

The current status of allergen immunotherapy (hyposensitisation)

Report of a WHO/IUIS working group

Members: *R.A. Thompson*, Regional Immunology Department, East Birmingham Hospital, U.K. Chairman of IUIS Clinical Immunology Committee, and Chairman of the Working Group. *J. Bousquet*, Service des Maladies Respiratoires Hôpital Aiguelongue, Montpellier, France. *S. Cohen*, National Institute of Allergy and Infectious Diseases, Bethesda, Md. U.S.A. *P.C. Frei*, Division d'Immunologie et d'Allergie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. *L. Jäger*, Institute für Klinische Immunologie, Jena, DDR. *P. H. Lambert*, Chief Microbiology and Immunology Support Services, WHO, Geneva. *M. H. Lessof*, Department of Medicine, Guy's Hospital, London, U.K. *R. H. Loblay*, Clinical Immunology Research Centre, University of Sydney, Australia. *H. J. Malling*, Allergy Unit, Rigshospital, Copenhagen, Denmark. *P. S. Norman*, Clinical Immunology Division, Good Samaritan Hospital, Baltimore, Md. U.S.A. *A. L. de Weck*, Institute for Clinical Immunology, Berne, Switzerland. President, International Association of Allergology and Clinical Immunology. *B. Weeke*, Allergy Unit, Rigshospital, Copenhagen, Denmark.

Allergen immunotherapy (or hyposensitisation) is the name given to the practice, first initiated by Noon in 1911, of administering gradually increasing quantities of an allergen extract to a clinically sensitive subject so as to ameliorate the symptoms associated with subsequent exposure to the causative allergen (42). This procedure has been widely used for the past 75 years to treat allergic disorders of the immediate hypersensitivity type, now known to be primarily mediated by allergen-specific IgE antibodies, but it is not used for other forms of adverse immunologic reactions. Good evidence now indicates that the procedure can be effective but more knowledge is needed of the circumstances which favour effective immunotherapy without the risks of anaphylaxis.

Most of the patients who have been given this form of therapy have had rhinoconjunctivitis or asthma, or experienced severe reactions to insect stings. While allergic symptoms due to foodstuffs are recognized, immunotherapy in food-related disorders is not indicated at present. Adverse reactions to drugs are sometimes treated by similar procedures in order to achieve short-term clinical tolerance, but the underlying mechanisms differ.

The availability of potent pharmacologic agents for the management of these conditions has caused a change in the use of immunotherapy in recent years. There has also been doubt about its efficacy and uncertainty as to the most appropriate therapeutic regimens. Some patients' symptoms also deteriorate despite immunotherapy, and a number of adverse reactions, including fatalities, have been reported. Immunotherapy is relatively easy to administer, both by specialists and nonspecialists, and in the majority of patients it is well tolerated. With inappropriate selection of patients or treatment regimens, however, poor results can be expected, and most of the fatalities associated with this therapy occur in relatively inexperienced hands. This has led to public concern and reports by quasi-Governmental agencies placing restrictions on this practice (13). Recent reports by the European Academy of Allergology and Clinical Immunology (11, 39), and several reviews of the subject by distinguished allergologists (16, 61) have kept a scientific balance in discussion of the issue.

This report, initiated by the Clinical Immunology Committee of the International Union of Immunological Societies, and the Microbiol-

ogy and Immunology Support Services of the World Health Organization, reviews the present status of allergen immunotherapy, its scientific basis and the clinical evidence of its efficacy. It also makes recommendations as to its indications and contra-indications, the most appropriate allergens and treatment regimens, and the avoidance and management of adverse reactions. Finally, it indicates future developments in this form of treatment.

Basic mechanisms (of action) of immunotherapy

A variety of immunologic changes have been observed in patients undergoing allergen immunotherapy, but it is not yet possible to determine the precise mechanism by which symptoms are alleviated in individual cases. Several possibilities, not mutually exclusive, have been proposed including altered regulation of IgE synthesis, production of "blocking" antibodies of other isotypes, and decreased reactivity of effector mechanisms.

