

Immunotherapy in the Prevention of Allergic Disease

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ABSTRACT

In response to lay and medical urgings for physicians to apply more effort in the prevention of disease rather than prescribing palliative symptomatic forms of treatment, immunotherapy offers a good setting for preventive medicine. Immunotherapy takes place primarily in an outpatient or private practice setting rather than in academic institutions. Only a small minority of the millions of atopic children receive appropriate immunotherapy. It has been clearly demonstrated that immunotherapy is clinically effective in the treatment of pollinosis, asthma, and perennial allergic rhinitis. Based on what is known about the natural history of respiratory allergy in children with and without immunotherapy, perhaps the situation requires more education of the lay public in order to give parents some voice in the decision-making about when and whether immunotherapy is indicated. Because the chances of a child's "outgrowing" his asthma without immunotherapy are slim and because early institution of immunotherapy may prevent complications of untreated hay fever, a closer consideration of the appropriate application of this form of therapy seems indicated.

INTRODUCTION

In the lay and medical literature much effort is made to urge physicians to pay more attention to the prevention of disease rather than the treatment of it. If the practicing pediatric allergist does his task well, he provides a classic example of preventive medicine. Immunotherapy as well as other aspects of the therapeutic management of such common atopic respiratory conditions as asthma, hay fever, and perennial allergic rhinitis and their complications take place almost exclusively in an outpatient setting rather than in academic hospitals. Physicians providing primary care to children learn soon after entering practice that respiratory allergies make up one-third of all chronic illnesses in American children.⁽¹⁾ As recently as 1975, asthma caused more than 2000 deaths and prompted 183,000 hospital admissions costing an estimated \$1.06 billion.⁽²⁾ However, in spite of this, only a

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small minority of allergic children receive immunotherapy.⁽³⁾ Why is this? Is it because their physicians believe it is unnecessary? Is it because academic pediatricians are not teaching medical students and house staff what the pediatric literature tells us about the natural history of allergic disease in children? Perhaps the situation requires more education of the lay public to press primary physicians, including pediatricians, to give parents some voice in the decision making about when or whether immunotherapy is indicated. Parents have a right to ask their child's primary physician what is known about the chances of an asthmatic child's "outgrowing" his disease with or without immunotherapy, as well as the risk of a child with hay fever developing asthma with or without immunotherapy. In these days of great concern about the cost of medical care it is "penny wise and pound foolish" to defer immunotherapy treatment of these children on the false hope that symptomatic medication will take care of the problem.

In the overview of what part immunotherapy plays in the treatment of allergic disease, it is important to focus on the general role it plays in the care of these conditions. Immunotherapy by itself does not constitute the whole treatment of any allergic child. It is only one part of the holistic⁽⁴⁾ approach to such treatment. There are four general parts to the treatment. If a primary physician focuses his attention on only one of these parts of the allergic management of an allergic child, he completely misses the point of optimal holistic medical management of the allergic child. Assuming that all of these factors receive equal attention by authors of medical articles may color the validity or credibility of their published results. These factors are:

1. Efforts to interrupt or lessen exposure to known offending allergens.
2. Judicious use of prophylactic and therapeutic pharmacologic agents. This assumes a knowledge of the appropriate uses of these drugs.
3. General advice including avoidance of nonspecific irritants such as tobacco and other strong odors, use of physiotherapy (chest clapping and postural drainage), home monitoring of symptoms, and educational and vocational counseling.
4. Appropriate immunotherapy. Immunotherapy is indicated for those IgE-mediated respiratory atopic conditions in which effective avoidance of suspected offending allergens is impractical.

Common causes of failure of immunotherapy include the following:

1. Use of nonspecific antigens (i.e., extract of *Rhus toxicodendron* or urine autoinjection therapy).⁽⁵⁾
2. Inappropriate dose of antigen. Too large a dose can induce anaphylaxis. An inadequate dose of ragweed in asthmatics alters neither the symptoms nor bronchial activity.⁽⁶⁾ The optimal dose for each patient is the largest dose he can comfortably tolerate without developing large local or systemic anaphylactic reactions.
3. Use of immunotherapy for conditions for which it is of questionable value, such as local reactions to insect stings or bites, urticaria, migraine, food allergy, contact dermatitis, anaphylaxis brought on by nonatopic, nonspecific mediator release resulting in classical or alternative pathway complement activation.
4. Use of poorly defined allergens that are not properly standardized.⁽⁷⁾
5. Inappropriate route and technique of antigen administration (sublingual, subcutaneous provocation and neutralization).⁽⁸⁾
6. Intranasal cocaine abuse.⁽⁹⁾

With these introductory considerations it is appropriate to review briefly how immunotherapy works. Noon's classical report⁽¹⁰⁾ on immunotherapy published in 1911 is still the basis of my response to parents who ask "How do allergy injections work? What do they do?" Noon noted that instilling a drop of timothy grass extract onto the surface of an eye of a hay fever sufferer immediately caused redness and itching of the eye. He then found that if he made numerous concentrations of the extract, people's reactions differed according to the degree of dilution of the extract to still evoke a positive response. When he repeated this same eye test after a period of immunotherapy, he then found that it took several times more concentrated material to produce the same symptoms. Something he had accomplished by giving injections of timothy extract somehow rendered these patients resistant to

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developing an itchy eye from instillation of the same concentration of grass pollen extract where pretreatment had evoked a response. While he had no concept of what we now consider a rational explanation⁽¹¹⁾ of his findings, the work was a masterpiece of clinical investigation.

