

Position Paper: Immunotherapy

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Preface

The only real argument for establishing a specific diagnosis in allergic diseases is the institution of a specific treatment. Allergen avoidance and immunotherapy represent the only specific treatments we are able to offer allergic patients. The capacity of drug treatment is limited to the elimination or diminishing of symptoms, and no studies have been able to show that pharmacologic treatment of allergic diseases, not even corticosteroids, modifies the spontaneous, long-term course of the disease. Cost-benefit studies of immunotherapy present problems, and we recommend that immunotherapy be an integrated part of the treatment of allergic disorders, thus reducing the disease severity, improving the quality of life of allergics, and diminishing the risk and cost of pharmacotherapy.

The first EAACI Immunotherapy Position Paper was published in 1988. New insights into the pathogenesis of allergic diseases and recent publications on immunotherapy have called for a revision of the Immunotherapy Position Paper. However, allergen-specific immunotherapy is a controversial treatment, and drafting this 1992 revised Position Paper is difficult since:

- 1) We intend to recommend that immunotherapy be performed in the most scientific way, but supportive data are not always sufficient.
- 2) Although clinical experience is encouraging, particularly with recent high-quality extracts, a further reduction in the number of patients treated by immunotherapy, while we wait for further scientific data, will make improvements more difficult, and eventually lead to a halt in the production of allergen extracts.

Our Position Paper, therefore, aims at reaching a consensus, balancing science, theory, and current practice in most European countries, at the same time intending to improve the scientific value of the 1992 revised EAACI Immunotherapy Position Paper.

The outlines of the 1992 revised EAACI Immunotherapy Position Paper were debated at a one-day meeting in February 1991, in Copenhagen, Denmark, sponsored by ALK, Denmark. The first edition was drafted at a three-day meeting in May 1991, in Madrid, Spain, organized by Dr Emilio Alvarez-Cuesta and kindly sponsored by Abelló, Spain. The final revised edition of the Position Paper represents the opinion of the members of the EAACI Immu-

notherapy Subcommittee and includes comments from the EAACI associate European national societies of allergology.

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Introduction

Immunotherapy has been used extensively for 80 years as a specific treatment of allergy. In the last decade, the clinical practice of immunotherapy has changed markedly in certain parts of Europe. In southern Europe immunotherapy still represents the cornerstone of allergy treatment, while in Scandinavia and the UK a decreasing number of allergic patients receive immunotherapy. In spite of the fact that a large number of recently published, well-performed clinical trials have documented the evidently beneficial effect of immunotherapy (23, 45, 52, 137, 143), the decrease is probably caused by a combination of some degree of uncertainty as to the clinical efficacy, the risk of side-effects, and the introduction of potent new drugs for prophylactic treatment of allergic diseases (196). Critics claim that immunotherapy is a potentially life-threatening treatment used for rather harmless, although inconvenient, diseases. It is undeniable that immunotherapy involves the risk of severe side-effects and even death (99). In this connection, it is worth bearing in mind that both the morbidity and the mortality of asthma are increasing (172) in spite of the introduction of more efficacious and potent drugs (8). The risks of theophylline, systemic corticosteroids, and, as recently pointed out (173), even inhaled short-acting β_2 -agonists, must not be ignored. The introduction of high-dose topical corticosteroids, β_2 -agonists, and nonsedating antihistamines (86, 87) has fundamentally changed the idea that immunotherapy is the first and best choice in the treatment of allergies.

The clinical efficacy of immunotherapy in hay fever has been convincingly documented (137). Short-sighted evaluations of the clinical efficacy and risk of immunotherapy in hay fever in relation to drug treatment do not favor immunotherapy. Hay fever is not a potentially life-threatening disease, and the immediate efficacy of antihistamines and topical steroids has, in one study using a low potency extract, showed a higher clinical efficacy than immunotherapy (82), although another study clearly documented clinical efficacy in rhinitic patients uncontrolled by standard

antiallergic drugs (antihistamines, intranasal corticosteroids, and sodium cromoglycate) (192). However, some fundamental aspects of allergic diseases must be borne in mind when deciding on the best treatment. A substantial number of patients with hay fever develop asthma at a later stage of the disease (180). Asthma represents a more severe disease, entailing an increased risk of death, a growing morbidity resulting in an increase in the expenses related to pharmacologic treatment and hospitalization, a reduced working capacity, and a diminished quality of life. Some studies have shown a significant efficacy of immunotherapy in reducing the further development of rhinitis into asthma (122). Evaluating 500 rhinitic patients at 5 years' follow-up, Bousquet (Bousquet, J., personal communication) observed a 5% risk of developing asthma in immunotherapy-treated patients, 12% in patients treated with H₁-blockers, and 23% in placebo-treated patients. Although there is a need for further studies evaluating the power of immunotherapy to reduce the risk of development of asthma in rhinitic patients, this aspect has to be seriously considered when deciding on the best treatment of hay fever patients.

The clinical efficacy of allergen-specific immunotherapy in asthma has been questioned (65). However, most controlled studies published during the last decade show a clear tendency towards a beneficial effect (23, 140, 179). The important point about clinical efficacy is whether the validation of efficacy is a reduction in symptom severity and drug intake that, from a clinical point of view, significantly reduces the morbidity of asthma (112). The expected magnitude of symptom and drug reduction is important. Since asthma is a very complicated and multifactorial disease, seldom caused by monoallergy, immunotherapy in most cases results only in a reduction in symptoms or the need for drug treatment. A significant decrease in drug intake will, however, imply a reduction in the risk, inconvenience, and cost of pharmacotherapy, thus improving quality of life.

Respiratory allergy as an inflammatory disease

Recent concepts of allergic diseases, especially asthma, focus on the inflammatory components in the pathophysiology of the disease (71, 89). Studies of bronchoalveolar lavage have clearly shown recruitment and activation of inflammatory cells caused by IgE-mediated mechanisms. The release of histamine, prostaglandins, leukotrienes, thromboxanes, PAF, etc. from mast cells, caused by the interaction of allergens and IgE bound to the type 1, high-affinity Fc-epsilon receptor, and from alveolar macrophages expressing the type 2, low-affinity Fc-epsilon receptor, is responsible for both the acute bronchospastic

component of the asthma disease and the smoldering, eosinophilic, desquamative chronic bronchitis (22, 24). Recent trends in the treatment of bronchial asthma have focused on these aspects, as anti-inflammatory drugs have become the first-line prophylactic treatment, while bronchodilators have been reserved for acute bronchospastic episodes (31). The inflammatory response resulting in desquamation of epithelial cells and exposure of nerve endings may very well play an important role in the nonspecific hyperreactivity characterizing asthma (130). The treatment of bronchial asthma should aim at preventing bronchial inflammation and epithelial damage in order to avoid irreversible destruction of the lower airways.

The anti-inflammatory effects of inhaled glucocorticoids have been clearly documented in clinical trials. A fundamental question concerning topical steroids is whether these drugs sufficiently prevent all the deleterious effects of the inflammatory cells (34). Short-term studies have shown the efficacy of inhaled steroids, but no long-term studies have shown that pharmacotherapy can impede the augmented decrease in lung function observed in asthmatic patients. From a rational point of view, an initial prevention of the release of mediators would have obvious advantages over the more or less completely secondary receptor-level blocking of activated inflammatory cell products; that is, interference with the initial activating steps in the inflammatory response seems to be a better approach than blocking the final activation of the target cells.

The IgE-mediated allergic reaction manifests itself as an early-phase reaction followed by a late-phase reaction. The severity of the disease is, however, more closely related to the late-phase reaction than to the immediate reaction (85). The IgE-mediated early reaction triggers the long-lasting inflammatory response, involving eosinophils, neutrophils, lymphocytes, macrophages, etc., which results in a smoldering clinical picture, with symptoms persisting well past the allergen exposure.

A fundamental advantage of immunotherapy in the treatment of allergy may be its interference with the pathophysiologic mechanisms responsible for mediator release (150). Blocking of mediator release may reduce the accumulation of the type 2 T-helper (Th2) effector cells observed during the late-phase reaction (50), and this, in turn, impedes the activation of B cells and the IL-4-dependent IgE synthesis (161). In venom allergy, immunotherapy has been shown to reduce the expression of the low-affinity IgE receptor on T and B cells (154).

Hypothetically, the mechanisms of immunotherapy could "turn off" the allergic reaction, thereby interrupting the chain of events characterizing allergic disease. Firstly, immunotherapy induces a switch

of the preferential differentiation into Th2-type effector cells to the Th1-type cells (50). The switch of cytokine profile to a primary IL-2 and INF- γ response results in inhibition of the IL-4-dependent IgE production, reinforced by a decrease in the production of IL-4 from Th2 cells. Secondly, the activity of mast cells is reduced because of a lack of IL-3-dependent activation, a reduced local production of IgE, and a decreased production of histamine-releasing factors (27, 91). A cytokine-independent decrease in mediator release from mast cells could concurrently be present, as well as a switch from IgE+ to IgE- (96).

The decreased activity of mast cells results in a decreased release of allergic mediators, thereby diminishing vascular permeability, smooth-muscle contraction, and the activity of chemotactic factors such as PAF and eosinophil chemotactic activity (156). In combination with a reduced production of IL-5, the activity of eosinophils is decreased, resulting in less inflammation and destruction (60).

Thus, the possibility does exist that blocking of the initial steps may interfere with the signal for further progression of disease. The untreated inflammatory response may further aggravate the nonspecific bronchial hyperreactivity induced by specific allergen sensitivity (129). Several immunotherapy studies have shown a reduction in the severity and frequency of the late asthmatic response (188). Using the nose as a model for allergic diseases, Creticos et al. (37) have demonstrated an immunotherapy-induced, dose-dependent reduction in mediator release after nasal pollen challenge, and a significant reduction in patient symptoms during the pollen season. Although still debated, the reduction in mediator release induced by immunotherapy may be the basis of the reduction in nonspecific hyperreactivity reported in some immunotherapy studies (23). A significant reduction in the release of mediators caused by immunotherapy may reduce the need for concomitant inhaled steroids, thus reducing both the risk of adrenal suppression and the risk of nonreversible, chronic epithelial damage, and, consequently, implying a decrease in asthma morbidity and mortality and an increase in the quality of life of asthmatic patients.

Modern treatment of allergic diseases, especially asthma, is largely based on inhaled corticosteroids. However, this treatment modality results in some problems. In the central airways, mediator release results in smooth-muscle contraction, inflammation, and epithelial damage. Inhaled drugs are primarily deposited in the central airways (92) and may normalize the lung function for many years. In the peripheral airways, inflammation and epithelial damage may not be sufficiently impeded by the inhaled corticosteroids, and, eventually, this may result in

chronic, irreversible lung disease (77, 100). The increase in asthma morbidity and mortality despite the introduction of potent and more efficacious antiasthmatic drugs for inhalation may point in that direction.