IgE regulation. Like other immune responses, IgE production is regulated by complex interactions between antigen-presenting cells, T helper (Th) and T suppressor (Ts) cells (28, 31). Atopic individuals may have a disturbance of one or more of these regulatory mechanisms, leading to the tendency to make inappropriate IgE responses to a variety of environmental allergens (52, 54).

During immunotherapy there is a reduction in the expected seasonal rise in IgE antibodies following environmental exposure and a slow decline over several years in the level of specific IgE (15). It has been suggested that selective stimulations of Ts cells may be responsible for suppressing IgE synthesis during allergen immunotherapy. In humans, isotype- as well as antigen-specific Ts cells have been found in patients treated with allergen immunotherapy but not in untreated controls (51, 55). However, the clinical relevance of these observations is uncertain since the benefit of immunotherapy does not correlate precisely with reductions in specific IgE levels in individual cases. Further-

more, because human studies are largely restricted to peripheral blood, and because of other technical limitations, suppressor cell assays are difficult to interpret. Animal experiments suggest that local suppression of IgE synthesis in the target organ and draining lymphoid tissues may be of more importance (25).

"Blocking" antibodies. Antibodies of the IgG and/or IgA class are induced by immunotherapy and may correlate reasonably well (though not absolutely) with clinical response (23, 29), especially in circumstances where allergen is disseminated via the bloodstream (e.g. Hymenoptera venoms). At the very least the presence of such antibodies indicates that a particular allergen preparation is immunogenic in the dose, route and form used. Recent observations that passive hyperimmune serum given together with allergen can inhibit the development of adverse reactions during immunotherapy provide compelling evidence that IgG antibodies can prevent clinical symptoms at least in the short term (10, 41). Prolonged immunotherapy results in a switch from IgG₁ to IgG₄ production (1, 58), and the blocking effect of the latter isotype is currently being evaluated. In some patients there is a lack of complete correlation between allergen-specific IgG titres and clinical response, and it has been suggested that in such cases the IgG response may be directed to a different epitope or antigen than the IgE response (30).

It has been assumed that "blocking" antibodies combine with the allergen at the mucosal surface (46), but this has not yet been definitively demonstrated. Among other possible mechanisms are anti-idiotypic or anti-isotypic regulation (9), or downregulation by antigen-antibody complexes on IgE-producing B cells via cross-linking of Fc receptors and membrane immunoglobulin (53), thereby reducing their IgE production.

Effector cell downregulation. Immunotherapy appears to be specific for the allergen used (43) and in many patients is associated with a specific reduction in skin test reactivity (33). Furthermore, a reduction in both the early and late

phase response to allergen provocation has been demonstrated during immunotherapy (19, 50). Early phase inhibition may be explained by allergen-specific mast cell downregulation (35). Late phase inhibition may be explained by a reduction of inflammatory cells infiltrating the tissue and reduced lymphocyte proliferation and production of lymphokines in response to allergen (26), and this may also account for a decrease in non-specific hyperreactivity. In addition, a nonspecific reduction in histamine release by blood basophils has been shown (60).

IgE-mediated drug hypersensitivity. Rapid increases to full doses have been achieved in urgent situations where it is essential to administer a drug, such as penicillin or insulin, to which the patient is allergic. There is no evidence that this induces immunologic changes in the short term, but the method is capable of achieving clinical tolerance which is lost on cessation of therapy. The mechanism is likely to involve hapten-inhibition (36).