Over the years since Noon's work, much has been learned about mechanisms of action of immunotherapy. In 1962 VanArsdel and Middleton showed that after hyposensitization therapy a greater concentration of specific antigen is needed for optimal histamine release from patients' basophils. While changes in leukocyte sensitivity are affected by specific immunotherapy, Lichtenstein *et al.*⁽¹²⁾ found that only half of their patients had a change in basophil reactivity. The tendency for patients with loss of basophil reactivity to have less severe symptoms had some clear exceptions. Changes in histamine release will account for some but not all beneficial results of immunotherapy. Changes in leukocyte sensitivity seem to occur more regularly in children than in adults.

Cooke *et al.*⁽¹³⁾ and Loveless⁽¹⁴⁾ called attention to the differences between what we now call skin-sensitizing IgE "reaginic" antibodies and IgG "blocking antibodies." Early attempts to understand how immunotherapy works centered on these blocking antibodies. These antibodies apparently bind allergens in order to effectively inactivate them. They appear in a patient's serum soon after injection of allergen and their concentration rises steadily with continued allergen injections. But they are somewhat unpredictable. For one thing, the level of IgG antibodies plateaus and even declines with repeated high-intensity desensitization, but the patients may continue to improve. Blocking antibodies do not sufficiently explain immunotherapy. In spite of the fact that the level of these antibodies rises with therapy, the correlation between a rise in blocking antibodies and clinical improvement is not perfect. A minority of treated patients with high antibody titers do not do well and some with low titers do well. But generally there is a positive relationship between antibody titer and clinical improvement. After several years of grass pollen immunotherapy Davey *et al.*⁽¹⁵⁾ found that the blocking antibodies being produced were of the IgG₄ type. Similarly, after years of bee stings, beekeepers' antibody response to stings results in the production of IgG₄⁽¹⁶⁾ antibodies to venom rather than the IgG₁ type of antibody they initially produce when first exposed to bee stings. After immunotherapy, there occurs also an increase in antigen-specific blocking IgA and IgG antibodies in nasal secretions.⁽¹⁷⁾

Immunotherapy results in a suppression of the usual seasonal rise in specific IgE antibodies⁽¹⁸⁾ compared to a group of equally sensitive placebo-treated controls who have been naturally exposed to pollens to which they are sensitive. Connell and Sherman⁽¹⁹⁾ demonstrated that prolonged treatment with ragweed antigen resulted in a decrease in the titer of skin-sensitizing antibody to the same antigen, whereas in the same patients, reactivity to other antigens remained constant. This suggests that immunotherapy is antigen-specific.

Recently allergists have begun giving more attention to the importance of the "late reaction" in some asthmatic children. When one performs a bronchial challenge test with an antigen to which the child is known to be sensitive, there occurs a drop in forced expiratory volume in the first second (FEV₁) within a few minutes of the antigen challenge. This is the classical immediate-type reaction. This is then followed in some patients by a second fall in FEV₁ at approximately 6 to 8 h after challenge or natural exposure to the allergen. This "late reaction" is thought to be the hallmark of chronic asthma. Warner *et al.*,⁽²⁰⁾ in an elegant double-blind controlled study of the efficacy of hyposensitization in children with asthma due to sensitivity to *Dermatophagoides pteronyssinus*, showed that the main effect of immunotherapy was on the late bronchial reaction. Similarly, Pienkowski *et al.*⁽²¹⁾ found that immunotherapy was associated with the suppression of the cutaneous late phase reaction on skin testing. The magnitude of the late phase reaction was correlated with the level of IgG anti-ragweed antibodies. They, like Warner, believe that the clinical efficacy of immunotherapy is directly related to the effects on late phase reaction.

Neutrophil granulocyte chemotaxis is affected by specific immunotherapy. Rubin *et al.*⁽²²⁾ described a group of patients with eczema, urticaria, and allergic rhinitis; each patient suffered many severe recurrent bacterial infections associated with exacerbation of their allergic disease. Following *in vitro* exposure of the leukocytes of these symptomatic untreated children to ragweed extract, a profound depression in chemotactic activity was noted. By contrast, the leukocytes of a group of children who

had been successfully treated with immunotherapy showed no depression of chemotaxis. The authors also demonstrated the antigen specificity of this phenomenon as well as the ability to transfer the depression of chemotaxis to normal cells suspended in the sera of untreated patients. The authors speculated that this phenomenon might explain the high incidence of recurrent infections in some allergic children. It might also explain the observation that many seriously allergic children seem to have fewer severe infections after they have been on immunotherapy.

Rocklin *et al.*⁽²³⁾ reported that lymphocytes of ragweed-sensitive patients produced greater than normal amounts of migration inhibition factor and mitagenic factor when challenged *in vitro* with ragweed antigen E. These same investigators reported in 1976⁽²⁴⁾ that immunotherapy of hay fever patients with extract of short ragweed resulted in a significant decrease in lymphocyte proliferation and production of mediators. In 1980 Rocklin *et al.*⁽²⁵⁾ demonstrated that ragweed immunotherapy injections induce production of antigen-specific T cells which suppress the expected lymphocyte proliferation.