The logical approach in the treatment of allergic diseases must be to impede the natural course of the disease. Not only the direct clinical benefit, but also the possible preventive aspects of immunotherapy should be evaluated in further studies.

The strategy of tomorrow's treatment of asthma should aim to:

- 1) reduce morbidity
- 2) prevent progressive decline in lung function
- 3) improve quality of life
- 4) reduce mortality.

1. Indications for immunotherapy

Immunotherapy is an effective treatment of allergic diseases under optimal conditions, including:

- 1) the demonstration that allergen sensitization plays a predominant role in eliciting symptoms and in the overall severity of the disease
- 2) the availability of a high-quality allergen extract and the administration of a proper dose.

In the individual patient, the relative importance of allergic and nonallergic factors, such as irritants (odors, nonantigenic particles), exercise, food additives, viral infections, drugs (aspirin and other nonsteroidal anti-inflammatory drugs), occupational factors, psychical stress, air pollution, gastroesophageal reflux, etc., in triggering allergic symptoms must be carefully evaluated.

Factors favoring the use of immunotherapy are, over a period of years, either progression of the severity of the allergic disease or progression from rhinitis into asthma, in spite of attempted allergen avoidance and pharmacotherapy.

Since the response to immunotherapy in individual patients is difficult to predict before initiating treatment, the best choice of treatment should be considered very carefully. The indication for immunotherapy must go beyond the mere facts of a diagnosis of allergic symptoms and positive diagnostic tests. Identifying the patients most likely to benefit from immunotherapy implies diagnostic procedures combining both the demonstration of IgE-mediated sensitivity to relevant allergens by appropriate diagnostic tests, and a clinical history correlating with laboratory findings and the exposure to the relevant allergen; moreover, one must perform a careful evaluation of whether the severity of the disease justifies this kind of treatment, balancing the relative benefits, risks, and inconveniences of immunotherapy.

1.1. Rationale for immunotherapy

1.1.1. Reduction in symptoms and the need for drug treatment

The advantage of immunotherapy is a reduction of the severity of symptoms and a shortening of the duration of serious complaints, combined with a reduction of the need for symptomatic pharmacotherapy.

1.1.2. Interference with progression of allergic diseases

Long-term studies of drug-treated asthmatic children show that three of four children continued to have asthma symptoms in adult life (55, 79, 81, 115, 165, 166). No studies indicate that pharmacologic treatment alone can modify the spontaneous course of asthma.

Some studies indicate that immunotherapy may change the spontaneous course of allergic diseases; that is, it may be a causal treatment. These investigations have obvious limitations as they are uncontrolled and use nonstandardized allergen extracts, including bacterial vaccines and other extracts presently not accepted. A study of the effect of immunotherapy (20 years' follow-up of 688 asthmatic children) showed that three of four children became asthma-free in adult life (155). In conformity with these results, Johnstone & Dutton (80) found that two of three hyposensitized children were free of asthma, as opposed to only one of four in the placebo group. It is strongly recommended that prospective studies using high-quality extracts be initiated to evaluate the long-term efficacy of immunotherapy in relation to reduced development of asthma in rhinitic patients.

1.2. Allergen reduction

Allergen avoidance or reduction, whenever possible, is preferable to immunotherapy. Immunotherapy should not be commenced without trying to eliminate the allergen whenever technically feasible (1). This is not possible in pollen or mold allergy. Animal-dander allergens may be removed from the patient's home (e.g. by removing pets), but unless the patient's social life is to become severely restricted, it is not possible to eliminate totally the indirect allergen contact of the patient by exposure to animal allergens in connection with nursery school, school, work, public transport, social contacts, etc. In theory, elimination of house-dust mites is possible, but, in practice, it has proved difficult to reduce the number of mites by ordinary cleaning. If allergens can be eradicated from the patient's environment, immunotherapy is seldom indicated (124). Immunotherapy should be seriously considered in patients with allergic diseases when allergen reduction is impossible, or when the disease

responds insufficiently to allergen reduction, even when symptomatic relief can be achieved with drug therapy (189). The latter point is controversial and needs further documentation.

1.3. Selection of patients

The indications for immunotherapy were rather restricted according to the previous recommendations of the EAACI Immunotherapy Position Paper (111) and the WHO/IUIS Status Report (179). The indications were confined to patients not responding adequately to drug treatment, or presenting with side-effects. These rather restricted indications for immunotherapy were based primarily on enthusiastic confidence in drug treatment, insufficient knowledge of the long-term efficacy of immunotherapy, and the risk of side-effects.

However, it does not seem logical that immunotherapy should be used in the late course of the disease, when damage may have occurred and the capacity to change the progression of allergic diseases may be limited.

Immunotherapy should be seriously considered in the following patients:

- 1) patients with rhinitis or asthma caused by allergens for which clinical efficacy and safety have been documented by placebo-controlled, double-blind immunotherapy studies
- 2) patients sensitive to allergens which cannot be sufficiently eliminated
- 3) patients with a need for daily pharmacotherapy for longer periods (prophylactic drug treatment during a pollen season or perennially).

1.3.1. Advantages of immunotherapy early in the disease process

Advantages in these circumstances include:

- 1) a better opportunity for immunotherapy to prevent rather than reduce the chronic inflammation
- 2) a possibility of preventing further development of severe disease (i.e. the development of asthma in a rhinitic patient), or the secondary development of new IgE sensitizations
- 3) a possible reduction in adverse reactions to immunotherapy as a result of a lower degree of sensitivity.

Because of the present lack of scientific evidence, individual physicians must make their own decisions with regard to the commencement of immunotherapy in the early or late course of allergic disease. We recommend that studies be initiated in order to evaluate the advantages of the early treatment of mild disease.

1.3.2. Immunotherapy as compared with drug treatment

Critics of immunotherapy often claim that it is inferior to drug treatment. A question remaining to be

completely answered is whether the combination of drug treatment and immunotherapy is more effective than drug treatment alone. Another important point is that drug treatment is effective only while being administered. When treatment is stopped, symptoms reappear. As for duration of disease, drug treatment has to be continued lifelong, while, according to prevalent opinion, immunotherapy has to be administered for about 3–5 years.

The indications for immunotherapy should be considered to be equivalent to those for long-term prophylactic drug treatment, i.e. topical steroids, and immunotherapy should be begun at the equivalent level of disease severity. Patients who need daily pharmacotherapy should be offered supplementary immunotherapy to obtain a multifactorial treatment approach that interferes broadly with the pathophysiologic mechanisms of allergic diseases. The demand of critics that immunotherapy show its superiority to available pharmacotherapy is based on a misunderstanding. The efficacy of immunotherapy as a single treatment should not be compared with that of drug treatment. Immunotherapy and pharmacotherapy should be integrated components in the treatment strategy for allergic diseases in order to gain the best result.

Current thinking should focus on the long-term advantages of instituting immunotherapy in the early course of allergic diseases in combination with the best pharmacologic treatment.

1.3.3. Age

Immunotherapy should be started early in the disease process, meaning rather early in the lives of most patients. Some immunotherapists recommend treatment in children at 1–2 years of age, but it is desirable to evaluate more closely in controlled studies the benefits of immunotherapy in patients below 5 years of age. In a study investigating mite allergen, systemic reactions were recorded more frequently in children below the age of 5 years (69). When immunotherapy is indicated in infants, it is mandatory that the physician have full experience in the treatment of systemic reactions and master the establishment of an intravenous line in that particular age group.

In elderly patients with a long duration of symptoms, immunotherapy may be proposed, but the efficacy is weaker than in younger persons (18). This phenomenon is a consequence of the development of chronic irreversible changes caused by the duration of the disease, rather than the actual age of the patients. Before starting immunotherapy, one must consider two factors: 1) the importance of IgE-mediated allergies may decrease with the age of the patient, and 2) in asthmatic patients, persistent bronchial inflammation elicits an accelerated, irreversible decline of the pulmonary function (23). Anaphylac-

tic reactions are more severe in elderly people because of factors such as concurrent cardiac disease; thus, the risk:benefit ratio of immunotherapy is usually higher. Therefore, immunotherapy should be started only in selected cases, except for insect venom anaphylaxis, in which the risk of severe sting reactions appears to be higher than in younger persons.

1.3.4. Quality of life

A point often neglected in discussion of the efficacy of drug treatment, but one that is of great importance to allergic patients, is quality of life. The constant intake of drugs, often several times daily, fixes patients in an invalid character which is psychologically inexpedient, and may interfere with patients' perceptions of normal life (136). Emotional unwillingness to undertake drug administration, rather than the drugs themselves, may be one of the main reasons for the increase in asthma mortality (172). The principle of immunotherapy, interfering specifically with the basic mechanisms of the disease, may be more attractive to a number of patients and be yet another justification for the treatment.

An active outdoor life adds to the quality of life of many allergic patients. The increased allergen exposure during the pollen season may restrict outdoor life and broaden the indication for immunotherapy.

1.3.5. Evaluation of the patient

Only allergens causing most of the patient's symptoms should be used for immunotherapy. In patients with multiple allergies, it is often difficult to define clearly the allergens mainly responsible for the combination of symptoms (1). Immunotherapy with one allergen is unlikely to be effective in the presence of multiple allergies. For practical reasons, immunotherapy will only rarely be indicated with more than three *unrelated* allergens at the same time (146).

Patients considered to be candidates for immunotherapy must be stabilized by adequate drug treatment. It is recommended that one evaluate the response to allergen avoidance and pharmacotherapy for a certain period of time in order to make observations of the severity and variation of the disease. In asthmatics, lung function should not be persistently below 70% of predicted value.

Chronic diseases such as nonallergic sinusitis, nasal polyps, COPD, etc. should be excluded before initiating immunotherapy.

1.3.6. Long-term efficacy of immunotherapy

Only limited knowledge exists about the optimal duration of immunotherapy and the duration of the therapeutic response achieved. The improvement in symptom scores is maintained for at least 2 years after long-term ragweed allergoid immunotherapy

has been discontinued (139). In grass-pollen rhinitis, the effect of immunotherapy continues for at least 6 years after termination (122), while for perennial aeroallergens such as that of the house-dust mite, available data bring into question the advisability of stopping immunotherapy (23). It is recommended that one continue treatment for 3–5 years before evaluating the long-term efficacy without immunotherapy. Patients with obvious clinical efficacy during immunotherapy whose disease relapses after terminating treatment should be offered a new, prolonged course of immunotherapy.

1.3.7. Preseasonal as compared with perennial treatment

Immunotherapy should preferably be given as perennial treatment (63, 80, 135, 146, 167). This way of administering allergen extracts provides the advantages of a reduction in the total number of injections, and an increase in the cumulative allergen dose. The risk of systemic side-effects is higher during the dose-increase phase than during maintenance treatment (99, 189), thus making perennial treatment safe.

Patient compliance is, however, asserted to be higher during short preseasonal treatment.