Studies with specific allergens

Over the years since the introduction of the method, clinical evaluation of the efficacy of immunotherapy has been hampered by: (i) lack of standardized allergen preparations; (ii) poor definitions of the desired level of benefit; (iii) variation in patients' perception of symptoms; (iv) differences between natural and presumed allergen exposure and (v) the coexistence of other allergies and non-specific triggers in patients undergoing evaluation of single allergen immunotherapy (16). Nevertheless, well-controlled studies show that specific immunotherapy is effective in IgE-mediated anaphylactic reactions, rhino-conjunctivitis and asthma. The specific allergens adequately studied include stinging insect venoms, pollens, house dust mites, animal danders and a few moulds.

Patients who have undergone generalized allergic reactions or frank anaphylaxis after a sting from an insect of the family of Hymenoptera can be fully protected after immunotherapy with doses of venom from the offending

insect, whereas injections of extract of whole body of the insect offer no more protection than placebo injections. The protection against a single sting performed in the laboratory is usually complete and is accompanied by a rise in IgG antibodies to venom constituents (27).

Evidence of efficacy in pollen-induced rhino-conjunctivitis and asthma has come from the controlled study of grass (20), ragweed (34), birch (62), mountain cedar (47) and *Parietaria* allergies (8). The techniques of evaluation include not only symptom reporting but also objective tests, such as skin tests, nasal, bronchial and conjunctival challenges as well as correlations with *in vitro* tests of immunologic response.

Although extracts of house dust have been employed for years in house dust sensitivity (2), current knowledge indicates that they should be replaced by extracts of the allergens regularly found in dust samples, such as mites and animal danders. House dust mite extracts appear to be an effective material in areas where mites are the major allergen in dust. Several double blind trials demonstrate efficacy in controlling symptoms, a decrease in responsiveness to allergen on nasal and bronchial challenge, a rise in specific IgG antibodies, and a decline in IgE antibodies (12, 17).

Immunization with cat pelt extract reduces the response to bronchial challenges by an aerosol of extract (56) or the ocular and pulmonary symptoms upon exposure to living cats (44), but significant improvement of the clinical state of asthma has yet to be demonstrated. Dog allergy has been less completely studied.

In studies of sensitivity to the moulds *Alternaria* and *Cladosporium* (38, 40), rhinitis and asthma patients treated with adequately standardized extracts have reduced nasal, ocular and bronchial responses to challenge, and some studies showed clinical improvement. However, as most mould-sensitive patients are allergic to multiple species, and commercial extracts have yet to be characterized and standardized, their clinical applicability is limited.

The concept of IgE-mediated allergy to the yeast *Candida albicans* is controversial and proof is lacking for the efficacy and safety of immunotherapy with *Candida* extract (45).

Bacterial vaccines have consistently failed to be efficacious in a number of controlled studies of the treatment of asthma (16, 61), and should not be used for allergen-specific immunotherapy.

Catalogues of allergen extracts from commercial suppliers usually contain lists of hundreds of other inhaled materials available to physicians for diagnostic testing and immunotherapy. Even though they may be useful for diagnosis, their use for immunotherapy depends on uncontrolled clinical observation without the support of evidence of immunologic response. To what extent the well-established information available from the study of a small list of allergens can be extrapolated to a limited number of other less well characterized but clinically relevant allergens is a matter for judgment by the individual physician.

Standardization of extracts

Allergen extracts are derived from biologic materials and are heterogeneous mixtures of multiple specific allergenic determinants and inert materials. Furthermore, the IgE responses to the allergenic determinants vary from patient to patient.

Although extracts are commonly labelled for potency in terms of wt/vol (dry weight of starting material/volume of extracting fluid) or PNU (1 protein nitrogen unit = 0.00001 mg protein nitrogen) (14), neither is necessarily related to allergenic activity or immunizing activity in immunotherapy, (5, 6). Units for labelling can more appropriately be related to biological activity by several *in vivo* and *in vitro* methods. Skin tests are employed for comparison of unknown extracts with standardized materials. Two specific techniques have achieved some acceptance, the HEP (histamine equivalent prick) system in the Nordic countries (3) and the AU (allergy unit) system in the USA (57). *In vitro*, RAST inhibition is widely used to assess the overall allergenic potency of batches of extracts (22). These tests require some additional characterization of extract composition such as isoelectric focussing, techniques derived

from immunoelectrophoresis or immunoblotting.