A technique which is said to monitor both effects of immunotherapy and changes in degree of sensitivity of patients was recently reported by Dreborg and Holgersson.⁽²⁶⁾ They studied changes in the size of prick skin tests to allergens before and after a period of immunotherapy. They found that after three months of immunotherapy a decrease of skin sensitivity corresponding to an increase in allergen concentration from 5 to 5000 times had occurred.

TECHNIQUES OF HYPOSENSITIZATION

Attempts at oral hyposensitization were reported in the American literature 25 years ago. However, it has not been popular with allergists, partly because of reports of occasional anaphylactic reactions to ingested pollens. In recent years several European groups have reported beneficial results using the oral route of hyposensitization for pollen allergy. Möller *et al.*⁽²⁷⁾ reported a study in which 30 children with birch spring pollinosis were given enteric-coated capsules containing either birch pollen or placebo. The pollen-treated children had less symptoms during the birch pollinating season as well as a decreased conjunctival provocation test after three months of therapy. They also had a decreased skin reactivity. None of the treated children developed asthma during the study, compared to five of the placebo-treated children who did develop asthma. Similarly, van Nielkerk,⁽²⁸⁾ in a study of South African grass and maize-sensitive hay fever patients found in a double-blind study of oral immunotherapy that treated patients had significantly fewer hay fever symptoms than did placebo-treated patients. Taudorf *et al.*⁽²⁹⁾ reported a study of oral hyposensitization with birch pollen extracts. After one year the sensitivity to birch pollen was significantly lower in the treated group than in the placebo-treated group when measured by conjunctival provocation and skin tests but not by nasal provocation tests. Contrary to the placebo group, the IgE anti-birch antibody level of the treated group did not increase preseasonally.

Croce and Zuppi³⁰ reported a novel technique at attempted hyposensitization. They treated 17 patients who had experienced asthma after inhalation challenge with either house dust or cat antigens. Each subject was given an inhalation of the most dilute extract of offending allergen capable of inducing bronchospasm, preceded by an inhalation of 40 mg of sodium cromoglycate dissolved in saline. This was repeated 2–3 times each week, slowly increasing the concentration of antigen given by inhalation challenge. Fifteen of the 17 subjects became “tolerant” to home exposure to the offending allergen.

Others have reported using intranasal administration of allergen. Welsh *et al.*⁽³¹⁾ reported on the effect of preseasonal intranasal ragweed immunotherapy in a double-blind 20-week study involving 33 ragweed-sensitive patients. Treated subjects received solutions of short ragweed intranasally 6 times per day for the 13-week prepollen period. Placebo subjects received solutions of buffered saline or histamine. The treated group reported more preseasonal symptoms. However, during the ragweed pollination season the treated group reported fewer symptoms of sneezing, nasal congestion, rhinorrhea, red, itchy eyes, itchy nose and throat, as well as coughing and wheezing. No significant changes

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were seen in the concentration of circulating IgE antibody to whole ragweed or to antigen E, Ra, e, or Ra 5 in either group. No significant production of IgG antibody to ragweed was seen in either group. In a similar study of intranasal administration by Nickerson *et al.*⁽³²⁾ comparisons of symptom-medication scores revealed a significant improvement in the ragweed treatment group compared to the placebo-treated group. On the other hand, Mathews *et al.*⁽³³⁾ in a trial of intranasal immunotherapy thought that it was clinically ineffective.

Attempts at hyposensitization in patients sensitive to drugs have been made with some success. Sullivan *et al.*⁽³⁴⁾ reported on their attempts at oral desensitization of 30 patients, suffering from life-threatening illnesses requiring penicillin therapy, who had a history of a positive skin test to penicillin. Beginning with an oral dose of approximately 100 units of penicillin, progressively doubled doses were given by mouth every 15 min until a dose of 400,000 units was reached. This was followed by three subcutaneous doses of 200,000, 400,000, and 800,000 units at 15-min intervals. Full therapeutic doses were then given. No deaths or anaphylactic reactions occurred and all 30 patients were able to receive planned antibiotic therapy.

Stevenson *et al.*⁽³⁵⁾ reported "desensitization" of aspirin-sensitive patients with rhinosinusitis and/or asthma by daily oral administration of aspirin. In some cases, however, this technique results in anaphylaxis requiring admission to an intensive care hospital unit. Consequently, this technique should be carried out initially only where there are adequate facilities to cope with potentially life-threatening anaphylaxis. The technique does not help in all patients on whom it is tried. When it has been successfully used in some patients, it results in relief of only asthma symptoms or only nasal symptoms but not both.

Changes in antigen formulation to improve their hyposensitization effectiveness have been investigated in recent years. Because conventional hyposensitization treatment requires repeated injections of aqueous extracts of allergens, numerous efforts have been made to modify the process. Loveless⁽³⁶⁾ reported a series of patients treated for hay fever with pollen extract emulsified in mineral oil. This method seemed to work but has been generally dropped from clinical use because of the finding that antigen-in-oil emulsion injections can induce plasma cell tumors in mice. This potential carcinogenicity has made them unacceptable to federal regulatory agencies. The use of alum precipitates of pollen extracts seems to offer a slight advantage in that it made it possible to reduce the number of injections required for preseasonal immunization. While this technique seemed to reduce the frequency of systemic reactions, there seemed to be large local reactions to them.