1.3.8. Safety of immunotherapy

Injection of allergens against which a patient has IgE antibodies may induce anaphylactic shock. The risk is highest during the dose-increase phase, but must not be ignored during maintenance treatment (205). The use of depot allergen extracts and adherence to recommended guidelines will, however, reduce the risk of anaphylactic shock to a minimum. Local swelling, redness, and itching are unavoidable, and serve as indicators with which to monitor treatment. Aggravated allergic symptoms such as rhinitis, asthma, urticaria, and angioedema appearing within 30–60 min after injection may herald the beginning of anaphylaxis and must be closely observed and adequately treated. In a study involving large numbers of patients (20 000 patients and 150 000 injections), systemic side-effects were observed in 0.1% of injections (155 patients), including two cases of anaphylactic shock (194). The study was hindered by being based on questionnaires and included a number of nonpotent allergen extracts. Frankland (57) in his work on anaphylaxis found one fatality in 750 000 injections of Allpyral®. A similar study found no fatalities in over 4 million Allpyral® injections (3). Since 1980, 11 fatalities have been registered in the UK (32), leading to strict requirements for full anaphylactic emergency equipment to be available for the attending physician, and increased observation time being required after the injections. In a survey of safety aspects, Lockey (99) found 46

fatalities in the USA during a 42-year period. Immunotherapy with the new potent extracts is not without risk, especially in asthmatic patients, and therapists must be prepared to treat immediately the early signs of anaphylactic shock (4, 151). About 60% of all systemic reactions with routine immunotherapy are without discernible cause, while the remainder include 27% related to shift of ampoule and 14% to error (in ampoule or dosage) and failure to take into consideration the time interval between injections (193).

These accounts of routine immunotherapy, in which the frequency of side-effects is based upon questionnaires, report fewer side-effects than in recent placebo-controlled studies using higher amounts of allergen. When evaluating systemic side-effects, it is essential to distinguish between life-threatening and non-life-threatening reactions. Life-threatening systemic reactions (severe asthma, angioedema, and anaphylactic shock) occur seldom in recent studies, ranging from 0% to very low percentage (49, 66, 132), but in some studies they range up to 20% (104). The noncritical systemic reactions (mild asthma and rhinitis) are noticed more frequently and in some studies with aggressive dosing have been reported in 20% of injections in most patients (107).

Local benign granulomas are seen when aluminium depot preparations are used (9, 104, 204). Immune complex disease has been described, but it occurs seldom during immunotherapy (84, 104, 185).

1.4. Diagnostic procedures

Although allergy screening may be undertaken by a nonspecialist, the specific diagnosis of allergy and the indications for immunotherapy should be assessed by a trained allergist only.

1.4.1. Methods

Diagnostic procedures aim at demonstrating IgE-mediated reactions and at possibly proving the relevance of allergen sensitization in the shock organ. When a careful clinical history has been obtained, many *in vivo* and *in vitro* methods can be used, e.g. skin prick tests for inhalant allergens (and possibly intradermal tests for venoms and drugs) and the titration of serum-specific IgE (105). As a means of substantiating the diagnosis or of proving that the shock organ is involved, challenge tests should preferably be used, but in clear-cut allergic conditions they appear to be less important. Some investigators have suggested that bronchial provocation tests should be performed and be positive before starting immunotherapy in asthmatic patients (1, 195). As bronchial provocation challenge differs from natural

exposure in a number of ways, its use as an ultimate diagnostic test remains controversial. Nasal challenges or conjunctival provocation tests may be performed in rhinoconjunctivitis.

1.4.2. Diagnostic criteria fulfilled

Clinical history, including estimation of allergen exposure, and the results of diagnostic tests should be compared to prove that symptoms are due to allergenic sensitivity (106). The severity of the disease should justify immunotherapy (patients with a need for prophylactic drug treatment).

Positive diagnostic tests are a necessary precondition for initiating immunotherapy. Skin tests that can be substantiated by specific IgE determinations are most often used. Challenge tests in the actual organ presenting with disease symptoms can be performed in order to substantiate the specific diagnosis and to evaluate the relevance of the allergen.

1.5. Specific indications

1.5.1. Hymenoptera venom allergy

Only patients with systemic reactions and positive diagnostic tests should be treated for this allergy. Further details are given in the EAACI Hymenoptera venom Position Paper (125).

1.5.2. Rhinoconjunctivitis

1.5.2.1. Disease. Pollen allergy mainly causes rhinoconjunctivitis but may result in asthma. Before one commences immunotherapy, the following points should be evaluated: 1) duration of the pollen season and number of days with symptoms, 2) severity of the disease – when nonsedative antihistamines and topical treatments alleviate symptoms, individual physicians are left to make their own decision with regard to the commencement of immunotherapy in either the early or late course of the disease – 3) that when asthma complicates rhinoconjunctivitis, immunotherapy is favored, and 4) that all the above may be modulated by the patient's occupation and motivation.

1.5.2.2. Pollens. Controlled studies have demonstrated the efficacy of immunotherapy in grass, ragweed, birch, mugwort, and mountain cedar rhinitis (6, 17, 26, 56, 144, 184, 189, 192, 200, 203). It may be postulated that immunotherapy for other pollen species is effective, but proper studies have yet to be performed. The study by Varney et al. (192) is of interest, as it shows a significant clinical efficacy in patients with severe hay fever uncontrolled by pharmacotherapy including antihistamines and intranasal corticosteroids.

Few studies have supported the efficacy of immunotherapy in pollen-induced eye symptoms (20, 83). A single study investigating the effect of pollen immunotherapy on the oral allergy syndrome induced by pollen cross-reacting allergens failed to show a beneficial effect (128).

Patients with multiple pollen allergies may respond less to immunotherapy than do those with single allergies because the priming effect of tree pollens may aggravate symptoms caused by species pollinating late (25). It is therefore recommended that one assess the clinically relevant allergens by a combination of diagnostic tests and history (combining diary cards with allergen exposure). In special situations, examination of cross-reactivities among pollen allergens may be helpful. Parker et al. (144) did not, however, observe any difference in the clinical outcome in patients with single positive skin test and patients with multiple positive tests.

1.5.2.3. Mites. During recent years the efficacy of mite immunotherapy in rhinitis has been clearly documented (36, 51, 117, 148). In rhinitis, immunotherapy may be started when 1) in spite of allergen avoidance, patients need prophylactic treatment with antihistamines and/or nasal topical treatment for a longer period, or 2) subclinical asthma (night cough, exercise-induced asthma) develops.

1.5.2.4. Animal danders. No studies have been performed to investigate the efficacy of animal dander immunotherapy in patients with exclusively animal dander rhinitis and no asthma symptoms. A reduction in rhinoconjunctivitis and in the conjunctival challenge test has been shown (28, 142, 187).

1.5.3. Asthma

1.5.3.1. Disease. The role of specific immunotherapy in asthma management is under continual investigation. Currently available asthma management strategies with patient education, avoidance measures, and pharmacologic treatment usually provide effective control of asthma. Specific immunotherapy may be considered when avoiding allergens is not possible and when appropriate medication fails to control asthma symptoms. The efficacy of immunotherapy in asthma was contested some years ago because, although allergen injections using well-defined and potent extracts had more effective results for many patients, they also resulted in a greater number of severe systemic reactions. It is therefore essential to consider several factors in order to appreciate the respective values of allergen avoidance and specific immunotherapy in comparison with other available therapeutic procedures (76). Because asthmatic attacks can disable and even kill, every

means of control should be explored. Less than complete control by bronchodilator drugs or inhaled steroids indicates that immunotherapy should be considered (141).

When immunotherapy in asthma is considered, the following points have to be evaluated: 1) the potential severity of the allergy to be treated, 2) the efficacy of available immunotherapy, 3) the cost and duration of each type of treatment, and 4) the risk incurred by the patient because of the allergic disease and the treatments.

1.5.3.2. Pollens. Controlled studies have shown that with appropriately selected extracts and safe administration of doses, specific immunotherapy with grass pollen is effective in asthma management (20, 21). These conclusions are restricted to grass-pollen allergy because conflicting results have been produced in studies of ragweed-pollen asthma and polysensitized patients (23, 143).

1.5.3.3. Mites. Many placebo-controlled studies have shown that asthma caused by mites improves in patients treated with potent high-quality extracts (18, 23, 123, 143). From an immunotherapy study with mites, Bousquet et al. (18) have published data showing an improvement in lung function tests evaluating both central and peripheral airways.

In chronic asthmatic subjects, prolonged inflammation results in irreversible airways obstruction and may lead to an accelerated decline of pulmonary function. Theoretically, immunotherapy may favorably alter these processes when initiated at an early stage of mite asthma. Nonspecific bronchial hyper-reactivity may decrease, increase, or remain unchanged (23).

1.5.3.4. Animal danders. Controlled studies have suggested that immunotherapy with cat or dog danders decreases the sensitivity of the shock organ (12, 23, 28, 97, 187, 190), but no definite proof exists that asthma can be completely controlled when the causative animal remains in the environment of the allergic patient. It is therefore highly desirable to achieve strict allergen avoidance.

Immunotherapy with animal allergens may be considered in: 1) some occupational allergies, e.g. those of veterinarians, farmers, laboratory workers; 2) highly sensitive patients in whom indirect exposure, as in contact with pet-holding persons, leads to severe symptoms in spite of allergen avoidance in their homes.

1.5.4. Molds

Although well-conducted, placebo-controlled studies have shown that some noncommercially available, high-quality extracts are effective in the treat-

ment of mold asthma (43, 74, 107), immunotherapy should, at present, be performed only in controlled trials because of the lack of standardized commercial extracts.

It has been suggested that mold extracts may cause nonimmediate adverse reactions (84, 168), and future trials should test this point before mold immunotherapy is recommended in clinical setups.

1.5.5. Occupational allergy

Except for one study investigating immunotherapy in baker's asthma (7) and animal-dander allergy (cat and dog), there is no suggestion that immunotherapy may be useful in the treatment of occupational asthma or rhinitis. Immunotherapy should be begun only exceptionally when flour allergy has been shown to be the major cause, and only after a positive challenge.

1.5.6. Drugs

Although an IgE-mediated mechanism is not always present in drug hypersensitivity reactions, desensitization may be performed by oral or parenteral routes (174) when the offending drug is essential to the treatment of the patient and cannot be replaced. This treatment is not comparable to classical immunotherapy, as the sensitivity of the patient has not changed when drug administration is discontinued (174). Some of the papers claiming to show effective desensitization to penicillin may, in fact, give examples of patients who presented with no reaction at rechallenge (53).

1.5.7. House-dust allergy

House dust is highly heterogeneous and cannot be standardized. In many countries, house-dust extracts have been withdrawn from the market. According to current knowledge, house dust should not be used for diagnosis and immunotherapy.