Several other immunologic techniques measure specific allergenic components directly by employing monoclonal or monospecific polyclonal antibodies (16). For example, in the USA the content of the major allergen of ragweed and of cat dander are given in mass units on the label of these extracts.

The Allergen Standardization Subcommittee of the International Union of Immunologic Societies has developed standard extracts of short ragweed pollen (24), timothy grass pollen (21), *Dermatophagoides pteronyssinus*, (18), birch pollen (4), dog dander (32) and Bermuda grass pollen (7), and has prepared large batches of glass sealed ampoules and has arbitrarily assigned to them international units (IU). These materials have been extensively tested for biologic activity and content of specific allergens by immunologic methods and the first five have been accepted by WHO as International Standard Preparations (ISP). Other ISPs are being developed.

In the future, standardization in accepted units based on actual measurements of biologic activity in comparison with a stable standard should replace standardization based on wt/vol or PNU content. Physicians and investigators will be able to communicate more intelligently about the sensitivity of their patients or the doses used in immunotherapy including the optimal dose. However, the variability in biologic measurements based on different groups of patients make it inevitable that some variability will be found in extracts standardized at different times and places, so that despite similar labelling, physicians should be cautious when changing the treatment of patients from extracts made by one company to extracts made by another company.

Patient selection: indications and contra-indications

Allergen immunotherapy is effective only in IgE-mediated allergic diseases. It is not indicated in the management of patients with chronic

bronchitis, emphysema, non-IgE-mediated rhinitis and non-IgE-mediated asthma, nor as yet in dermatologic, gastrointestinal, rheumatologic or neurologic diseases. In choosing patients for this form of therapy, strict criteria are essential for safe and effective results. The selection of patients for immunotherapy should be made by clinicians experienced in allergology. For all patients a variety of factors must be taken into account, but it is essential first to establish the IgE-mediated nature of the condition (39).

The only absolute indication for immunotherapy is in patients who have experienced severe IgE-mediated anaphylactic reactions to Hymenoptera venom stings, and in whom the likelihood of subsequent exposure exists. For patients with asthma and/or rhinoconjunctivitis, factors which favour consideration for immunotherapy are: (i) definite evidence of IgE mediated disease in which allergens are considered to be the major triggers; (ii) failure of allergen avoidance; (iii) inadequacy of drug therapy or the presence of undue side effects; (iv) the availability of suitable allergen extracts; (v) a limited spectrum of allergen sensitivities; (vi) patient compliance; (vii) the absence of other general contra-indications (39, 61).

Patients with severe exacerbations of asthma should not be excluded from consideration for immunotherapy, but it should be avoided in patients with severe chronic asthma whose FEV₁ is consistently below 70% of the predicted value despite adequate pharmacotherapy (39).

Diagnosis. Taken alone, no single test method provides sufficient diagnostic information. The presence of IgE-mediated disease can be diagnosed in most instances by correlating the appropriate history, skin tests and/or the *in vitro* detection of specific IgE antibodies. In some cases it may be more difficult and may require direct challenge of the shock organ (39, 61).

Pharmacologic treatment. The benefits, side effects, cost and duration of symptomatic treatment must be balanced against those of immunotherapy. Immunotherapy by itself achieves various degrees of symptomatic relief, which may

be short of complete remission. Patients receiving immunotherapy should not discontinue pharmacologic therapy without advice.

Age. Remission is more likely to occur in children than in adults, but immunotherapy is less well tolerated in small children and is seldom indicated below 5 years (39).

Compliance. Because of the importance of adhering to the dose schedule and the avoidance of adverse effects, patient compliance is essential. Patients should be carefully informed of the nature of the procedure, its possible side effects and be encouraged to keep records of their symptoms to help evaluate the response (39).

