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IMMUNOTHERAPY AND ASTHMA

Jay E. Brown, MD, and Paul A. Greenberger, MD

There is a growing body of data suggesting some clinical role for immunotherapy (IT) in the management of asthma; however, more than 80 years after Noon's first study of IT, indications for this treatment in the asthmatic patient remain controversial. In this article, we discuss the importance of extrinsic asthma, why this therapy's role in asthma has been arduous to define, and the data on efficacy as it relates to specific antigens, then as it relates to specific subsets of patients. We then review the current understanding of the duration of benefits provided by IT, the risks of this therapy, and the current understanding of the mechanisms of IT's action in the asthmatic patient.

THE CLINICAL IMPORTANCE OF EXTRINSIC ASTHMA

Not all patients with asthma have IgE-mediated bronchospasm, but allergen inhalation commonly results in asthma from aeroallergens such as pollens from trees, grasses, and weeds, as well as dust mite fecal particles, animal danders, and fungal spores. There also has been increasing concern regarding the role of other indoor allergens, such as cockroach remnants or proteins from rodent urine that become airborne.[38, 66] An example of data supporting the importance of extrinsic asthma was provided by Reid et al,[75] who found a strong correlation between grass-pollen counts and asthma-related emergency room (ER) visits and hos-

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pital admissions ($r = 0.9$, $P<0.001$ and $r = 0.72$, $P<0.01$, respectively). Pollart et al[68] found higher anti-allergen IgE concentrations to a variety of aeroallergens in 102 asthmatic patients (age <50 years) presenting to an ER with an acute exacerbation than levels in patients presenting to the same ER for reasons unrelated to respiratory problems. They found IgE levels for the measured aeroallergens to be fourfold greater in the ER patients with asthma ($P<0.05$).

It can be very helpful to learn local pollenation patterns and inquire as to the presence of pets at home, occupational exposures, and seasonal exacerbations of asthma. Recent insights into the nature of some of the common aeroallergens have been reached. For example, Spores of *Aspergillus fumigatus* are 2 to 3.5 μm in size and are able to reach distal airways to cause fungal spore-induced asthma. The main allergen in cat dander, Fel d 1, is heterogeneous in size, with some allergen about 10 μm (less likely to penetrate deeply in airways) and smaller particles of fewer than 2.5 μm. Upon entering a room in which a cat recently has been, respirable allergen particles containing Fel d 1 can cause immediate and, perhaps, late airway responses. In contrast, dust mite allergens are larger in size (20 μm) and are less likely to remain airborne. A patient might report symptoms after dusting or use of a vacuum sweeper, which circulates dust mite allergens. Low amounts of dust mite allergen may cause chronic but unrecognized asthma because some dust mite allergen reaches bronchi. Compared with cat exposure, explosive onset of severe asthma from dust mite inhalation is uncommon.

Avoidance of allergens at home and in the workplace can reduce symptoms, medication requirements, and bronchial reactivity. Despite IT's goal of altering the immune system response to allergen and, ultimately, reducing symptoms, avoidance measures must not be overlooked in patients receiving allergen IT.

DIFFICULTIES UNIQUE TO THE STUDY OF IMMUNOTHERAPY

There is substantial variability in the outcomes of the more than 50 studies of IT and asthma. The difficulty in defining a role for IT is attributable to three factors. First, IT is a treatment given over a period of months to years and requires a firm commitment on the part of the patient. As such, recruiting patients for this kind of study is a challenge, especially for randomized, placebo-controlled studies in which a patient must maintain a commitment to treatment that often requires dozens of visits to the doctor, knowing that the treatment he or she is receiving may be a placebo. As a result, drop out in some of the studies discussed later often is higher than one might hope. Second, IT can be given in a plethora of ways:

- Chronology of therapy
  - Duration of treatment (e.g., 3–5 years per representative patient)
  - Co-seasonal, preseasonal, and perennial therapies; the latter is preferred
  - Standard, semi-rush, and rush build-up phases
- Allergens
  - Many aeroallergens (grass, tree and ragweed pollens, dust mites, dust, molds, animal danders, cockroach, etc.)
  - Many preparations of these allergens
    - Alum precipitation
    - Alum precipitated, pyridine-adsorbed (allergenicity is reduced greatly)
    - Repository therapy (allergoids, glutaraldehyde modified and tyrosine adsorbed, polymerized allergen, Ag-Ab complexes)
  - Variations in standardization
    - Multiple ways to measure potency (cutaneous end-point titration, radioallergosorbent test (RAST) inhibition, leukocyte histamine release, immunoelectrophoresis, concentration of known antigens like Amb a 1 for ragweed or Fel d 1 for cat)
    - Multiple ways to express potency (weight/volume, protein nitrogen units/mL, biologic units, and allergy units)
- Different routes of administration (subcutaneous and oral): the former is customary and preferred