1.5.8. Extracts with unproved efficacy

In the past, bacterial and *Candida albicans* extracts were widely used in the treatment of allergic patients. In spite of the fact that these microorganisms may be involved in allergic reactions, these extracts are totally unstandardized, and controlled studies have failed to show any efficacy (146). Therefore immunotherapy with such extracts is not advisable.

Some anecdotal evidence has given the impression that food allergens might be used to treat patients. Tolerance to milk can be induced in some cases of milk intolerance or IgE-anaphylactic reactions. Moreover, foods may cause life-threatening anaphylactic reactions. Immunotherapy with food allergens should not be initiated unless efficacy has been proved in controlled trials.

1.5.9. Other diseases

Although IgE is often highly elevated in atopic dermatitis, there is no clear relation between specific IgE and symptoms. Two noncontrolled studies of immunotherapy in patients with severe atopic dermatitis have shown some effect (164, 202), but immunotherapy in atopic dermatitis cannot be recommended until the clinical value has been proved in controlled studies. No controlled studies have shown clinical efficacy of immunotherapy in gastrointestinal, hepatic, rheumatologic (including RA), neurologic (including headache), and non-IgE-mediated ocular disease, or in behavioral conditions.

There are some suggestions that an IgE-mediated mechanism may be involved in some nephrotic syndromes (160), but no controlled trials indicate efficacy of immunotherapy.

1.6. Contraindications

1.6.1. Absolute contraindications

1.6.1.1. Concurrent diseases. Immunotherapy entails manipulation of the patient's immune system. Although extensive studies fail to reveal increased collagenous, autoimmune, or lymphoproliferative disease in patients treated with immunotherapy over many years (95, 171), immunotherapy should not be started when serious immunopathologic conditions or malignancies are present (146).

1.6.1.2. Adrenaline contraindications. Adrenaline is the most effective drug in the treatment of anaphylactic shock (99). Immunotherapy should not be undertaken in patients with diseases or conditions rendering the treatment of anaphylactic reactions difficult, as in symptomatic coronary heart diseases, severe arterial hypertension, and treatment with β -blockers (70, 181). Exceptions are patients who present with life-threatening reactions following Hymenoptera sting, and who are at high risk of developing fatal reactions because of the underlying disease.

1.6.1.3. Patient compliance. Since a reasonably successful result of immunotherapy is dependent upon active participation by both patient and allergist, lack of cooperation and severe psychologic disorders are contraindications for treatment.

1.6.2. Relative contraindications

1.6.3.1. Young children. Immunotherapy in young children (below the age of 5 years) should be performed only by specialists with full capability of treating anaphylactic reactions in that particular age group.

1.6.3.2. Pregnancy. Even though studies have failed to show any teratogenicity during immunotherapy, treatment should not be started during pregnancy because of the risk of anaphylactic shock with consequent abortion or other detrimental effect on the fetus during the dose-increase phase (120). However, in an already commenced and well-tolerated immunotherapy, the risk of anaphylactic shock is so slight that treatment may be continued if pregnancy occurs. The slightest hesitation on the part of the patient should, however, lead to discontinuation of the treatment.

1.6.3.4. Severity of allergic disease. Not all asthmatic patients should be treated. If nonallergic triggers (in particular, chronic sinusitis, aspirin intolerance, sulfite intolerance, etc.) or other perennial allergic sensitivities (in particular, foods, mold, animal dander, or occupational allergy) coexist with mite sensitivity, the relative importance of mite allergy should be carefully assessed. The lability of asthma is a key factor. Patients with uncontrolled asthma have been shown to experience significantly more systemic reactions during immunotherapy (19). The more severe the asthma, the less the benefit to the patient from immunotherapy (16). The consequent implications are that before starting immunotherapy in a patient, the therapist should establish the diagnosis of a pulmonary disease with a reversible component. In severe asthma, patients should be examined for allergen-induced bronchospasm and the reversibility of a decreased lung function by, for example, a trial with systemic steroids. An FEV₁ persistently below 70% of predicted values in patients on optimal pharmacologic treatment is likely to indicate a weakly reversible airways obstruction, implying, therefore, that immunotherapy may have a poor clinical effect and elicit more side-effects (19). Patients requiring continuous systemic corticosteroids should only exceptionally be considered to be candidates for immunotherapy.

1.6.3.5. Severe atopic dermatitis. Since some investigators report aggravation of atopic dermatitis, care should be taken to treat this disorder effectively before commencing immunotherapy in severely affected patients.

1.7. Discontinuation of immunotherapy

1.7.1. Successful clinical outcome

It is generally recommended that immunotherapy be stopped for patients who have been symptom-free or have experienced a drastic reduction in symptoms for at least 1–2 years. Treatment periods of less than 3 years result in a high frequency of relapses (23). From experience with venom allergy, Keating et al.

suggest that immunotherapy should be continued for 5 years (90).

1.7.2. Nonresponders

In practice, a few patients allergic to inhalant allergens do not respond adequately to immunotherapy; that is, they do not show sufficient clinical benefit. Patients who after 1 year of maintenance treatment have shown no clinical efficacy should be referred to a specialist for reevaluation of the advisability of their continuing immunotherapy.

1.7.3. Anaphylactic reactions

Patients developing repeated life-threatening anaphylactic reactions during immunotherapy should be referred to a specialist for consideration of the advisability of their continuing treatment. Repeated anaphylactic reactions during a correctly performed immunotherapy will often elicit the feeling that treatment should be discontinued.

1.7.4. Poor cooperation

For patients cooperating poorly during immunotherapy, treatment should be discontinued because of the risk of eliciting severe side-effects.

1.7.5. Development of contraindications

If conditions mentioned above under "Contraindications" develop, immunotherapy should be discontinued.

2. Allergen extracts

Knowledge of quality control and standardization of allergen extracts is of crucial importance in immunotherapy (159). For details of allergen standardization, see the EAACI Allergen Standardization and Skin Tests Position Paper (48). The present paper deals only with aspects related to immunotherapy.

2.1. Standardization

2.1.1. Raw material

The allergen raw material should be selected from relevant allergen source material. Detailed instructions for harvesting, storage, extraction, purification, etc. have been given by the IUIS (International Union of Immunologic Societies) (5), in the Nordic Guidelines (134), and by the EC (Production and quality control of allergens, III/9271/90-EN draft No. 5). Manufacturing of allergen extracts should be based on Good Manufacturing Practice (GMP).

2.1.2. Methods of allergen standardization

Details of allergen standardization and calibration are given in the EAACI Allergen Standardization and Skin Tests Position Paper (48). A major problem affecting allergen standardization is that allergen

extracts are standardized in relation to IgE reactivity, to diagnose IgE-mediated diseases. This may not be the most relevant parameter with regard to extracts used for immunotherapy, but no therapeutic units have been convincingly documented.

2.1.3. Calibration of allergen extracts

It is recommended that allergen manufacturers produce well-characterized, in-house reference standards for calibration of future productions. The method used for calibration should be stated. In-house standards should be biologically standardized and calibrated in terms of total allergen activity, if possible in conformity with international standards (138).

2.1.4. Nomenclature

The nomenclature for individual components of allergen extracts should be stated according to the WHO bulletin of 1986 (114).

2.1.5. Units

So far, the activity of allergenic extracts has been stated in many different units. Only those giving potency (total allergen activity) and concentration of individual components are regarded as relevant and should be used (134, 138).

2.1.6. Declaration

The vials may be declared by labeling the potency (total allergen activity) in relevant units obtained by a documented method. The expiry date must also be stated on the vial. The package insert could state in IU the concentrations of a selected number of important individual allergens, but absolute units might also be used. Methods should be stated. Inserts should also include potency (total allergen activity) determined as biologic units by quantitative skin testing, stating the method used. The rationale behind this recommendation is that the potency of the extract should be clearly stated on the vial, but the physician wishing to compare extracts from different sources can find these data on the package inserts, and only figures for concentration of individual components will be directly comparable.

2.2. Allergen extracts for immunotherapy

2.2.1. Aqueous extracts

The great majority of previous immunotherapy studies have been performed with crude aqueous extracts, i.e. crude mixtures of allergen and nonallergenic material. At present, most aqueous extracts on the market are partly purified; that is, nonallergen, low-molecular-weight substances have been removed. These allergen preparations can easily be standardized, and have, in fact, some obvious ad-

vantages when immunotherapy is involved (93). They may be used for rush immunotherapy (continuous injections with intervals of 30–60 min until maintenance dose) or clustered immunotherapy (2–5 injections per visit). The disadvantages of aqueous extracts are the rapid degradation of allergens, and the fact that the frequency of side-effects is higher than when depot or modified extracts are used (52), but, on the other hand, serious systemic side-effects are elicited within 30 min after injection, while the patient is still under medical supervision.

2.2.2. Depot and modified extracts

In an attempt to make immunotherapy more effective and reduce side-effects, depot and modified allergen extracts have been developed. The principle of modified extracts is to reduce or remove allergenicity, i.e. the ability to induce IgE-mediated reactions, and at the same time preserve or increase immunogenicity, i.e. the ability to stimulate the immune system, so that the extracts remain clinically effective (64). The problems of the structural alterations of allergens are complex and far from clear. A reduction of native epitopes (IgE-reacting determinants) means that higher doses of allergens can be administered before side-effects occur. Whether the IgE-reactive epitopes are of significance in the clinical effect, or the antigen sites are placed physically near the IgE epitopes, the modification means that the potency of the extracts is actually reduced. Larger amounts of allergen need to be administered to achieve an effect, and therefore the same risk of side-effects is taken as with native allergen extracts. It is not known whether it is possible totally to modify the IgE-binding epitopes and retain the immunologically active extract.

Generally, in order to replace the corresponding unmodified extract, any modified extract should be equal or superior to it in both efficacy and safety. The degree of efficacy, as measured by symptom/medication score, in relation to placebo or unmodified allergen preparations with scientifically well-documented clinical properties should be established. It is essential that dose-efficacy relationships be established, and dose-safety trials must be started at an early stage in the development of new products.

It is presently not possible to ascertain whether all epitopes are retained in modified extracts, a fact which calls for clinical trials for the standardization and evaluation of these preparations.

2.2.3. Types of modification

2.2.3.1. *Physical modification.* Physical modification includes adsorption, absorption, inclusion, etc. of allergens which can all be regarded as depot ex-

tracts. Examples of carriers are aluminum hydroxide, calcium phosphate, tyrosine, and liposomes (194).

2.2.3.2. *Chemical modification.* Chemical modification applies to polymerized extracts, e.g. the so-called allergoids such as formaldehyde modified extracts, glutaraldehyde modified extract, and alginate modified extract. Other examples are nonpolymerized extracts, e.g. methoxypolyethylene glycol modified extract (47).

2.2.3.3. *Combinations of modification.* Combinations of physically and chemically modified extracts include tyrosine glutaraldehyde modified extracts and aluminum pyridine.

2.2.4. Standardization and control of modified allergen extract

Standardization should always include the following two items: 1) standardization of the starting material used in the modification process, and 2) documentation of the reproducibility of the modification process.