Multiple sensitivities. In general, patients with multiple unrelated sensitivities, e.g. to pollens, dust mites, animal danders, and moulds, have more severe or more complex disease and do less well on this form of therapy.

Other general contra-indications. These include: a) diseases of the immune system, or other relevant organic disease; b) conditions which make the management of adverse reactions more difficult, such as coronary artery or hypertensive disease, or patients on treatment with beta-adrenergic blockers; c) patients developing repeated severe reactions during treatment; d) pregnancy, unless the patient is already on treatment before the commencement of the pregnancy. However, in insect venom anaphylaxis immunotherapy may be cautiously commenced.

Recommended procedures

The following recommendations, based on the cumulative experience of allergologists over the years, are included for guidance (39, 61).

Types of extracts. Allergens may be administered as aqueous extracts, depot extracts (allergens bound to aluminium or calcium salts, or tyrosine) or modified extracts.

a) *Aqueous allergen extracts:* are rapidly absorbed from the site of injection, so that systemic

side effects, if any, appear immediately (within 2–30 min after injection). Many studies to validate the efficacy of immunotherapy have used aqueous extracts. They may, however, be less stable than the others.

- b) *Depot allergen extracts*: are widely used. They are slowly absorbed from the site of injection, so that systemic side effects, if any, are generally milder. Anaphylaxis, if it does occur, appears as quickly as with aqueous extracts.
- c) *Modified allergen extracts*: the principle in modified allergen extracts is to reduce allergenicity and side effects while retaining immunogenicity. Studies have shown that some modified extracts are efficacious while others are not.

Allergens. There are a large number of allergen extracts available, few of which are well standardized biologically (59). The combination of different allergens in a mixture may offer difficulties in achieving an effective maintenance dose for each constituent and may be less effective.

Storage. The extracts should be stored in a refrigerator (2°–4°C) and only removed for the minimum time necessary. Dilutions prepared for storage should be made up in an appropriate protein stabiliser. All non-aqueous extracts should be shaken before use.

Mode of administration. Injections should only be given under medical supervision. Subcutaneous administration is the most widely used, best documented and generally recommended. Intravenous injection should be strictly avoided. Other forms of administration such as oral, nasal, sub-lingual and bronchial have been used experimentally, but the data concerning their clinical use is still inconclusive, and they are not recommended for routine purposes.

Timing of immunotherapy

Immunotherapy for seasonal allergens should not be started during the allergen (pollen) sea-

son, as initiation of therapy during the allergen season increases the risk of side effects. Instead, treatment should be started so as to reach maintenance dose before the season. Both perennial and pre-seasonal treatment are effective.

Dose schedules

Usual dose schedule. Injections are usually given once or twice weekly until reaching the maintenance dose. As the dose tolerance varies from patient to patient, guidelines which are often supplied by the manufacturer should only be considered as suggestions. While high maintenance doses increase efficacy, the dose of the more potent extracts may be limited by side effects. Methods based on skin test titrations and very low maintenance doses have been shown to be ineffective.

Modified dose schedules are both efficacious and rapid in reaching the maintenance dose, at the expense of some increased risk of anaphylaxis. They are used in patients who need acute protection, or who may require a shortened course for socio-economic reasons. Both types of therapy can only be used with aqueous extracts.

Rush immunotherapy is a course of increasing doses, administered in a short time at 30–60 min intervals for one half to a few days, depending on the sensitivity of the patient.

Clustered immunotherapy involves the administration of increasing doses of allergen in a series of several injections, with 30–60 min intervals, separated by several days.

Immunotherapy of children. The indications are the same as in adults, but for the children between 5 and 12 years, a lower dose schedule may be necessary.

Change of allergen batch

When a change to a new batch of non-standardized extracts is made it is recommended that the dose is reduced. For biologically standardized material, adequately stored, this may not be necessary.

Supervision

The patient must be under direct medical supervision for at least 30 min after each injection.