As a result, a meta-analysis of the many studies done on IT would be very difficult. Finally, the results of IT can be assessed in a number of different ways:

- **Clinical**
  - Symptom diaries
  - Medication scores
  - Physician's evaluation
  - Home peak expiratory flow rate (PEFR)
  - Height/weight changes (in children)
  - "Blinded" patients' subjective assessment
- **Laboratory**
  - Pulmonary function parameters
  - Bronchial provocation tests
    - To specific allergen
    - To nonspecific bronchospastic agonists (methacholine, histamine)
  - Immunoglobulin responses (IgG and its subclasses, IgE, IgA to allergen)
  - Immediate skin test results
  - T-cell responses (blastogenesis responses)
  - Production of histamine-releasing factors (HRF)
  - Eosinophil infiltration into bronchi

EFFICACY STUDIES

As just mentioned, many strategies can be used to assess benefit to the patient. Because the goal of therapy is clinical improvement, the ideal

parameters to assess usefulness are the patient's symptoms. Symptom diaries are used to document episodes of wheezing, shortness of breath, nocturnal symptoms, and so on. Some studies use complete resolution of asthma symptoms as their end point. Medication scores determined by assigning a point value to various anti-asthmatic medications have been used. Other options include growth parameters in children, a "blinded" examiner's clinical assessment, days lost from work, emergency room visits, and days hospitalized. In the case of animal dander–induced asthma, some researchers have assessed the amount of time a patient can spend in a room with the animal to which they are sensitive.

There are also laboratory methods of determining benefit. Bronchial challenge tests, also known as bronchial provocation tests, are performed by determining the amount of allergen required to produce a drop equal to or greater than 20% in a patient's forced expiratory volume (FEV_1). Late asthmatic responses can be assessed by measuring the FEV_1 several hours after a bronchial challenge. Several studies have determined "nonspecific" bronchial reactivity by doing bronchial challenge tests with histamine or methacholine. The clinical relevance of some of these laboratory end points is subject to interpretation. It is uncertain, for example, how decreased bronchial sensitivity to a given antigen in the laboratory relates to the clinical exposure to antigen, which occurs over a much longer period of time and at far lower concentrations of allergen. Because this type of test is objective and reproducible, however, it often is used in studies of IT and asthma.

The clinical indications for IT in the management of asthma are the subject of much debate. There is a sizable body of research to guide this decision, however, and we can begin to answer the question "Which subset of patients with extrinsic asthma are likely to benefit the most from immunotherapy?" Some of the variables that might influence the clinical outcome include the types of aeroallergens to which the patient is allergic, the severity of the patient's asthma, the age of the patient, the location of the patient, history of prior immunotherapy, and the gender of the patient. Because the literature is organized primarily by specific antigens, we first discuss the data on specific aeroallergens, then present an evaluation of specific subsets of patients most likely to benefit from this treatment.

DUST AND DUST MITES

The plurality of asthma and IT studies have been done on asthma related to house dust. Because dust mites were not recognized as the main component of house dust responsible for dust allergies and asthma until the late 1960s,[95] studies prior to and shortly after that time used unstandardized house dust; after the discovery of the dust mite, most studies were performed with *Dermatophagoides pteronyssinus* and *Dermatophagoides farinæ*. Extensive crossreactivity exists between the major antigens from these two species.[65] Only two studies have compared the

effects on asthma of IT using unstandardized house dust with dust mite. In 1971, Maunsell et al[48] reported improvement as assessed by a "four-point scale based on the patient's opinion of his condition, on the number of attacks, and on the daily need for medication" in 14 of 18 patients (78%) receiving *D. farinæ* but only 6 of 16 patients (38%) receiving house dust ($P<0.05$). Side effects were not problematic in either group; he reported "no untoward reactions were observed."[48] In 1972, Smith and Pisarro[80] were unable to detect any advantage of injections of *D. pteronyssinus* compared with injections of house dust; however, they used an extract one-tenth the strength of the extract used by Maunsell and gave it over a much shorter period of time. They concluded "the concentration of *D. pteronyssinus* extract possibly was too dilute for clinical use."