2.3. Mixtures of allergen extracts

Traditionally, allergen extracts for immunotherapy have been prescribed by physicians on an individual basis. Manufacturers have supplied allergen extracts as either single allergens or mixtures. Both mixtures of related and unrelated allergens have been distributed on the basis of individual prescriptions.

In future, the following types of allergen extracts may also be distributed, provided the potency, composition, stability, etc. have been documented:

- 1) single allergens
- 2) mixtures of some related, cross-reacting allergens including grass-pollen extracts, deciduous-tree-pollen extracts, related mite-allergen extracts, etc.
- 3) mixtures of other allergens, provided stability data are available.

We recommend that one not use mixtures of unrelated allergens. A number of related allergens have epitopes in common, leading to cross-reactivity. Examples of such interrelated extracts are those derived from *Dermatophagoides farinae*, and *D. pteronyssinus*; temperate grasses such as *Phleum pratense*, *Lolium perenne*, *Poa pratensis*, *Secale cereale*, etc.; *Alnus gincana*, *Betula verucosa*, *Corylus avellana*, etc.; and *Parietaria judaica* and *P. officinalis*. In these cases, cross-sensitization practically always occurs, and for the major allergens a sequence homology of more than 80% exists. It would therefore make no practical difference whether one uses a single extract or the mixture (59, 127, 200). On the other hand, single allergen species may be less effective because some relevant epitopes may be lacking.

For all noninterrelated allergen extracts, mixtures should be avoided for the following reasons: 1) they may be less stable in aqueous solution, since interactions between allergens may occur and enzymatic degradation of epitopes has been demonstrated; 2) it is more difficult to standardize mixtures; and 3) the patient's optimal dose is not identical for the various allergens in the mixture, leading to low-dose immunotherapy for some allergens.

We believe that a careful diagnosis can identify the few dominating sensitizing allergen sources, which should then be used as single allergen extracts injected separately during immunotherapy. The different allergen components in an allergen extract derived from one single allergen source may, of course, limit the dose administered. This problem can only be solved by administering single epitopes, and this is not practicable.

3. Monitoring of immunotherapy

Before starting immunotherapy, patients should be carefully instructed regarding efficacy and safety of immunotherapy. It is essential that the patient be informed of and completely understand the principle of the treatment and its risks and benefits. The patient should be carefully instructed and involved in the monitoring of immunotherapy, assuming part of the responsibility.

Monitoring of immunotherapy has three aims:

- 1) to register the patient's conditions and reactions to allergen injections as a guide for the treatment, i.e. safety monitoring
- 2) to evaluate the effect of immunotherapy, i.e. efficacy monitoring
- 3) to collect data for the fullest information of physicians, staff, and patients, i.e. data collection.

In everyday practice, monitoring should be undertaken in all patients; however, in clinical trials, monitoring should be more intensive.

3.1. Safety monitoring

Side-effects should be prevented, if possible, but the risk of allergic reactions is always present, since material to which the patient is allergic is injected in high doses. Safety monitoring is undertaken with the aim of reducing the risk of reactions due to immunotherapy, and includes:

- 1) evaluation of the patient before, after, and between injections
- 2) definition and grading of side-effects
- 3) registration of safety parameters.

Safety monitoring should include verbal and written information and instructions involving the patients in the monitoring of immunotherapy, with the aim of making patients more responsible for their own

safety. Monitoring should be supervised by the staff.

3.1.1. Patient condition

The patient's general and allergic condition before, after, and between injections should be monitored, including reactions to the previous injection. A checklist is recommended.

3.1.2. Definition and grading of side-effects

3.1.2.1. Local reactions. Local reactions may be divided into the following categories:

- 1) Immediate reactions appearing within 30 min. This type of reaction is mediated by the interaction of allergen and specific IgE on mast cells. If immediate local reactions exceed 5–10 cm in size, they are regarded by many clinicians as a warning sign of impending immediate systemic reactions, but there are no firm data to confirm this.
- 2) Delayed reaction with or without pronounced immediate local reaction. They do not precede systemic reactions and should be considered only when they cause inconvenience to the patient.
- 3) Local subcutaneous nodules (especially after the use of alum-containing extracts) at the site of injection (58). The nodules may itch, normally disappear after some time, and do not indicate that immunotherapy should be stopped.

3.1.2.2. Systemic reactions. The systemic reactions are defined as "symptoms, elicited by immunotherapy, remote from the injection site". They can be divided into: 1) focal symptoms, e.g. mild rhinitis and mild asthma; 2) urticaria, itching or flushing, itching of the throat, and angioedema; and 3) multiple symptoms terminating in anaphylactic shock.

Systemic reactions most frequently occur for three different reasons:

- 1) A dose higher than planned/scheduled is injected by accident (staff).
- 2) Too high a dose is injected in view of the actual sensitivity of the patient (patient/staff).
- 3) A (partial) intravenous injection is given by accident (staff).

Most severe systemic reactions occur within 30 min (69). However, delayed systemic symptoms, most frequently urticaria and angioedema (66), may develop within the first day(s), especially when depot allergen extracts are used.

3.1.2.3. Grading of systemic reactions. There are several methods of grading systemic reactions, one of which is a scale of 0–4 (Appendix 1).

The time of onset of systemic reactions should also be considered. The earlier symptoms occur, the higher the risk of progression of symptoms into

shock. Especially when occurring shortly after injection, any nonlocal reaction may progress into severe anaphylaxis. In the evaluation of systemic reactions, it is important to distinguish clearly between mild reactions responding adequately to minimal drug treatment, and severe, life-threatening systemic reactions requiring intensive pharmacotherapy. In the case of mild systemic reactions, immunotherapy may be continued by a more cautious dose-increase regimen. In the event of life-threatening systemic reactions, the advisability of continuing immunotherapy should be determined by a specialist (141).

3.1.3. Environmental control

A prerequisite for performing immunotherapy with allergens present in the patient's environment is that the patient be instructed to avoid contact with these allergens to the greatest possible extent. Any recent exposure causing symptoms should be considered before injections.

3.2. Efficacy monitoring

The only methods which truly reflect clinical efficacy are clinical evaluations. *In vivo* and *in vitro* laboratory tests have been used to evaluate immunotherapy, but such tests are only of value when associated with clinical efficacy. When the role of immunologic parameters in clinical efficacy is evaluated, a correlation must exist between the timing and magnitude of the alterations and the clinical response, before a relationship can be accepted. Furthermore, one has to be aware of epiphenomena, i.e. changes of parameters caused by immunotherapy, but with no association with clinical efficacy. The best parameter would be one with a causal relationship to clinical efficacy which could serve as a predictor of the clinical outcome in the early phase of treatment. When clinical efficacy is considered, it is crucial to accept only reductions in symptom severity and drug intake which, from a clinical point of view, significantly reduce the morbidity of allergic diseases (113).

No universal standard for clinical efficacy is available. Challenge tests reflect changes in shock-organ sensitivity which do not, per se, imply a reduction in disease severity and in the need for drug consumption. Clinical methods have limitations because of individual scoring of symptoms and need for pharmacotherapy, variations in allergen exposure and other nonallergenic triggers, etc.

Considerable evidence indicates that neither physicians nor patients can distinguish between an effective and ineffective procedure for allergic and immunologic disease without performing a proper trial. For example, before controlled trials, for at least 40 years, low-dose immunotherapy with ragweed pollen extract was considered to be an effective treatment for ragweed hay fever. In recent years, a number of controlled trials have demonstrated that low-dose immunotherapy for ragweed hay fever was no more ef-

fective than placebo, whereas immunotherapy with high doses of ragweed extract was highly effective. Nevertheless, many patients who had received low-dose immunotherapy or placebo were of the opinion that they had received an effective treatment. An unproven procedure should be considered to be experimental and likely to be ineffective until it has been proven effective by conducting a proper trial. (35)

Methods used to monitor efficacy should be validated properly. The same methods should be used before, during, and after immunotherapy. In everyday practice, evaluations should be performed at least once a year, at the same time of the year as the primary preimmunotherapy evaluation. In clinical trials, randomization to different treatment regimens is crucial for ensuring equal disease severity in various treatment groups. The best way to do this is to perform pretreatment evaluations applying symptom and drug scoring for an appropriate period; that is, in seasonal allergy for one season before starting immunotherapy. As no laboratory tests convincingly reflect the clinical severity of allergic diseases, this method represents the best way of allocation into comparable groups.

3.2.1. Clinical evaluations

The results of all methods mentioned should possibly be related to allergen exposure as measured by universal or individual pollen/spore counts, or to exposure to mite or animal-dander allergen in house dust, measured according to international standards.

3.2.1.1. Symptom and medication score. Symptom and medication scores should be registered in parallel, since they influence each other. Many scoring systems have been proposed. Simple systems that ensure good patient compliance should be used, e.g. 0–3 (0 = no, 1 = mild, 2 = moderate, and 3 = severe symptoms) for each organ involved. A similar scoring system for pharmacotherapy should be used, starting with one drug, and then adding others according to defined rules. In everyday practice, changes in drug consumption are useful in the evaluation of changes in symptoms between years. In clinical trials, strict rules should be applied to symptom and medication scoring systems.

3.2.1.2. Daily peak-flow measurements. Daily peak-flow measurements are part of the monitoring of asthma, and they are also part of the safety monitoring of immunotherapy. These data may be used in the evaluation of the efficacy of immunotherapy in asthmatic subjects. Similarly, nasal peak flow may be used in monitoring immunotherapy in rhinitis.

3.2.1.3. Subjective evaluation. Subjective evaluation scales comprising evaluation once a year are particularly suited for monitoring immunotherapy in everyday practice (163). Grading is often made ac-

cording to scales of 0–3 or 0–10. Another possibility is to use a so-called visual analog scale, i.e. a 10-cm line with indications of “much worse” to the left and “much better” to the right, and a short vertical line at the midpoint, corresponding to preimmunotherapy symptoms (Appendix 2). The patient marks changes in symptoms in relation to pretreatment level. This system may also be used in clinical trials.

3.2.1.4. Physician's evaluation. The physician's evaluation of improvement is obtained partly by interviews at patients' visits and partly by information obtained from objective investigations. It therefore has the same drawbacks as the patients' self-evaluation.

3.2.1.5. Exposure tests. Testing exposure to a given environment, e.g. a specified cat, or an occupational situation, may be of value, especially if combined with objective measurements such as peak flow, and registration of the time lag until objective signs appear (73, 142). In sophisticated setups, such exposure tests may be performed in a blinded fashion.

3.2.1.6. Other parameters for evaluating the condition of the patient. Included in this category are the following: 1) registration of days off work or school, 2) days of hospitalization or number of admissions to hospital, 3) number of respiratory infections, and 4) quality of life.