Duration of immunotherapy

Immunotherapy is a long-term treatment. However, immunotherapy should not be continued without regular re-evaluation of the patient's response. The optimal length of treatment is unknown. Usually a treatment period of at least 3 to 5 years is recommended. As a general guideline for the duration of immunotherapy, the patient should be symptom-free or have experienced substantially reduced symptoms for 1–2 years before discontinuation of treatment.

Treatment failures. Treatment may be unsuccessful because of incorrect diagnosis, insufficient allergen dosage, and the development or aggravation of other allergies. In addition, a proportion of patients do not respond to immunotherapy.

Adverse reactions

Local reactions to the injection of allergen extracts include the immediate development of wheals and erythema at the site of the injection and the development of more diffuse swellings which persist for several hours or, in severe cases, for a day or more. In addition, there may be immediate systemic reactions, including anaphylaxis and life-threatening exacerbations of asthma.

Apart from these reactions provoked by injections, there have been anecdotal reports of persistent worsening of the original condition and rarely of the development of connective tissue disorders (48). However, evidence of a causal relationship is lacking.

Incidence. Local reactions of some degree are

almost invariable and are not a contraindication to further treatment. The prevalence of more severe systemic reactions has been analysed in the UK, where the frequency of such reactions, both fatal and non-fatal, has varied from 1 in 63 for potent extracts, to 1 in 28,000 treatment sets for other extracts (13). These figures may be an underestimate, because many adverse reactions are not reported, but patients with asthma appear to have been particularly susceptible. The prevalence of serious reactions appears to have increased substantially as more potent extracts have come into use. Between 1957 and 1986 the British Committee for Safety in Medicines noted 26 deaths from anaphylaxis caused by allergen extracts. When safety aspects in the USA were reviewed by Lockey and his colleagues, they were able to trace 46 fatalities over a period of 42 years (37).

Precautions and prevention. Since a significant proportion of deaths are due to errors in dosage and timing, meticulous care must be given to the procedures followed (49). The following are recommended:

- Direct medical supervision of allergen administration.
- Adequate training of personnel who should be capable of providing external cardiac massage and mouth to mouth breathing.
- Adequate observation period after each injection, with a view to the early recognition of local and systemic reactions, and prompt treatment.
- Available facilities should include supplies of epinephrine (adrenaline), oxygen, and intravenous fluids.
- In the case of asthmatics, clinical evaluation and where possible peak flow (or equivalent) readings should be made before each injection and repeated before the patient departs.

A waiting period of 30 min after each allergen injection has been widely used throughout the world, since there is no convincing evidence that a longer wait can alter the fatality rate. This observation period should be extended if,

on direct questioning, the patient admits to have developed symptoms of a general reaction, even if they are mild.

Attempts to anticipate reactions in high risk groups have met with limited success. Prophylactic antihistamines are sometimes used. Adverse reactions are more likely to occur with high concentrations of extract (61) but they may also occur at low doses. Where there is a high degree of sensitivity, as indicated either by the clinical history or strongly positive skin tests, it is common practice to use a reduced starting dose for immunotherapy. If there has been a recent exacerbation of asthma or rhinitis or an intercurrent infection, the next dose should be delayed or reduced. When asthma, rhinitis or urticaria, hypotension or angioedema occur after an injection, the next dose should be reduced to a third (61), and a reduction is also advisable in the case of severe local reactions. Nevertheless, this policy cannot provide complete protection. Of 26 fatal reactions reported in Britain to the CSM, only six had a history of adverse reactions to previous injections (13).

Management. Most local reactions require no specific treatment. Severe ones which may last for periods of a few days can be managed by simple measures such as antihistamines or steroids.