Of the 12 studies evaluating the efficacy of dust and dust mite IT with medication scores or symptom diaries, four failed to demonstrate benefit in this regard.[11, 20, 21, 24] One of these studies used house dust "collected by means of vacuum cleaners from about 100 homes in the London area," however, not dust mite extracts.[21] Another noted that "possibly our failure to show any benefit . . . was due to the low strength of the vaccine."[24] A third study[20] found no statistically significant improvement in medication scores or symptom diaries, but did find improvement as assessed by responses to a questionnaire completed by patients blinded to the type of therapy they had received. After 12 weeks of treatment, the treated patients in this study reported that their asthma was improved ($P=0.02$), and that their dust tolerance was better ($P=0.05$) versus placebo-treated patients.[20] The fourth study that evaluated clinical parameters and failed to demonstrate a benefit failed to show an increase in house dust mite-specific IgG, suggesting the possibility that the doses were too low, although the maintenance dose was "the maximum tolerated dose"—up to 1 mL of a 0.33% aqueous extract.[11]

Of the eight studies reporting improvement on the basis of symptom or medication scores,[4, 9, 48, 53, 63, 70, 79, 98] there were some impressive results. Warner and Soothill,[98] in a double-blinded, placebo-controlled study using a tyrosine adsorbed *D. pteronyssinus* extract, found a significant decrease in medication scores ($P<0.007$) and a decrease in night coughing and wheezing ($P<0.05$) after 1 year of treatment. Using some of the same patients for an additional year, Price and Warner et al[70] treated 13 children with "perennial asthma inadequately controlled by conventional treatment." The children were treated for a total of 2 years with a tyrosine adsorbed *D. pteronyssinus* extract and 10 children improved. Also evaluated in this study were 12 children treated for 1 year with *D. pteronyssinus* followed by 1 year of placebo and 21 children for 1 year with placebo followed by 1 year of *D. pteronyssinus*. In the second year, drug scores worsened in those patients switched to placebo ($P=0.012$). There was an improvement, though not statistically significant, in the symptom scores after 2 years of treatment as well.[70] In one of the largest studies ever performed on IT and asthma, Bousquet et al,[9] using a lyopholized, aqueous extract of *D. pteronyssinus*, reported significant improvement in medication scores ($P<0.0001$) and in the severity of asthma

($P<0.0001$) when treated patients were compared with either pretreatment scores or to untreated control patients. Smith,[79] also using a *D. pteronyssinus* extract, found improvement in symptoms assessed by number of days with breathlessness ($P<0.005$) and nocturnal asthma ($P<0.005$). In addition, 10 of 11 treated patients needed no further treatment, compared with 5 of 11 placebo treated patients ($P<0.05$).

Growth in children was used as a clinical end point in a study of the effects of "house mite-fortified house dust" IT done by Taylor et al.[84] They reported that "eight patients [of 21] in the active treatment group improved their height or weight centiles compared with one [of 21] in the placebo group ($P<0.025$)." He noted, however, that the "improvement in height also could have been affected by the pubertal growth spurt, and there happened to be a larger number of such children in the treated group."[84]

Two of seven studies seeking to demonstrate a benefit of dust mite IT using pulmonary function tests were able to do so.[9, 21, 58, 63, 79, 84, 98] One showed improvement in the maximum mid-expiratory flow rate and vital capacity ($P<0.001$), and in FEV_1 ($P<0.0001$) in treated patients compared with either placebo-treated patients or with their pretreatment values.[9] Another study demonstrated improvement in the peak expiratory flow rate (PEFR) ($P<0.05$).[63] One study that failed to show a significant improvement in PEFR noted that "symptoms were effectively controlled [with medication] before injections started, so significant improvements in symptom scores and lung functions were difficult to achieve."[98]

Eleven studies have used bronchial provocation tests to evaluate the effects of dust and dust mite IT.[1, 4, 8, 22, 49, 54, 58, 89, 90, 96, 98] Six studies found significant improvement in treated patients compared with their pretreatment values,[1, 4, 8, 49, 54, 96] whereas three studies found no improvement.[89, 90, 98] Two of the three studies that were unable to demonstrate an improvement in the provocative dose of allergen causing a 20% drop in the FEV_1 (PD_{20}) compared with pretreatment values were performed on the same group of patients evaluated after 1 year and then 2 years of treatment.[89, 90] Although these two studies failed to show an increase in the PD_{20}, they did show a significant reduction in the mean drop in FEV_1 compared with control patients after a bronchial challenge ($P<0.028$).[89, 90] Four studies found improvements in PD_{20} that were significantly better than a placebo control group.[1, 8, 22, 58] One study reported increased nonspecific bronchial reactivity to histamine after a course of dust mite IT compared with pretreatment values, but no significant difference when IT-treated patients were compared with placebo-treated patients.[22] Another study demonstrated increased bronchial sensitivity in eight children treated for 1 year with *D. farinæ* IT compared with five placebo-treated children ($P = 0.008$).[55] The clinical relevance of this increased nonspecific bronchial hypersensitivity is not clear, and has not been reported in other studies.