3.2.1.7. Conclusion. The most convenient way of evaluating in clinical practice the effects of immunotherapy in individual patients is to combine patients' self-evaluation with the physician's evaluation.

In clinical trials, precise information should be obtained regarding the patients' symptom and medication scores and peak-flow measurements.

3.2.2. Laboratory evaluations

In vivo laboratory methods

In vivo laboratory methods reflect the specific or nonspecific reactivity in the shock organs of the patient, but cannot replace the more laborious clinical methods in the evaluation of clinical efficacy.

3.2.2.1. Allergen provocation tests. Allergen provocation tests reflect the sensitivity of the shock organ under artificial conditions and do not always reflect natural exposure. Provocation tests investigating immediate and delayed reactions may be useful parameters during immunotherapy (189). Allergen provocation tests should be performed with either lyophilized, standardized allergen preparations, native pollen or spores and mycelia, or powdered

allergen materials. Especially in clinical trials the use of freeze-dried, standardized allergen preparations from the same batch is recommended.

3.2.2.2. Conjunctival and nasal provocation tests. Conjunctival and nasal provocation tests should be performed to evaluate the effect of immunotherapy on shock-organ sensitivity in rhinoconjunctivitis (140). They are not considered to be appropriate in the evaluation of the efficacy of immunotherapy in asthma.

3.2.2.3. Bronchial provocation tests. Bronchial provocation tests should be applied for evaluation of the effect of immunotherapy on shock-organ sensitivity in asthmatic patients (23). It is essential that validated methods for evaluation of the immediate and the delayed asthmatic response be used (118).

3.2.2.4. Provocation tests evaluating nonspecific hyperreactivity. Inhalation of histamine, methacholine, cold air, exercise, etc. may be used for measurement of bronchial nonspecific hyperreactivity (23). Some of these methods are also useful in the evaluation of hyperreactivity of the nasal mucosa.

3.2.2.5. Skin tests. The immediate and late skin reaction decreases during immunotherapy (108, 144, 152). An association has been found between changes in symptom and medication scores, and shock-organ or skin sensitivity (17). The most reliable method of establishing changes in skin sensitivity is parallel line bioassay, but simpler methods have been described (44). Skin tests for scientific monitoring of immunotherapy require at least duplicate tests and the use of several concentrations of allergen (46). A reference substance may be used (134). The precision of the skin test method is important (103), and simple methods of skin testing in the evaluation of immunotherapy cannot therefore be recommended at present.

3.2.2.6. Other techniques. Techniques recently applied in clinical trials to elucidate the mechanism of the efficacy of immunotherapy include skin and mucosal biopsies, nasal and bronchoalveolar lavage, and skin chamber techniques.

In vitro methods

In some clinical trials, changes in *in vitro* parameters have been shown to correlate with clinical efficacy (203). However, in many cases, there is no absolute correlation on an individual basis (26), and *in vitro* tests cannot replace the clinical evaluation of efficacy (23). The methods listed below have been investigated.

3.2.2.7. Allergen-specific IgE antibodies. Allergen-specific IgE frequently increases during the first months of immunotherapy (68, 108, 117). At the same time, shock-organ and skin sensitivity decreases (108). The immunotherapy-induced early increase in specific IgE does not seem to be pathogenic, probably as a result of a reduced affinity to the Fc-receptor (110), or to a switch from IgE+ to IgE- (96). During long-term immunotherapy, specific IgE shows a slow decline (59). Changes in specific IgE do not seem to be related to the clinical outcome.

3.2.2.8. Allergen-specific IgG antibodies. An increase in specific IgG is noted in most patients receiving immunotherapy with standardized allergen extracts, although most studies fail to correlate the response with the clinical efficacy in individual patients (13, 23, 112, 145). Specific IgG can show that relatively high doses have been administered. No exact limit ensuring clinical efficacy can be given. Increase in specific IgG as such is no indication of clinical efficacy.

3.2.2.9. Allergen-specific IgG subclass antibodies. In the early phase of immunotherapy, allergen administration induces an intense IgG1 subclass response, which gradually declines during prolonged exposure to allergens, unlike the long-lasting IgG4 response (41). Changes in IgG4 and IgG4/IgG1 antibody ratios have been shown to correlate with both a decrease and an increase in symptoms (42, 109, 117, 183). The time course and clinical relevance of such IgG responses should be further investigated, but available data do not indicate that IgG subclasses are useful in predicting the clinical outcome of immunotherapy (131).

3.2.2.10. Allergen-specific antibodies of other classes in serum. Allergen-specific IgA, IgM, and IgD antibodies have been investigated in a few trials, but no conclusive data are available (23, 38).

3.2.2.11. Allergen-specific antibodies in secretions. It has been postulated that secretory IgA and IgG in secretions exert a local blocking effect on the allergen activation of mast cells in mucous membranes. The concentration of such antibodies increases during immunotherapy; there are, however, no convincing data suggesting correlation with clinical improvement (23, 149).

3.2.2.12. Leukocyte histamine release. Basophil mediator releasability has in some studies been shown to decrease, and to correlate with the clinical outcome of immunotherapy (110).

3.2.2.13. Anti-idiotypic antibodies. The association of changes in anti-idiotypic antibodies with clinical efficacy is still debated (29).

3.2.2.14. Mediators of inflammation and interleukins. Changes in eosinophil and neutrophil chemotactic activity and eosinophil cationic protein levels have been observed during immunotherapy (60, 116, 156). Inflammatory mediators and cells induced by allergen challenge decrease during immunotherapy (75). Likewise, a switch from IL-4- to γ -interferon-producing T-helper cells has been found (50). The relevance of these parameters should be further studied. Analysis of these parameters cannot presently be recommended for routine immunotherapy.

3.2.2.15. Conclusion. No convincing data support the view that *in vitro* or *in vivo* parameters can replace clinical evaluation of efficacy or predict clinical outcome. Clinical efficacy is indicated by a reduction in symptoms and in need for drugs, i.e. a reduction in the morbidity of allergic disease.

3.3. Data collection

The specialist initiating immunotherapy in the patient is responsible for:

- 1) providing structured information to the patient
 - 2) monitoring immunotherapy
 - 3) providing continuous information to colleagues, nurses, and patients involved in immunotherapy.
- All physicians involved in immunotherapy are responsible for data collection and for following the guidelines given by specialists.

3.3.1. Aims of data collection

There are three aims of data collection: 1) to improve contact between patients, physicians, and staff involved in the treatment, thereby increasing the safety of immunotherapy; 2) to obtain full information on the status of patients at visits, after visits, and between visits; and 3) to obtain continuous information on safety and efficacy parameters from groups of patients.

3.3.2. Modes of data collection

Different kinds of recording forms, preferably adapted for electronic data processing, should be completed.

3.3.2.1. Form to be completed at each visit. This form should register: 1) allergen extract, concentration, volume, and dose; 2) patient's condition, including physical examination and peak flow before and 30 min after injection; 3) side-effects, including nature, timing, severity, and treatment given; and 4) recent exposure to allergens, e.g. pollen counts, mold spore

counts, mite concentration at home, and direct or indirect contact with animals.

3.3.2.2. Form to be completed by the patient. A form to be completed by the patient should be available. This form should register: 1) reactions appearing after leaving the clinic, and 2) graded symptoms, drug consumption, and peak flow, at least in patients with bronchial hyperreactivity, registered daily for 3 days preceding the visit.

3.3.2.3. Form to be completed at least once a year. A follow-up report completed by the treating specialist should include: 1) the patient's subjective evaluation of treatment result, e.g. by a visual analog scale; 2) *in vivo* (and *in vitro*) efficacy parameters, e.g. skin prick test, provocation tests, lung function tests, etc.; 3) physician's evaluation of the state of the allergic disease and safety of immunotherapy; and 4) a conclusion, including recommendations for further immunotherapy.

This registration should result in an overall view of the patient's status. It should be undertaken by the specialist responsible for initiating immunotherapy.

4. Practical immunotherapy

4.1. Recommendations for the organization of immunotherapy

The organization of the allergen-specific diagnosis and treatment (immunotherapy) varies among the various countries with EAACI membership.

Immunotherapy is administered by specialists in allergy, other specialists, general practitioners (GPs), and nurses, in hospitals, clinics, and offices (179).

The evaluation of the diagnostic tests and advising patients about allergen avoidance and immunotherapy call for a certain degree of experience of the physicians and the staff. It is recommended that the initial evaluation of an allergic patient, including the specific diagnosis and the indication for immunotherapy, be undertaken by an experienced specialist. Furthermore, the same specialists and their staff should administer immunotherapy injections until the maintenance dose. The patient may continue maintenance treatment by the specialist or by the GP in close collaboration with the specialist. The principle of immunotherapy requires a very close collaboration between the patient, the specialist, and the treating physician (141).

Regular controls, once a year or more frequently if indicated, should be carried out by the specialist undertaking the evaluation of the efficacy of the treatment by appropriate methods.

Physicians and nurses giving injections and administering immunotherapy should also be regularly

informed of recent scientific advances in immunotherapy, and trained in practical skills, e.g. injection technique, supervision, and emergency treatment (179). A trained nurse may give injections under supervision of a responsible physician. The practical organization should be arranged on a national basis, adapting to the situation in the individual country.

4.2. Patient information

When a doctor decides to prescribe immunotherapy for a patient, it is very important:

- 1) to inform the patient in such a way that the principle of treatment, efficacy, and the risk of side-effects are comprehended and to ensure that the patient agrees to the treatment
- 2) to establish an optimum of contact between the patient and the treatment staff.

The patient should receive verbal and written information about immunotherapy including descriptions of efficacy and possible complications and practical details of the duration of treatment, observation, cost-benefit, who is to administer the injections, etc.

The information to the patient should be given in such a way that the patient feels at ease with the treatment and can decide whether or not to accept the treatment. This information should focus on the following points:

- 1) Immunotherapy is a treatment aiming at increasing the patient's clinical tolerance of an allergen by regular subcutaneous injection of successively increasing doses of the allergen.
- 2) Immunotherapy is administered daily, weekly, or biweekly in the beginning (dose-increase phase), and then monthly or bimonthly for at least 3 years.
- 3) Immunotherapy aims at administering the optimal maintenance dose.
- 4) Immunotherapy supplements drug treatment and allergen avoidance.
- 5) Immunotherapy is potentially dangerous because allergen material is injected in a sensitized person; therefore, a 30-min observation period* after each injection together with observation of delayed reactions in the patient is essential.

An example of a patient information statement is shown in Appendix 3.

After the patient decides on immunotherapy, the initial treatment is started. During the dose-increase phase, it is of special importance to educate the patient in immunotherapy and to build confidence in the treatment and the staff. During this initial period, the patient's motivation for the treatment increases and the treating staff learn how the patient reacts. A

* In the UK the current observation period, by law, is 2 h.

well-started immunotherapy improves compliance with the treatment.