Systemic reactions, including bronchospasm, hypotension, angioedema and urticaria are first treated with 0.5 ml 1:1000 epinephrine subcutaneously or intramuscularly. If a dose is to be calculated, as in the case of children, 0.01 ml/kg can be given and repeated, if necessary. The site at which the epinephrine is injected is not crucial. The administration of oxygen is also helpful. Hypotension is treated by vasopressors, by intravenous fluids and, despite their slow action, by corticosteroids.

Asthmatic reactions are treated by conventional means, using injected or nebulised bronchodilators (beta-adrenergic agonists), oxygen, intravenous aminophylline infused slowly, and corticosteroids. Stridor due to laryngeal oedema may require inhaled or parenteral epinephrine, oxygen, intubation and, rarely, tracheostomy.

Future prospects and studies in the immunotherapy of allergic diseases

Improvements in current procedures of immunotherapy.

Improvements may be expected from better standardization of allergens, the use of adjuvants, and the use of depot preparations as a means of regulating allergen availability and presentation. These may lead not only to improved efficacy but also to a decrease of side effects. It may also be possible to monitor more effectively the likelihood of adverse reactions by measuring IgG specific antibodies in the first months of immunotherapy.

New approaches to the modulation of IgE responses. In experimental animals, allergens which have been chemically denatured or coupled to "tolerogenic" residues have induced IgE tolerance more efficiently without eliciting anaphylactic reactions or similar side effects. This, however, applies only to unprimed or recently primed animals and cannot be extrapolated to human allergic disease. Clinical trials with such chemically modified allergens have not, as yet, fulfilled early expectations. Structural characterization of major allergenic epitopes in combination with the techniques of molecular biology may enable the development of modified allergens of greater potency, e.g. linkage with vaccinia virus or lymphokine genes to create genetically engineered allergen preparations.

Suppression of the IgE response in the normal non-atopic individual is apparently due to T suppressor cells and/or various factors, which may be allergen-specific (T suppressor factors) or non-specific. Consequently, it might be possible to use substitution therapy, with such suppressor factors or other cellular products by DNA recombinant technology or to reinfuse the allergic patient with clonally expanded subsets of specific suppressor T lymphocytes. Alternatively, simultaneous administration of allergens with immunosuppressive agents may induce specific unresponsiveness.

Considerable interest is now developing in the ability of lymphokines or lymphokine inhibitors

to dampen or restore suppression in the IgE network of atopic patients who are prone to multiple sensitization.

When the regulatory functions of immunoglobulins have been more precisely defined this may provide opportunities to develop further passive immunization procedures, both to react with allergens and in modulating the IgE response. For example, both in bee venom (10) and grass pollen allergy, such attempts have been sometimes helpful, particularly in initiating immunotherapy in highly sensitized patients.

Anti-idiotypic antibodies directed against IgE idiotypes (i.e. specific mirror images of the allergen) develop during the IgE response and also during immunotherapy. Investigations in experimental animals have shown that the IgE response may be controlled and suppressed in this way. However, the complexity of the anti-idiotypic response makes its applicability in man uncertain.

IgG anti-isotypic antibodies directed against IgE develop during immunotherapy. These auto-antibodies may have different functional roles: some may block the function of IgE carrying effector cells, others may potentiate IgE mediated reactions.

Identification of the gene(s) associated with the high IgE response of atopics may allow the better identification of high risk individuals, currently possible only by IgE determination at birth. This may permit the early institution of preventive measures or active intervention.

Blocking reactions at the effector level. In addition to the continuing pharmacologic approaches in developing antagonists to inflammatory mediators or drugs which block the activation of, or mediator release from, inflammatory cells, several other approaches are now emerging. These involve interference with IgE binding to its specific receptors on effector cells, interference with IgE receptor expression and turnover or its permanent blockade by peptides or other structures mimicking IgE. Other approaches may involve interference with the lymphokine-mediated priming of effector cells, which appears to be required for the secretion of inflammatory mediators.

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Address:

Dr. R. A. Thompson

Regional Immunology Department
East Birmingham Hospital
Birmingham B9 5ST
U.K.