POLLENS

In contrast to dust and dust mites, which can cause perennial symptoms, the study of IT's role in pollen-induced asthma is complicated by the seasonal variation of pollen counts, which may fluctuate, not only in the course of a year, but also from year to year. A study may have more difficulty demonstrating a benefit in a group of treated patients if the evaluation is made during a particularly mild pollen season. In addition, there are geographic variations in flora. For this reason, a study showing significant improvement in pollen-induced asthma may have little application in a different geographic region. Many physicians believe that pollens are responsible for a significant amount of morbidity in certain asthmatic patients.

The majority of studies on pollen IT in the treatment of asthma have been performed using grass pollen. In 1954, in the first double-blinded, placebo-controlled trial of IT in asthma, Frankland and Augustin,[23] using pollen from both Timothy and Cocksfoot grasses, evaluated 200 patients evenly divided into four treatment groups, which received injections of either (1) crude pollen extract, (2) partially purified pollen protein, (3) the ultrafiltrate from the protein purification process, or (4) saline solution. They reported that 94% of the asthmatic patients in groups 1 and 2 recorded "good" results (meaning the patient felt the treatment was "well worthwhile") or "excellent" results (meaning a complete resolution of all symptoms), versus 30% of patients in groups 3 and 4 with "good" or "excellent" results ($P \leq 0.001$). Four years later, Citron and Frankland[16] used an early type of bronchial challenge test, in which the patient inhaled mixed grass pollen and then had his or her FEV_1 measured. In patients treated with grass pollen IT, 12 of 14 patients had improved results, versus 3 of 5 untreated patients. There was no discussion of statistical significance.

About a decade after Citron and Frankland reported their results, McAllen[50] treated 35 asthmatic patients in a double-blinded fashion with an alum-precipitated grass pollen extract containing pollens from five grasses, a "depot emulsion" using a mineral oil-suspended extract containing pollens from 12 types of grasses, or placebo injections. In these three groups, respectively, 64%, 62%, and 25% of patients reported subjective improvement. The statistical significance of these results was not discussed, however.

In 1982, Østerballe[62] reported the disappearance of asthma symptoms in seven of seven patients treated for 2 years with a whole pollen extract. A group of four asthmatic patients treated with a "purified pollen" and a group of four asthmatics who received no treatment did not have resolution of their symptoms. In a study also done in 1982, Hill et al[32] reported no improvement in 11 children treated with preseasonal IT with an aqueous rye grass extract compared with nine placebo-treated children, although they did not "discount the possibility that others with asthma due solely to grass-pollen sensitivity might benefit." The patients in this study also did not have an elevated grass pollen-specific IgG at

the end of treatment, suggesting the possibility that the doses were too low.

In 1984, two studies from Italy observed clinical improvement in grass pollen-sensitive asthmatics treated with IT. Using immunotherapy, Ortolani et al[61] reduced the amount of shortness of breath, wheezing, and coughing reported in the symptom diaries of eight treated adults compared with seven placebo-treated patients ($P<0.01$). No significant change in the PD_{20} was observed, however. Cantani[14] reported "good results," defined as "better than at the onset of the trial" in 12% or "excellent results," defined as "marked improvement since the onset of the trial" in 0% of the 57 control patients (not given injections) versus 55% of the 67 patients with "good results" and 39% with "excellent results" over a 3-year period of an alum-precipitated, pyridine-extracted grass pollen extract. Of note, there are good data demonstrating that pyridine extracts lose potency and should not be used in lieu of aqueous extracts.[44]

In 1985, Stevens et al[81] reported improvement in the symptoms of 43 patients treated with grass pollen IT over a 1-year period using either a standard protocol or a semi-rush protocol ($P<0.01$). In this study, designed to compare these two dosing schedules, however, there was no control group, and rhinitis and asthma symptoms were evaluated together.

In the only North American study, Reid et al[75] treated 18 grass-sensitive asthmatic patients with IT. Half the patients received an extract containing grass pollen and half did not. He reported an improvement in combined symptom/medication scores in patients receiving the grass pollen compared with those who did not ($P<0.05$). In another recent study, Bousquet et al[10] treated four groups of patients in France for 8 to 9 months with either a placebo extract, a formalinized grass pollen allergoid, a fractionated high-molecular-weight component of the formalinized grass pollen allergoid, or a standard aqueous extract. The latter two preparations proved better than placebo for the reduction of symptoms ($P<0.05$ and $P<0.01$, respectively), and the high-molecular-weight allergoid was very well tolerated.