Another modified material combines extracts of allergens with the organic solvent pyridine followed by alum precipitation. Pyridine affects different allergens variably. Antigen E of ragweed is almost entirely denatured by it.⁽³⁷⁾ Marsh *et al.*⁽³⁸⁾ developed an "allergoid" by treating rye grass antigen with formaldehyde under mild conditions. Preliminary trials of allergoids in ragweed-sensitive patients showed that it seems safe and produces good antibody responses.

Glutaraldehyde may also be used to produce aggregates or polymers. Such polymers are more slowly absorbed than untreated allergens. They produce somewhat greater antibody responses than aqueous solution injections. Hendrix *et al.*⁽³⁹⁾ have shown good clinical efficacy in its use in ragweed hay fever. Local reactions were minimal and no systemic reactions were noted. This system also requires significantly fewer reactions per year than aqueous antigen injections. The FDA has not yet released it, however, for general clinical use.

Allergens have also been treated with glutaraldehyde and adsorbed onto suspensions of l-tyrosine.⁽⁴⁰⁾ With some allergens the incidence of systemic reactions was reduced to the point where treatment was accomplished in three injections. Metzger *et al.*⁽⁴¹⁾ reported a double-blind controlled study using glutaraldehyde-modified tyrosine-adsorbed ragweed extract. Some moderate late local soreness occurred at the site of injections. Symptom scores for the treated group were significantly lower than scores of the placebo-treated group. Sera from treated patients showed a 200-fold increase in ragweed-specific IgG antibody concentration, whereas the placebo-treated group showed no change. Similar studies have been reported using short ragweed couples to the nonimmunogenic polymer D-glutamic acid:D-lysine. Patients receiving this type of injection mixture fared clinically as well as

long-term standard hyposensitization with aqueous ragweed injections, and both groups were improved compared with placebo-treated controls.

It is important to consider, also, conditions for which immunotherapy is thought to be ineffective. For years bacterial vaccines have been used empirically for children whose asthma attacks seemed to be triggered by febrile respiratory infections. This concept seemed to be validated by the observations of Flensburg⁽⁴²⁾ and Crump⁽⁴³⁾ who reported that a significant portion of children in their studies with "infectious asthma" who were given autogenous bacterial vaccines prepared from bronchial washings developed asthmatic symptoms after injections of their own vaccines." But there are problems with accepting the recommendations of these authors for several reasons. Bernstein⁽⁴⁴⁾ pointed out that "There is little justification for the use of autogenous vaccines inasmuch as respiratory tract bacterial flora vary from day to day." McIntosh *et al.*⁽⁴⁵⁾ studied pharyngeal cultures of asthmatic children over one winter. They found no difference in the bacterial flora during wheezing and non-wheezing periods. However, there were 25 distinct respiratory syncytial viral infections in the group. Wheezing occurred with 24 of these 25 viral infections. This strongly suggests that viral, rather than bacterial, infections are the common "infectious trigger" of asthma attacks in young children. Further support of this view is found in studies of effectiveness of bacterial vaccines in asthmatic children. In 1959 Johnstone⁽⁴⁶⁾ reported on a prospective controlled study in which he could demonstrate no difference between results in vaccine-treated and placebo controls with "infectious asthma." These findings were independently corroborated by Aas *et al.*⁽⁴⁷⁾ in Norway and by Fontana *et al.*⁽⁴⁸⁾ in New York City.

Another condition for which immunotherapy is of doubtful value is atopic dermatitis. While a significant proportion of children with atopic eczema develop asthma and allergic rhinitis, Rasmussen and Prevost⁽⁴⁹⁾ have pointed out that "There is no proof that hyposensitization therapy shortens the duration of atopic dermatitis." However, if a child's eczema seems to be significantly related to inhalable allergens which the patient cannot easily avoid, hyposensitization may be tried. One placebo-controlled study by Kaufman and Roth⁽⁵⁰⁾ reported that improvement in the treated group was "significantly greater" than the improvement found in the placebo group. In the author's clinic as well as in private practice in Rochester, New York, the percentage of children with eczema thought to be appropriate for immunotherapy is very small. Also, it is important to remember that the dose of injected allergens used in treating atopic eczema must be kept smaller than those used for respiratory allergies. Hill⁽⁵¹⁾ pointed out that a dose of injected allergen required to control rhinitis or asthma is usually larger than that tolerated by patients with eczema. Thus, if a child's atopic dermatitis seems to flare specifically on the day he received his allergy injection treatment, one should suspect that the dose of his injections exceeds his clinical tolerance. Under these circumstances injection therapy must be drastically altered or discontinued.

Parents sometimes ask, "Are there unpleasant side effects or dangers from taking allergy injections?" There may be minor reactions seen in some patients. Early in therapy there is often a wheal and minimal erythema at the injection site. This appears approximately 20 min after the injection and usually subsides within a few hours. Some patients experience a local itchy or reddened swelling in the general area of the injection site beginning 2–4 h after the injections. This reaction reaches a maximum in 18–24 h and subsides in a day or two. These local reactions are usually of no importance and require no adjustment in the dosage schedule unless a rapid or great progression in the dosage leads to a large uncomfortable swelling at the injection site.