In patients with bronchial asthma, including allergic rhinitis with bronchial asthma, it is essential that all regular antiasthmatic drugs be continued. This is of special importance on the day of injection. In asthmatic patients, peak flow should be measured before and 30 min after the injection (179). Injections should be postponed in patients with peak flows below 70% of normal value. Likewise, caution is needed, and the injection must be postponed, when there are signs of an ongoing or recent viral infection, when there is recent allergen exposure, or when the patient has forgotten to use routine drugs. It is mandatory that the patient wait in the physician's office or waiting room for 30 min after the injection. The patient is instructed to report immediately any symptoms appearing during the observation period. The site of injection has to be inspected before the patient leaves the office. The patient must be instructed to consult a physician in case of a (serious) late reaction. The patient should also be instructed to avoid intense physical exercise, prolonged hot bathing, and contact with relevant allergens (especially pets) on the day of injection. Patients should carry their antiasthma medication, i.e. β_2 -agonist inhalers. Vaccination against infectious diseases should be separated from immunotherapy injections by an interval of at least 1 week.

4.3. Technique and supervision

4.3.1. Before injections

At each visit the physician has to evaluate patients' conditions and to assess their suitability to receive immunotherapy in order to decide on the appropriate dose (141).

The evaluation of patients should include detailed information about the following: 1) intercurrent infections; 2) intercurrent diseases; 3) intercurrent vaccinations; 4) drugs taken during the last 3 days; 5) recent changes of drugs (especially antiallergic drugs); 6) new drugs (especially β -blockers, ACE inhibitors, NSAIDs); 7) severity of allergic symptoms during the last 4–7 days; 8) history of late reactions after the last injection, including the character and severity (local erythema and swelling, systemic reaction, need of additional antiallergic treatment); 9) history of increased exposure to relevant allergens, especially animal dander or foods; 10) severity of atopic dermatitis; and 11) pregnancy. A patient record form should preferably be used. An example is shown in Appendix 4.

In all asthmatic patients, peak-flow recording (179), and, if needed, physical examination, should be performed before injections.

A detailed record form, including allergen extract,

physical evaluation, peak flow before injection, allergen batch number, concentration, volume, date of injection, site of injection, time of injection, etc., has to be completed by the physician (Appendix 5).

Before injections the allergen extract vial should be checked with respect to allergen extract, batch number, concentration, and expiry date. The allergen extract should be stored, handled, and injected according to the instructions of the manufacturer. Before administering injections, staff must be thoroughly trained in emergency treatment, and equipment and drugs should be immediately and easily accessible. Some guidelines (4, 141) for a basic list of drugs and resuscitation equipment for the treatment of side-effects are given in Appendix 6.

4.3.2. During injections

Injections must be given subcutaneously, and care has to be taken to avoid either intracutaneous, intramuscular, or intravenous injections. A 1-ml graduated tuberculin syringe is recommended (141). The recommended sites of injections are the lateral aspect of the upper arms or the dorsal aspect of the forearms.

The angle of injection should be about 40°. Lyophilized extracts should be totally reconstituted, and bubbles of air, clots, etc. must be avoided. Gentle aspiration should be performed before the injection and repeated once or twice, depending on the volume, in a gradually given injection.

In the case of immunotherapy with more than one allergen, the allergens should be injected separately, since the allergen in an allergen mixture to which the patient is most sensitive will limit further dosage increase of other allergens. By separate injections of different allergen extracts, it is possible to perform a titration to the optimal tolerated dose for each allergen extract. When two or more extracts are injected, it is recommended that injections be given in different anatomic sites at 30-min intervals to facilitate interpretation of possible systemic reactions. Patients with severe disease, especially severe asthma treated with more than one allergen extract, should receive injections on separate days.

4.3.3. After injections

The patient is instructed to report immediately any symptoms appearing during the observation period. After injections, patients should be supervised by nurses and/or physicians in the office/hospital for at least 30 min. Local reaction and peak flow should be registered on the record form 30 min after injections, before the patient leaves.

Children should be supervised by an adult the first hours following the injection, as, in case of symptoms, they might panic and fail to seek help.

Patients should be instructed to avoid contact with

relevant allergens and to avoid physical exercise on the day of injections. If side-effects occur, the physician has to treat the patient immediately with relevant drugs and to observe the patient intensively until all symptoms have subsided. Early recognition and appropriate treatment without any delay probably represent the best ways of avoiding life-threatening side-effects.

The treating physician must make written observations of the time of onset of side-effects related to the injections; the character and severity of local and systemic reactions; and doses, route of administration, and time sequence of pharmacotherapy needed. Serious and life-threatening side-effects should be reported to national authorities, and it is recommended that they be reported to the EAACI Immunotherapy Subcommittee in order to record data of side-effects for nonofficial registration (Appendix 7).

The patient must be instructed to consult a physician in the event of a systemic late reaction. The physician may supply the patient with antiallergic drugs for self-treatment of local side-effects.

4.4. Prevention and treatment of side-effects

4.4.1. Prevention of side-effects

In order to minimize the risk of eliciting side-effects, the patient should be assessed carefully, and the appropriate dose decided on before the injection is given. Particular attention should be paid when there is a history of increased exposure to relevant allergens, recent viral or bacterial infections, intake of drugs on the day of the allergen injection increasing the risk of immunotherapy (especially in asthmatic patients), recent history of exercise-induced asthma, and increased need for antiallergic drugs. It is advisable to continue the administration of antiallergic drugs until the maintenance dose has been reached.

Meticulous care should be taken to avoid mistakes involving patients, allergen extracts, allergen concentration, and volume injected (99).

In some centers, prophylactic antihistamines are used before injections to reduce the number and severity of side-effects. A placebo-controlled, double-blind study of pretreatment with terfenadine in honeybee-venom-allergic patients showed a reduction in cutaneous symptoms but no reduction in the more severe respiratory and cardiovascular symptoms (10). Such regimens need further evaluation before they can be recommended for general use.

4.4.2. Treatment of mild to moderately severe adverse reactions

Mild adverse reactions include local swelling, mild urticaria, or rhinitis, and these may require treatment

with oral or parenteral antihistamines. Large local swellings may be treated successfully with ice bags or topical glucocorticosteroids. For immediate, mild, or moderately severe bronchial obstruction, especially when occurring in patients treated with depot extracts, it is advisable not only to use a β_2 -agonist, but also to add oral corticosteroids to prevent late reactions. For severe bronchial obstruction ($FEV_1 < 50\%$ of the predicted value), some centers prefer to use adrenaline given by inhalation.

Patients with urticaria should be observed carefully, as this may be an early warning of an impending, more serious reaction.

4.4.3. Treatment of serious reactions

Anaphylactic reactions may progress rapidly, causing death within a few minutes. The early signs and symptoms of anaphylaxis include pruritus of the palms and scalp, intense erythema of the skin, conjunctival injection, and cough. Angioedema, laryngeal edema, severe asthma, hypotension, and shock may follow rapidly.

Subcutaneous or intramuscular adrenaline should be injected immediately, and the patient should be placed in a supine position. An intravenous line should be set up, and intravenous fluids should be administered rapidly. Steroids and antihistamines should be given, and antiasthmatic drugs and oxygen may also be required. In some patients, local injection of adrenaline around the site of the allergen injection combined with a tourniquet may be helpful (141, 189).

In severe cases of anaphylactic reactions, further doses of adrenaline may be required. In the event of poor peripheral circulation and no response to subcutaneous or intramuscular adrenaline, intravenous injections of diluted adrenaline may be needed. Patients should be observed in hospital for at least 24 h because of the risk of delayed anaphylactic reactions.

A scheme of the suggested treatment of side-effects in adults and children is given in Appendixes 8a and 8b.

4.5. Dosage schedules

Most dosage schedules involve administration of incremental doses at 1–2-week intervals, followed by maintenance injections given at intervals of 1–2 months. Depot preparations should be preferred for conventional immunotherapy. Aqueous extracts should be used in special conditions, such as rush or cluster immunotherapy. Various schedules are used to reach the patient's individual maintenance dose, often by duplicating the last dose.

A number of studies have clearly shown that low-dose immunotherapy does not sufficiently ensure

high clinical efficacy. On the other hand, high-dose immunotherapy increases the risk of eliciting life-threatening side-effects. Ideally, the maintenance dose achieved should be the highest tolerated dose not eliciting side-effects, i.e. the optimal dose. Based on the content of purified major allergens, this dose ranges between 5 µg and 20 µg (140).

The maintenance dose may be below the one recommended by the manufacturer, but it may also be higher. The manufacturer's schedule should therefore be used as a general guide only. In sensitive patients this must be modified, implying smaller doses, repetition of doses, and/or reduced increments. Highly sensitive patients may need smaller initial and top doses.

4.6. Dose modifications

The scheduled dose should be modified to give either a reduced dose, the same dose as the previous injection (i.e. no increment), or no dose in the case of adverse reactions. The following guidelines may be recommended, but it is of crucial importance to adjust allergen doses to individual variation in patient sensitivity and allergy state:

- Postpone injection under the following circumstances:
 - 1) respiratory tract infection within the last week; intercurrent disease with systemic symptoms within the last 3–4 days
 - 2) when peak flow is reduced by 20% from usual values
 - 3) recent deterioration of asthma
 - 4) in patients with exacerbations of atopic dermatitis
 - 5) intercurrent treatment with beta-blockers.
- No increment of allergen dose in the following circumstances:
 - 6) immediate large local reaction:
 - adults: > 5 cm
 - children below 12 years: > 3 cm
 - 7) delayed large local reaction > 8 cm or smaller if inconvenient to the patient
 - 8) when there has been an increased interval between injections.
- The dose should be reduced in relation to the preceding injection in the following situations:
 - 9) systemic reactions (immediate or late)
 - 10) increased environmental exposure to allergens, i.e. coseasonal treatment
 - 11) when changing to a new batch of nonstandardized allergen extract.

The magnitude of the dose reduction is dependent on the severity of the reaction. Generally, the safety of the patient is the most important aspect, and it is advisable to reduce the dose in cases of uncertainty.

5. Alternative immunotherapy

With the overall aim of improving the safety of immunotherapy and making it more convenient to patients, routes other than the subcutaneous administration of allergens have been investigated. Placebo-controlled studies, however, are limited, and alternative procedures of immunotherapy are still controversial in many ways.

5.1. Oral immunotherapy

Although several trials have been performed in the past decades, few have been carried out optimally, i.e. as controlled (usually placebo) studies. This small number of studies has produced controversial results. With enteric-coated tablets protecting the allergen from intestinal fluid, a clinical efficacy has been demonstrated in patients sensitive to birch-pollen (14, 126, 178) and mugwort-pollen allergens (estimated by a decrease in bronchial response) (94). An inadequate efficacy was demonstrated in oral-grass-pollen-treated patients (33, 121, 177, 182). In only one study have acceptable results been obtained (191).