Only one group of investigators have evaluated tree pollen IT in the management of asthma. Rak and coworkers[71] in Sweden were able to show a reduction in medication requirements in 20 treated patients compared with 20 untreated control patients at the close of the birch pollen season ($P<0.05$). In a later study, the same group showed increased nonspecific bronchial reactivity to histamine in untreated patients during the birch pollen season compared with before the season ($P<0.05$), but there was no significant change in patients treated with birch pollen IT.[72]

The very existence of ragweed pollen-induced asthma has been debated. In 1975, Bruce et al[13] found no difference in the PD_{35} (the amount of antigen required to produce a 35% drop in the FEV_1) in two groups of patients in the Baltimore area, both of whom had positive skin tests to ragweed, one with just rhinitis symptoms and the other with asthma. Another study[78] demonstrated that whole pollen grains were unable to produce a reduction in airway conductance in 12 asthmatic patients, even when the dose exceeded the "maximum daily exposure in season." But when the whole grains were prepared as fragments, six of the seven asthmatic patients tested demonstrated bronchial sensitivity to them. In a study conducted in Ontario with asthmatic patients who were skin test-reactive to ragweed but negative to *Alternaria* and *Hormodendrum*, two fungi with spores present in the atmosphere at the same time ragweed pollen appears, seasonal asthma occurred and nonspecific bronchial reactivity increased in association with the seasonal ragweed pollen exposure.[7]

Only two controlled studies have assessed the effects of ragweed pollen IT on asthmatic patients. In 1957, Johnstone[36] published the results of a trial in which four groups of children were given a maximum dose of ragweed pollen extract of up to 1:200 weight per volume (w/v), 1:5,000, 1:10,000,000, or saline. He reported that 68%, 60%, 19%, and 7% respectively of the 26 to 31 children in each group had "lost" their asthma after treatment for 2 to 3 years. This was significant for the two groups who received the higher concentrations ($P<0.001$, $P<0.001$, $P<0.1$ for the three treatment groups compared with the placebo group, respectively). Almost exactly 20 years after Johnstone's study was published, Bruce et al[12] were unable to demonstrate any significant change in medication scores, symptom scores, or ragweed pollen bronchial provocation tests in 29 ragweed-sensitive asthmatic subjects treated for 8 months with an aqueous ragweed pollen extract. Bruce observed, however, that "the failure of these patients to show a response to immunotherapy could be due to a combination of the relatively low dose of ragweed extract and their sensitivity to other antigens [15 of the 29 evaluated patients had significant correlation of their asthma symptoms with both *Alternaria* and *Hormodendrum*]."

MOLDS

The importance of fungal spores in extrinsic asthma was demonstrated by O'Hollaren et al[59] who found that 10 of 11 asthmatic patients suffering respiratory arrest were prick test–positive to *Alternaria alternata*, compared with 31 of 99 asthmatics who had not experienced respiratory arrest ($P<0.001$). Unfortunately, the study of immunotherapy in mold-sensitive asthmatics has been confounded by the difficulty of standardization of allergen preparations. At least nine factors might independently influence the antigen content of a mold culture.[74] In 1986, however, Dreborg et al[19] reported the results of a multicenter, placebo-controlled trial using a "highly purified, biologically standardized and potent *Cladosporium herbarum* preparation with known antigenic and allergenic composition." This group observed a reduction in the medication scores during the 2 weeks of the mold spore season when the spore counts were the highest ($P<0.01$). They also noted a reduction in the PD_{20} of the treated patients compared with pretreatment values or hista-

mine control-treated patients ($P<0.01$ and $P<0.05$, respectively). No improvement in symptom diaries was observed, however, perhaps because when a patient's "asthma improves due to immunotherapy, they prefer to decrease medication rather than continue the same medication but with fewer symptoms." Another study with *Cladosporium herbarum* documented clinical improvement when symptom and medication scores were combined ($P<0.03$).[47] Of the treated patients, 81% were unchanged or improved in symptom scores, compared with 27% of the placebo group ($P=0.01$). This manipulation was justified by the authors, who noted that the mold spore counts were two to three times higher than the prior year and "unchanged symptoms are regarded as clinically improved disease." Horst et al[33] conducted a study in which 13 patients were treated with an extract containing *Alternaria* and 11 received placebo. Each of the 24 patients had rhinitis symptoms and five in each group had asthma as well. After 1 year of treatment, there was significant improvement as measured by combined symptom–medication scores ($P<0.005$) and as assessed by the opinion of the "blinded" patients ($P<0.001$). The combined symptom–medication scores and the patients' subjective view of the efficacy of treatment did not separately evaluate asthma and rhinitis symptoms, however.