Occasionally a child will develop generalized itching, hives, nasal stuffiness, or signs of bronchospasm within a few minutes after his injection. For this reason, every child receiving allergy injections should always be properly identified before his injection to be sure that he receives his proper dosage. Also, he should be instructed to wait in the doctor's office a minimum of 30 min after injections, since almost all immediate reactions occur within this time frame. While most "constitutional" reactions are mild, they are potentially serious and require prompt treatment with a subcutaneous injection of epinephrine. The patient must be kept under observation for signs of shock. Administration of corticosteroids for several days after a severe constitutional reaction usually prevents

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a recurrence of hives and angioedematous swellings. However, these drugs have no effect on the immediate anaphylactic response itself.⁽⁵²⁾

In a search for possible other serious adverse reactions to immunotherapy Levinson *et al.*⁽⁵³⁾ found that atopic individuals receiving five or more years of immunotherapy with allergens showed no increase in autoimmune collagen, vascular, or lymphoproliferative diseases. They found no evidence of immune complexes in the sera of these patients undergoing long-term immunotherapy. Similarly, Stein *et al.*⁽⁵⁴⁾ found no statistically significant differences in the incidence of Clq-binding immune complexes, cryoglobulinemia, rheumatoid factor, or complement depletion in patients receiving immunotherapy compared with the normal population. Recently, Umetsu *et al.*⁽⁵⁵⁾ reported a single case of serum sickness which they theorized was triggered by anaphylaxis in a child receiving a maintenance dose of immunotherapy. Because they were unable to prove an alternative cause for the serum sickness, they concluded that immunotherapy might be the cause.

Greenberger and Patterson⁽⁵⁶⁾ did a literature search for the effects of symptomatic medications as well as immunotherapy in pregnant women. They concluded that properly carried-out immunotherapy may be safely given to pregnant women.

On the whole, then, the use of immunotherapy as a safe and effective mode of therapy has been well documented.⁽⁵⁷⁾

For which patients is immunotherapy indicated? Immunotherapy with selected antigens is effective in ameliorating symptoms of allergic rhinitis and extrinsic asthma. It is also helpful in preventing anaphylaxis from Hymenoptera stings. A typical candidate for immunotherapy is sensitive to several allergens and has found that despite avoidance precautions and use of over-the-counter medications, the symptoms are not adequately controlled. In the majority of allergic rhinitis, extrinsic asthma, and Hymenoptera-sensitive patients, immunotherapy provides a significant reduction in their symptoms. Several studies support this contention (Table 1).

TABLE 1. HOW EFFECTIVE IS IMMUNOTHERAPY?

<i>Investigator (year)</i>	<i>Antigens used</i>	<i>Number in study</i>	<i>Results</i>
<i>Allergic rhinitis double-blind studies</i>			
Frankland and Augustin (1954)	Grass (preseasonal)	200 children & adults	Treatment better than placebo
Johnstone (1957)	Ragweed (perennial)	72 children	High-dose treatment better than placebo or low-dose antigen
Lowell and Franklin (1963)	Ragweed (perennial)	164 children & adults	Treatment better than placebo
Sadan <i>et al.</i> (1969)	Ragweed (perennial)	35 children	Treatment better than placebo. Immunological findings correlated with clinical findings
Lichtenstein <i>et al.</i> (1969)	Antigen E (preseasonal)	40 (age not given)	Treatment patients had fewer symptoms
<i>Extrinsic asthma double-blind studies</i>			
Johnstone and Crump (1961)	Multiple aeroallergens	173 children	High-dose treatment better than placebo or low-dose treatment
Forgacs and Swan (1968)	House dust	70 children & adults	No difference in clinical response
Aas (1971)	House dust (perennial)	80 children & adults	Treated patients had less bronchial sensitivity by inhalation challenge. Good correlation with clinical improvement
Warner <i>et al.</i> (1978)	House dust mites	51 children	Treated patients improved more than did controls
Hills <i>et al.</i> (1982)	Grass	20 children	No benefit demonstrated

HAY FEVER

The most abundant evidence for the usefulness of immunotherapy in children is in the treatment of pollen hay fever. Frankland and Augustin⁽⁵⁸⁾ reported the first placebo controlled clinical trial of hyposensitization comparing both crude and partially purified grass pollen extracts in both children and adult patients with hay fever and pollen asthma. They reported that "94% of the patients treated with either pollen extract tested had good clinical results, whereas only 30% of those given placebo injections had similar results."