A combination of standard subcutaneous immunotherapy in the dose-increase phase with extension treatment by the oral route does not seem to be effective (158, 169, 186). A single study using Pollinex grass pollen has shown the combination of three preseasonal injections with oral maintenance treatment or three additional injections of the top dose to be more successful than the three preseasonal injections alone (72).

A puzzling question about oral immunotherapy is how it works (153). Even with enteric-coated tablets, there is a marked variation in the rate of allergen release, and allergen denaturation makes the calculation of the amount of absorbed allergen difficult (201). The major argument in favor of oral immunotherapy is its safety (15). Although oral ingestion is likely to be less dangerous than injections, the variable results obtained are not sufficient to define the degree of risk. The regimen of daily intake would be practical only if it could be administered at home (153). However, we lack evidence that oral immunotherapy is safe enough for home use. Another problem is the cost of allergen extracts. The top dose of allergen used for oral immunotherapy is about 4000 times higher than the one used for conventional subcutaneous immunotherapy, reducing the practicability of this kind of treatment.

Despite the fact that good clinical results have repeatedly been obtained with enteric-coated birch pollen, oral immunotherapy is presently not a practical option in routine work. There is still a need for more controlled trials to document the results with

this method, to define the limits of this method, to clarify the real risk, and to come to a better understanding of the way this method works.

5.2. Sublingual immunotherapy

The documentation of the clinical efficacy of low-dose, sublingual application of allergens is meager. Two placebo-controlled, double-blind studies have shown a beneficial effect of low-dose sublingual therapy in mite-allergic patients (170, 176). This treatment principle is highly controversial (2, 197), and these pilot studies are interesting, but call for further documentation. More conclusive data are required before low-dose, sublingual therapy can be recommended for routine treatment of allergic disorders.

5.3. Local nasal immunotherapy

Immunotherapy administered locally in the shock organ has been investigated intensively in rhinitis patients. The clinical efficacy has been demonstrated in several studies (40, 62, 78, 119, 133). The use of aqueous extracts is generally associated with significant rhinitis symptoms. It is a question of whether nasal application does, in fact, provoke mild symptoms over a long period, as opposed to the severe symptoms registered with nontreated patients in the short pollen season (198, 199). Some studies using modified extracts have shown an adequate reduction in seasonal symptoms with no serious side-effects (62, 133). Another possible way to avoid local discomfort is pretreatment with cromoglycate, for example. A potential risk connected with nasal application is the induction of asthma by inhalation of allergens into the lungs.

No studies have compared the clinical efficacy of local nasal immunotherapy with conventional subcutaneous immunotherapy. The place of local nasal immunotherapy in the treatment of allergic patients has not been defined. We recommend further studies investigating the relative benefits and inconvenience in relation to conventional immunotherapy.

5.4. Local bronchial immunotherapy

On the basis of experience with nasal immunotherapy, Italian investigators have performed a double-blind, placebo-controlled study of local bronchial immunotherapy with *Dermatophagoides* extract in asthma (39). They observed a reduction in early bronchial sensitivity and in the severity of the late reaction. No significant differences in symptom score, drug consumption, and peak flow were seen. Side-effects were limited to episodes of bronchial obstruction.

5.5. Experimental immunotherapy

Several possible methods of manipulating the immune system have been tested in animal models (88). In human studies, allergen-specific T-suppressor cells modulating the IgE response have been generated (175). Immunotherapy during cyclosporine administration to achieve immunologic tolerance might be a potential approach in the treatment of allergic patients. In an attempt to achieve tolerance, the clinical efficacy of the injection of allergens and homogeneous IgG in allergen-antibody complexes (11, 101, 102) or in allergens coupled to T lymphocytes (162) has been investigated. The elimination of IgE-producing B-lymphocyte clones has been attempted, involving extracorporeal radiation (157) and injection of radioactive, "high-hot" labeled allergens (54). The use of lymphokines, and other regulatory molecules or monoclonal antibodies may produce a specific suppression of the IgE synthesis (30). Inhibition of mediator release can theoretically be undertaken by using monovalent allergens (which impede the bridge formation between two IgE molecules). Enzymatic degradation of allergens with retention of T epitopes and reduction of B epitopes has shown a significant clinical efficacy (98). Antibodies against IgE receptors, and synthetic monovalent peptides imitating sequences of the heavy-chain Fc portion of the IgE molecule may be used (61, 67).

Although immunomanipulation is still in its experimental stage, it opens up exciting prospects for the future treatment of allergic disorders.

Concluding remarks

A significant clinical efficacy of immunotherapy has been documented in a number of controlled studies. The capacity of drug treatment is limited to the elimination or decrease of symptoms, and no studies have been able to show that pharmacologic treatment of allergic diseases, not even corticosteroids, modifies the spontaneous, long-term course of the disease. We recommend that immunotherapy form an integrated part of the treatment of allergic disorders, thus reducing the disease severity, improving the quality of life of allergics, and diminishing the risk and cost of pharmacotherapy. Recent concepts of allergic diseases, especially asthma, focus on the inflammatory components in the pathophysiology of the disease. A fundamental advantage of immunotherapy in the treatment of allergy may be its interference with the pathophysiologic mechanisms causing mediator release. The logical approach in the treatment of allergic diseases must be to impede the natural course of the disease. Not only the direct clinical benefit, but also the possible preventive aspects of immunotherapy should be considered.

Indications

Identifying patients who would be most likely to benefit from immunotherapy requires diagnostic procedures combining both the demonstration of IgE-mediated sensitivity to relevant allergens by appropriate diagnostic tests, and a clinical history correlating with laboratory findings and the exposure to the relevant allergen. The patient should be carefully evaluated to determine whether the severity of the disease justifies this kind of treatment by balancing the relative benefits, risks, and inconvenience of immunotherapy. Factors favoring the use of immunotherapy are, over a period of years, either progression of the severity of the allergic disease or progression from rhinitis to asthma in spite of attempted allergen avoidance and pharmacotherapy. Immunotherapy should not be commenced before trying to eliminate the allergen whenever feasible. We recommend that immunotherapy begin early in the disease process in order to reduce the risk of side-effects, and to prevent the further development of severe disease.

The indication for immunotherapy should be considered to be equivalent to that for prophylactic drug treatment, and immunotherapy should be started on the same disease severity. Patients who need daily pharmacotherapy should be offered supplementary immunotherapy to obtain a multifactorial treatment approach interfering broadly with the pathophysiologic mechanisms of allergic diseases. We should focus on the long-term advantages of instituting immunotherapy in the early course of allergic diseases in combination with the best pharmacologic treatment. We recommend that treatment be continued for 3–5 years before evaluating the long-term efficacy without immunotherapy. Patients with obvious clinical efficacy during immunotherapy whose disease relapses after terminating treatment should be offered a new, prolonged course of immunotherapy. Immunotherapy should not be started during pregnancy, or when serious immunopathologic conditions, malignancies, treatment with β -blockers, and lack of cooperation are present.

Allergen extracts

Quality control and standardization of allergen extracts is of crucial importance in immunotherapy. The raw material should fulfil IUIS guidelines. The vials should be declared by labeling the potency (total allergen activity) in relevant units obtained by a documented method. Allergen extracts should not include nonallergenic material, and all relevant epitopes should be represented. Modification of allergen extracts should be used only on condition that the therapeutic capacity is not reduced. Although this is

controversial, we recommend that mixtures of unrelated allergens not be used.

Monitoring

The patient should be carefully instructed and involved in the monitoring of immunotherapy, assuming part of the responsibility. The objective in monitoring allergen immunotherapy is safety, efficacy, and data collection. Clinical efficacy is indicated by a reduction in symptoms and need for drugs, i.e. a reduction in the morbidity of allergic disease. The only methods which truly reflect clinical efficacy are clinical evaluations. *In vivo* and *in vitro* laboratory tests are only of value when associated with clinical efficacy. In clinical practice, the most convenient way of evaluating the effects of immunotherapy in individual patients is to combine patients' self-evaluation with the physician's evaluation. No convincing data suggest that *in vitro* or *in vivo* parameters can replace the clinical evaluation of efficacy or predict clinical outcome.

Practical immunotherapy

The evaluation of the diagnostic tests and advice to patients about allergen avoidance and immunotherapy call for a certain degree of experience of the physicians and the staff. It is recommended that the specific diagnosis and the indication for immunotherapy be undertaken by an experienced specialist. Furthermore, the same specialists and their staff should administer immunotherapy injections until the maintenance dose. The patient may continue to receive maintenance treatment from the specialist or from the GP in close collaboration with the specialist. The principle of immunotherapy requires very close collaboration between the patient, the specialist, and the treating physician. The patient should receive verbal and written information about immunotherapy, including a description of efficacy, possible complications, practical details of the duration of treatment, observation, costs, who is administering the injections, etc. The information to the patient should be given in such a way that the patient feels quite at ease with the treatment and can decide whether to accept the treatment.

At each visit the physician has to evaluate patients' conditions and assess their suitability to receive immunotherapy in order to decide on the appropriate dose. In patients with bronchial asthma, including allergic rhinitis with bronchial asthma, it is essential that all regular antiasthmatic drugs be continued. This is of special importance on the day of injection. In asthmatic patients, peak flow should be measured before and 30 min after the injection. Injections should be postponed in patients with peak

flows below 70% of normal value. Likewise, caution is needed, and the injection must be postponed, when there are signs of an ongoing or recent viral infection, or recent allergen exposure, or when the patient has forgotten to use routine drugs. It is mandatory that the patient wait in the physician's office or waiting room for 30 min after the injection.

Side-effects should be adequately treated without unnecessary delay. Adrenaline is the best drug for serious systemic reactions and anaphylaxis. Steroids, antihistamines, antiasthmatic drugs, oxygen, etc. may be necessary to resuscitate the patient. It is recommended that injection be postponed in cases of intercurrent disease, exacerbations of allergic disease, and intercurrent treatment with β -blockers. There should be no increment of allergen dose in cases of large local reaction or increased interval between injections. The dose should be reduced, in relation to the preceding injection, for systemic reactions (immediate or late) and increased environmental exposure to allergens, i.e. coseasonal treatment, and when changing to a new batch of nonstandardized allergen extract.

Alternative immunotherapy

With the overall aim of improving the safety of immunotherapy and making it more convenient to patients, routes other than the subcutaneous administration of allergens have been investigated. Placebo-controlled studies, however, are limited, and alternative procedures of immunotherapy are still controversial in many ways. Despite the fact that good clinical results have repeatedly been obtained with birch-pollen treatment, oral immunotherapy is presently not a practical option in routine work. More conclusive data are required before low-dose sublingual therapy can be recommended for routine treatment of allergic disorders. Immunotherapy administered locally in the shock organ has been investigated intensively, and its clinical efficacy has been demonstrated in several studies. The position of local immunotherapy in the treatment of allergic patients has not been defined. Although still at its experimental stage, immunomanipulation of allergic diseases opens up exciting prospects for the future treatment of allergic patients.

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