ANIMAL DANDERS

The effect of asthma made worse by a family pet impacts on the patient both emotionally and physically. Although there is agreement that animal danders are an important component of extrinsic asthma in a significant number of asthmatic cases,[40, 68] views are very divergent on the utility of IT for this problem.[27] The cornerstone of therapy in the management of animal dander–induced asthma is avoidance; IT should not be offered in lieu of avoidance unless the contact with animals is unavoidable, as is the case with a veterinarian or with a blind patient who requires the help of a seeing eye dog.[26] In fact, none of the studies done with animal danders attempted to affect asthma in patients living with the animal to which they were allergic; rather, the goal of therapy was to reduce the amount of symptoms experienced upon incidental contact with a dog or a cat.

Three studies evaluated the effect of a "natural" exposure to cat or dog before and after a course of IT;[60, 83, 93] although all three studies found a reduction in symptoms for a majority of treated patients, only one[60] was able to demonstrate a statistically significant outcome. In that study, Ohman et al used IT with a purified fraction of a cat pelt extract that is not yet commercially available to prolong the time before the onset of symptoms in the treated group versus its pretreatment values or placebo-treated group ($P<0.05$ and $P<0.03$). The median time before onset of symptoms improved after treatment—from 30 minutes to greater than 90 minutes. Prior to treatment, the actively treated patients had an average drop in their PEFR of 9% (from 453 ± 90 to 414 ± 80, $P<0.001$), but after treatment, there was no significant change in FEFR before and after cat exposure. The treated patients also reported a lesser subjective intensity of pulmonary symptoms after cat exposure than the placebo-treated group ($P<0.03$). One study done with dog dander IT was unable to demonstrate a significant change in the medication or symptom scores,[45] and another study carried out with both dog and cat danders found no significant change in PEFR,[93] although physicians conducting these studies advised patients to limit their the daily exposure to these animals.[93, 45] Some studies have observed an increase in anti-cat albumin IgG after a course of IT.[60, 92] The clinical importance, if any, of this anti-cat albumin IgG is uncertain.

Seven studies used bronchial provocation tests to assess the benefits of IT in dog and cat asthma; all seven gave cat IT; four gave dog IT as well. Of the seven studies using allergen bronchial provocation responses to assess the benefits of cat IT,[6, 45, 60, 77, 83, 84, 92] all but one demonstrated significant improvement.[77] Two[6, 77] of the four studies[6, 45, 77, 83] evaluating bronchial provocation after a course of dog dander IT were able to show significant improvement at the end of the course of IT. One group of patients treated with cat dander IT had a decrease in nonspecific bronchial reactivity to histamine after 1 year[83] but not after 2 years[45] of treatment; treatment with dog dander in the same study did not affect nonspecific bronchial reactivity at either 1 or 2 years. Four other studies failed to show any significant change in nonspecific reactivity after treatment.[60, 77, 84, 92]

OTHER AEROALLERGENS

The idea that cockroach antigens may cause asthma is gaining acceptance. Kang and colleagues[38] conducted a trial in which study patients received IT to "all inhalant allergens, including cockroach allergens, to which they showed significant positive wheal and flare" and the control group "received immunotherapy with all inhalant allergens except cockroach allergens." Patients were "severe perennial asthmatics" who "frequented emergency rooms and were hospitalized one or more times per year." Although the study was hampered by a high dropout rate in the control group (only two of the original 13 control patients completed the 5-year study), a striking improvement in both medication and symptom scores was demonstrated ($P<0.01$ for both).[38]

The prevalence of occupational asthma precipitated by exposure to wheat flour has been estimated to be as high as 30% of bakers. Armentia and coworkers[3] treated two groups of wheat flour-sensitive bakers, one group of eight for 10 months and another group of eight for 20 months. When these two groups were compared with 10 patients treated with placebo injections, they were able to demonstrate improvement as assessed subjectively by treated patients ($P<0.001$) and a reduction in nonspecific bronchial hyper-reactivity to methacholine for both the group treated for 10 months ($P<0.003$) and the group treated for 20 months ($P<0.001$).[3]

MULTIPLE ALLERGENS

Only two studies[37, 87] have attempted to evaluate the efficacy of IT in patients with asthma aggravated by sensitivity to multiple aeroallergens. Limiting the study population to patients only sensitive to a single allergen facilitates the statistical analysis; however, because the patients recruited for such single-allergen studies, at least ideally, are affected by only that antigen, enrollment often is problematic. Furthermore, these single-allergen studies do not reflect the management of typical extrinsic asthma patients who have sensitivity to multiple antigens and, when treated with IT, usually receive multiple extracts.