In spite of the report of Frankland and Augustin, controversy over the value of immunotherapy in seasonal allergic rhinitis persists in the minds of many pediatricians and family physicians. This is partly because of the differences in the natural history of hay fever in children and adults. In an effort to study factors of importance in the natural history of hay fever in children and to find some basis for the indications for the use of immunotherapy, a controlled prospective study was carried out by Johnstone.⁽⁵⁹⁾ The assumption at the start of the study was that to use immunotherapy for children with ragweed hay fever was of no value. The goal of the study was to find evidence to either support this thesis or disprove it. In a blind fashion children with ragweed hay fever were assigned to either a treatment group or a placebo group. They were followed for five years with symptom score cards, clinical evaluations by physicians who did not know a study was in progress, as well as periodic review of the records for evidence that the patient had been seen either in the clinic or hospital emergency room with symptoms of bronchospasm. The most dramatic finding was the fact that 50% of the placebo-treated group developed asthma for the first time during the study. They developed it first during a ragweed season and then most of them developed it also at other times of the year. Most of them also developed rhinitis in nonpollen seasons during the study period. None of those who received high doses of ragweed injections developed asthma during the study, if they had not already had asthma before the study began. A review of the study population revealed no distinguishing features of anyone in the placebo group which would indicate increased risk of developing asthma. Consequently, the author concluded that although he could have prevented asthma in only a portion of the children in the placebo group, children with pollen hay fever should receive immunotherapy regardless of the severity or mildness of their allergic symptoms. This points out one difference in the natural history of hay fever in children compared to adults. In adults the chances of an untreated hay fever patient over 30 years of age developing asthma because he did not receive immunotherapy are perhaps as low as 1 or 2 per 1000. However, parents need to know that the odds of this happening in children are significantly higher. Knowing this, if a parent should decide to defer beginning immunotherapy, he or she should at least participate in the decision making. Brown *et al.*⁽⁶⁰⁾ showed that patients with hay fever, but without asthma, may show diminished vital capacity during the pollen season. Townley *et al.*⁽⁶¹⁾ demonstrated a significant increase in bronchial reactivity to inhalation of extracts of methacholine, histamine, as well as pollen extracts in patients with hay fever but not asthma. Also, it is important to keep in mind that some patients with a single diagnosis of allergic rhinitis may be shown to have abnormal pulmonary function tests.⁽⁶²⁾ This suggests that pulmonary function tests should be performed on children with hay fever who are old enough to perform these tests. It may pinpoint those children in whom it is more urgent not to delay institution of immunotherapy.

Pedvis *et al.*⁽⁶³⁾ reported on a retrospective study of 43 children who attended the allergy clinic at Montreal Children's Hospital. They reported that a significantly greater proportion of children, whose hyposensitization therapy was delayed more than 2 years after hay fever symptoms first occurred, developed asthma than did children who began their treatment in the first two years after symptoms began. This is another bit of evidence suggesting that delaying beginning of immunotherapy for hay fever in children increases the risk of asthma.

Studies by Broder *et al.*⁽⁶⁴⁾ and by Smith⁽⁶⁵⁾ suggested that they could not corroborate the concept that early hyposensitization treatment of a child with hay fever prevented the subsequent development of asthma. In the first of these studies in which interviews of families in a small town in Michigan

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were carried out, it is of interest that the investigators asked about a history of asthma or hay fever in only a few of the children between the ages of 6 and 8 years. However, "neither asthma nor hay fever was uniformly asked about in the remainder of six- and seven-year-olds and all those under 6 years of age. This entire group has been excluded from this report." Every pediatrician knows that the onset of these conditions occurs well before 6 years of age in most allergic children. In the second part of their study⁽⁶⁶⁾ they reported on the sequence of onset of asthma in hay fever in persons with both of these conditions. In 23% of their patients, hay fever preceded asthma by at least one year. During the period of the study only 10% of those at risk, however, had actually developed asthma at the time of their report. However, four years later they again surveyed the same population. They reported the number of "probably allergic" as well as "highly suspect" asthmatic and hay fever cases, but only the probable cases were used in the analysis of the onset sequence of hay fever and asthma. They noted, "Methods of ascertaining and diagnosing allergic rhinitis and asthma were different in the first and second surveys." Thus, it is not surprising that the cumulative prevalence rates increased 60% from the first Tecumseh study to the second survey.^(67,68) They found that 25% of the persons who were thought to have probable asthma as well as hay fever had not previously been diagnosed as having either one. As expected, when they went back and asked the same patients, "The cumulative prevalence of allergic disease was higher in the twice-examined persons." Thus, they may have missed some crucial pediatric hay fever patients the first time they surveyed the town. Using the Tecumseh data at face value may lower the percentage of children with hay fever at risk of developing asthma. Nevertheless, their data do not gainsay the principle proposed in our Rochester study.⁽⁵⁹⁾

Fontana *et al.*⁽⁶⁹⁾ reported in 1966 that they found no benefit from immunotherapy in childhood hay fever. However, in reviewing this report, Sly⁽⁷⁰⁾ pointed out that the symptom score system used did not assess severity or duration of symptoms. Also, relatively small doses of pollen extracts were used. Over the years it has become a rather well-accepted clinical principle⁽⁷¹⁾ that clinical response to immunotherapy is related to the dose of antigen administered in patients with rhinitis as well as asthma.

A study by Sadan *et al.*⁽⁷²⁾ confirmed the value of immunotherapy and detailed the immunologic basis for clinical improvement in childhood hay fever. Thirteen of 18 treated children had fewer hay fever symptoms than any of the 17 control patients. There was a significantly greater rise in ragweed-specific IgG blocking antibody concentration in the sera of the treated children at the end of the study compared to the sera of the control group. The leukocytes of the control patients persisted with specific antigen sensitivity as shown by *in vitro* basophil histamine release studies. The cells of one-third of the treated children became unable to respond maximally to any concentration of antigen tested. Treated children whose cells showed the greatest decrease in reactivity to ragweed antigen *in vitro* had essentially no symptoms attributable to ragweed hay fever that year.

