional medical management. To date this aspect of AII has barely been addressed and yet many thousands of asthmatic patients receive courses of AII each year.
2. The influence of immunotherapy in modifying the progression or ultimate severity of allergic disease. (It has been claimed that treating rhinitis by AII may prevent the development of asthma in later life, but this has yet to be formally tested.)
3. Better methods of standardizing allergen extracts.
4. Evaluation of different AII dose schedules in terms of efficacy and safety.

5. Optimum duration of AIT treatment.
6. Factors contributing to adverse reactions. Our knowledge of this important area is incomplete.
7. The safety of immunotherapy in pregnancy. Current clinical practice is geared towards safety issues, but there are anecdotal reports that the development of atopic disease in infants born to atopic mothers may be attenuated by continuing immunotherapy during pregnancy. These observations deserve further examination, and as safer allergen extracts become available, the risks of such a study may become more acceptable.
8. Further studies of the mechanism(s) of successful AIT with particular emphasis on the effect of AIT on T-cells, cytokines and eosinophils.

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