In 1968, Johnstone and Dutton[37] published the results of a 14-year study of IT used for the treatment of asthma. Children were divided into four groups whose maintenance dose was either the maximum tolerated dose, up to 1:250 w/v, 1:5,000 w/v, 1:10,000,000, or saline injections given as a placebo. The data were evaluated by grouping the two higher-dose groups (82 children in all) and comparing their clinical status with that of the children receiving either the 1:10,000,000 maintenance dose or the saline-treated children (91 children in all). The most striking benefit was observed in patients who began the study with more than 10 days of wheezing per year. In the higher-dose group, 34 of 46 children (74%) were "free of asthma" when they reached their 16th birthday, compared with 6 of 44 children (14%) of the placebo/low dose group. Although no "*P* value" was given, this result was described as "highly significant."[37]

Although this study demonstrated the most impressive benefit to asthmatic patients of any study we evaluated, it was not without shortcomings. The actual duration of therapy for these children was not clearly delineated. No informed consent was obtained from parents or children, as the authors write: "No mother or child in the study knew that any sort of study was underway." Also, the blinding in the study was problematic: ". . . we found it impossible to maintain a strictly double-blind study over the 14-year period. . ." Finally, the treatment was remarkably well tolerated, with only one reported systemic reaction resulting in a decrease in dosage: "this reaction consisted of a complaint by the child's mother that he seemed to be wheezing 30 minutes after his injections were given on one occasion." Given the thousands of injections in this "14-year study," with 32 children completing the study in the "highest tolerated dose" group, the single systemic reaction is truly remarkable. By comparison, a recent prospective study found the incidence of objective systemic reactions to be about 6% of treated patients.[29] Admittedly, the tolerance may have been related to very gradual dosing, but details on this were not provided in Johnstone's paper.

In contrast to the dramatic results achieved by Johnstone,[37] Tuchinda and Chai[87] were unable to attain any clinical improvement in a group of 10 children treated with multiple antigens over a 5 to 10 month period. They were, however, able to reduce bronchial hyper-reactivity, although there was no mention of the statistical significance of this improvement.

Obviously, the short duration of treatment might have contributed to this disappointing clinical outcome.

THE LATE ASTHMATIC RESPONSE

The late asthmatic response is defined as a drop in FEV_1 that occurs 4 to 8 hours after antigen exposure and after recovery from the immediate asthmatic response.[15] This late response can persist for longer than 12 hours after a bronchial challenge.[17] This phenomenon has been observed in about half the asthmatic patients who have an immediate asthmatic response to inhaled allergen.[64] The late asthmatic response warrants special consideration because "symptoms in patients with allergic disease more closely resemble the late rather than the immediate response to antigen."[41] In addition, Mosbech[52] observed that "occurrence of late-phase bronchospasm to pretreatment Dp-challenge [*Dermatophagoides pteronyssinus* challenge] increased the chance of clinical improvement [from IT] approximately three-fold ($P<0.05$)."

Several studies have evaluated the ability of IT to reduce the late asthmatic response. VanBever and Stevens[90] observed a loss of the late asthmatic response in 5 of 15 patients treated with dust mite IT for 1 year; a group of eight control patients had no change in their late reaction to bronchial challenge ($P<0.04$). Furthermore, the 15 treated children had a very significant reduction in the mean drop in FEV_1 during the late phase ($P<0.0001$).[90] Another study by the same authors[89] involved 19 children, all treated with dust mite IT. Nine of these children continued immunotherapy for an additional year; the remaining 10 received placebo injections. After the first year, all but one patient had a decrease in the severity of the late asthmatic response ($P<0.0001$). When treatment was changed to placebo for 10 of the children in the second year of the study, they had a significant worsening of their late asthmatic response ($P=0.038$), but the children who continued treatment for the second year maintained the benefit they had attained in the first year.[89]

Warner and Soothill noted a late asthmatic response in 37 of 51 children 6 hours after dust mite bronchial challenge.[98] Twenty-four of these 37 children (about 59%) received IT, yet 91% of those showing a loss of their late asthmatic response were in the treatment group ($P<0.05$).[98] When IT was continued for a second year, "the association [between treatment and loss of the late asthmatic response] was less strong in the second year."[70] There also was a very impressive relationship between the loss of the late asthmatic response and improvement in drug scores ($P<0.001$).[70]

Mosbech et al[54] found that, after 2 years of dust mite IT, 9 of 20 patients lost their late asthmatic responses, compared with 2 of 6 placebo-treated patients, but this difference was not found to be significant.