Norman and Lichtenstein⁽⁷³⁾ conducted a study which demonstrated that immunotherapy is clinically as well as immunologically specific.

BRONCHIAL ASTHMA

Many primary physicians tell mothers of wheezing infants and children that their children will "outgrow" their disease. This, in turn, is given as an argument against allergic evaluation of the child to determine the causative allergens as well as the use of immunotherapy to lessen the child's allergic load. If, indeed, the natural history of atopic extrinsic bronchial asthma in childhood were the same with or without immunotherapy, as some immunologists⁽⁷⁴⁾ have suggested, there clearly would be no advantage in giving asthmatic children allergy injections. In each of four long-term studies⁽⁷⁵⁻⁷⁸⁾ on the follow-up of asthmatic children who had *not* received immunotherapy, at least three-fourths of these children persisted with symptoms of asthma into adolescence. On the other hand, Rackemann and Edwards⁽⁷⁹⁾ reported on a 20-year follow-up of 688 asthmatic children, all of whom had received immunotherapy. The authors found that approximately three-fourths of their

patients were free of asthma 20 years after hyposensitization therapy began. These studies suggest that the proportion of asthmatic children expected to be free of symptoms by late adolescence was almost exactly the opposite, depending on whether or not they had received specific immunotherapy. Also, Blair⁽⁷⁸⁾ pointed out that unless follow-up studies of childhood asthmatics extend until the age of 18 years, a false impression of the natural history of childhood asthma will ensue. There are special subclasses of asthmatics which may not fit neatly into the above data. Buffum and Settupane,⁽⁸⁰⁾ reporting on a 10-year follow-up of 518 asthmatic children, found that those children who had a strongly positive scratch test to egg white and a history of atopic eczema as well as the onset of asthma before 2 years of age often became intractable to usual treatment.

To compare the long-term course of symptoms in asthmatic children, Johnstone and Dutton⁽⁸¹⁾ followed the clinical course of 210 asthmatic children who received either specific hyposensitization therapy or placebo injections over a 14-year period. Of the placebo-treated children, 22% were free of asthmatic wheezing for at least one year by the age of 16 years. Of the children who received specific hyposensitization therapy, 72% were free of symptoms at the same age. In the treated group the chance of outgrowing one's asthma seemed greater the higher the dose of antigens received in treatment injections. The treatment group had been divided into three dose schedules. Of those in the treated children who received the maximum tolerable dose of injected antigen, the percentage free of asthma at the end of the study exceeded 84%. In this study the likelihood of a child's outgrowing asthma appeared to be in no way affected by the age at onset of the asthmatic symptoms. A previous history of seasonal hay fever, however, significantly increased the likelihood of a child's asthma persisting into adolescence.

In a study of the effectiveness of hyposensitization for asthma caused by ragweed allergy⁽⁵⁹⁾ Johnstone followed a group of pollen-sensitive asthmatic children for five years. Half the children in the study received ragweed extract injections, while the other half received placebo injections. Two-thirds of the treated group of pollen asthmatics lost their symptoms by the fifth year of the study. By contrast, there was a 16% increase in the prevalence of asthma in the placebo-treated group.

In another study of childhood asthmatics, Aas⁽⁸²⁾ studied 93 children with rather severe bronchial asthma due to house dust allergy. He substantiated the diagnosis by bronchial provocation challenge with house dust extract. The effectiveness of immunotherapy with two different house dust extracts compared to a group treated with placebo injections was assessed by estimation of the degree of bronchial sensitivity before and after treatment. Eighty children completed the study. Specific hyposensitization was found to be superior to placebo injections as concerned improvement in allergic responsiveness of the bronchi to specific dust inhalation provocation tests. More than 76% of the maximum possible improvement in bronchial response to dust inhalation was achieved in 45 of 51 children who received dust extract injections. By contrast, only 9 of 28 children who had received placebo injections did this well. Changes in bronchial sensitivity before and after immunotherapy compared well with the clinical improvement observed.

Warner *et al.*⁽²⁰⁾ in a study which demonstrated the efficacy of immunotherapy in childhood asthmatics allergic to *Dermaophagoides pteronyssinus*, found that the main effect of immunotherapy in these children was on the late phase bronchial reaction. With the loss of the late reaction, the children's asthmatic symptoms were controlled without drug therapy, even though the IgE or immediate reactions, such as persistence of positive skin tests to the same antigen or immediate bronchial challenge reaction to the antigen, persisted. One cooperative English study⁽⁸³⁾ of treatment with house dust extract "in rather modest doses" revealed no relief after 15 weekly injections. Norman⁽⁸⁴⁾ suggested that the difference between the success of Aas or Soothill⁽²⁰⁾ compared to the study of Forgacs and Swan in England may be explained by the observations of May *et al.*⁽⁸⁵⁾ that unusually large amounts of house dust extract are necessary in order to obtain an effective blocking antibody response.

Immunotherapy with animal dander extracts has not been thought to have been beneficial. The lack of standardization of dander extracts has complicated the interpretation of variable responses to immunotherapy. However, Aas⁽⁸⁶⁾ showed a decrease in bronchial sensitivity to animal dander extracts in a few children after two or more years of immunotherapy. Recent studies by Anderson *et al.*⁽⁸⁷⁾

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more carefully defined clinically active cat antigens, and they have made practical the carrying out and evaluation of clinical trials of cat antigen extracts for immunotherapy in patients with asthma due to cat sensitivity. Taylor *et al.*⁽⁸⁸⁾ reported a double-blind trial of immunotherapy with cat antigens with evaluation of bronchial responses to inhalation challenge with cat antigen. The five patients who received cat pelt extract showed a reduction in skin reactivity to cat pelt extract as well as a significant mean reduction in bronchial reactivity on challenge to the same extract. Placebo-treated, cat-sensitive patients showed no significant changes in skin reactivity or bronchial sensitivity to cat pelt extract.

Valovirta *et al.*⁽⁸⁹⁾ recently reported a study of 20 children who experienced asthma from exposure to dog. They demonstrated the safety of using an aqueous, standardized dog dander and hair extract. Five of 11 subjects receiving rush hyposensitization showed a decreased conjunctival sensitivity after the fifth day of treatment. They reported that the conjunctival, bronchial, and skin sensitivity decreased in the treated group. Those receiving aqueous extract achieved these three measures of improvement significantly earlier than dog-sensitive asthmatic children who were given aluminum hydroxide-bound dog extract. No placebo group was used.

INSECT ALLERGY

Although the number of patients requiring evaluation for allergy to Hymenoptera insect stings is small, parents of such children need understandable assurance that they may carry on normal daily activities without risk of subsequent sting anaphylaxis. With the development of purified venoms nine years ago it was hoped that the clinical problem of venom anaphylaxis would be rapidly resolved. Unfortunately, there turns out to be no simplistic relationship between the presence of venom-specific IgE in a patient's serum and subsequent reactions. Positive venom skin test reactions occur in a few patients who have only normal reactions after Hymenoptera insect stings. There appears to be no relationship between specific antibody titer and the severity of clinical systemic reactions. In the initial study confirming the efficacy of venom immunotherapy at Johns Hopkins,⁽⁹⁰⁾ 40 patients believed to be venom-sensitive, on the basis of a past history of sting anaphylaxis and the presence of venom-specific IgE antibodies, failed to react to an intentional sting challenge. Based on deliberate sting challenges carried out by Parker *et al.*⁽⁹¹⁾ the authors concluded that "no *in vitro* or *in vivo* tests predicted with certainty the clinical and immune status of a sting-sensitive person." The clinical and immunological data did not differentiate between the subsequent reactors and nonreactors. These data tend to agree with those of Shubert *et al.*⁽⁹²⁾ who showed that in children who have had only urticarial reactions to stings, the subsequent risk of anaphylaxis without venom immunotherapy is less than for individuals who sustained generalized anaphylaxis following stings.

These data present a perplexing problem regarding the appropriate choice of individuals who should receive venom immunotherapy.⁽⁹³⁾ For the time being, it appears most reasonable to discuss with the parents current recommendations of using immunotherapy for any child who sustains anaphylaxis following a sting and inform them of present controversies concerning whether or not children with generalized urticarial reactions may defer immunotherapy. Parents can be assured that such immunotherapy is almost 100% effective in preventing subsequent reactions.

FUTURE POSSIBILITIES OF ALTERING OR REPLACING IMMUNOTHERAPY TO CONTROL ATOPIC DISEASE

While allergists have come a long way since the pioneer work of Noon⁽¹⁰⁾ in their understanding of immunotherapy and improving its application to clinical problems, we still have an imperfect system. Our antigens are impure and we have difficulty getting a large enough dose of antigen into patients safely. We are still finding new wrinkles concerning how immunotherapy works and why it does not always work in the same way in each patient. Several groups of investigators have been working to elucidate factors which affect the antigen-specific suppressor cells as well as regulatory factors which seem able to enhance or suppress the production and action of IgE. While Marten's

group⁽⁹⁴⁾ has been able to show in mouse experiments factors which can regulate the IgE response, thus far no practical use of this information in humans is yet at hand. Marcelletti and Katz⁽⁹⁵⁾ have shown also in mice the production of "IgE-induced regulant for B cells" (EIR/B), which regulates IgE-receptor expression by B-cells. This initiates simultaneous production of stimulating and suppressing substances. The activated B-cells interact with Ly 1+ cells to produce "suppressive factor of allergy (SFA)." SFA then causes Ly 1+ T-cells to secrete IgE-SF (IgE suppressive factor), described by Ishizaka. But one trouble with factors inhibiting or enhancing IgE is the lack of antigen specificity. Once the factor is there, it can influence IgE production against many antigens. This, in turn, jeopardizes protection against parasites and infection. As Nagaya⁽⁹⁶⁾ pointed out, one danger in such a system is an acquired immunodeficiency syndrome with a reversal of the normal ratio of suppressor cells to helper T-cells. Such a situation could result in one's seeing patients with no defense against any type of infection. Nevertheless, the tireless efforts of investigators like Rocklin, Martens, and Katz may, some day, radically change our present concepts of the usefulness of immunotherapy.

Meanwhile, if primary physicians who treat allergic children familiarize themselves with those situations in which immunotherapy is of established clinical value and apply it appropriately, huge rewards can ensue for the allergic child and the community in which he lives. To fail to do so or to ignore the abuses of it described in this review seems indefensible.

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