In a study of 10 "atopic asthmatics . . . who were symptomatic during the mold season," the early asthmatic response was improved in only one subject, but the late asthmatic response was "decreased by 67%,

which is not adjusted for an increased antigen dose."[51] Finally, Rohatgi et al[77] observed the loss of the late asthmatic response in one of four cat IT-treated patients and one of one dog IT-treated patients.

SUBSETS OF ASTHMATICS WHO BENEFIT THE MOST

Only one study has stratified patients on the basis of the severity of their asthma as assessed by symptom and medication scores to determine how the severity of asthma impacts on the benefit provided by IT.[9] Bousquet and coworkers[9] found that milder asthmatic patients demonstrated the most improvement with dust mite IT; specifically, patients with asthma who had an FEV_1 less than 70% of the predicted value prior to IT did not show any improvement with this treatment. In contrast, Mosbech[52] noted that patients with improvement after IT to dust mites (defined as a ≥10-fold increase in bronchial tolerance to *D. pteronyssinus*, Dp) were initially more sensitive to *Dp* on bronchial challenge and had a lower FEV_1 ($P<0.05$). He also observed that the chance of improvement with treatment was increased threefold if the patient had a late phase bronchial response ($P<0.05$).[52] In addition, he reported that "in patients improving, the median allergen concentration on mattresses was equivalent to 1000 mites/g compared with fewer than 250 mites/g in patients showing no improvement."[52]

Some of the studies that documented a greater benefit for the patients with more pronounced disease have suggested that these more severely asthmatic patients exhibited relatively greater benefit with IT because patients with minimal disease at the start of treatment were not able to achieve as substantial an incremental improvement.[37, 52] No studies have attempted to specifically assess the benefit of IT accorded to oral steroid–dependent asthmatic patients. Also, no studies have attempted to compare IT's effects on patients with multiple allergen sensitivities versus the effects on patients with relatively few allergen sensitivities, although most studies have targeted patients in the latter group in an effort to limit confounding variables.

It does not appear that the sex of the patient[9] or a prior history of IT[50] have much impact on the outcome of treatment. Bousquet[9] found that, in the case of dust mite IT, children improved more than adults. Obviously, correlating the patient's symptoms with exposure to an aeroallergen to which that patient has a positive skin test—making the correct diagnosis—is a prerequisite for successful treatment.

DURATION OF BENEFIT AFTER IMMUNOTHERAPY

To date, no data suggest the optimal duration of therapy that might provide a sustained benefit after the completion of IT used in the treatment of asthma. Similarly, the duration of benefit after the completion of therapy has not been delineated. Two studies do observe the loss of

clinical benefit attained after 1 year of dust mite IT when those patients were switched to placebo injections.[70, 89] Although data are limited regarding optimal duration of IT and subsequent duration of benefit after the completion of therapy for asthma, there is a broader experience with patients with rhinitis. Randolph and Franklin[73] evaluated 26 patients who benefited from 3 or more years of pollen IT used in the treatment of rhinitis. The patients were interviewed by telephone 10 years after IT was discontinued. Of the 26 patients, 11 reported a recurrence of symptoms and the median time of recurrence was 9 years.[73] Improvement usually is observed after relatively high doses are achieved (in our practice, 0.5 mL of a 1:100 w/v aqueous solution), and progressive improvement can occur during the first 1 to 3 years of treatment. If patients fail to improve after 1 or more years of treatment, the diagnosis and the need for continued treatment must be reconsidered.[91]

RISKS OF IMMUNOTHERAPY

The risks of allergen IT include reactions that occur at the site of an injection, vasovagal reactions, and systemic reactions, which are the most severe and potentially life-threatening reactions. In an analysis of fatalities from IT, Lockey et al[46] were able to obtain data on 24 patients whose deaths occurred during IT. Four of the 24 patients had prior reactions, 11 had shown "a high degree of sensitivity," and four were given newly prepared extracts.

Stewart and Lockey[82] reviewed 24 studies of IT with conventional schedules and unmodified allergen preparations used in the treatment of both rhinitis and asthma. The reported incidence of systemic reactions per course of treatment ranged from 0.8% to 46.7% with a mean of 12.9%. They concluded that the percent of patients who have systemic reactions is small and that a waiting period of 20 minutes after the injection is reasonable, with exceptions made for "high-risk subjects" including patients on a rush protocol, those with "unstable asthma," seasonal exacerbations, a high degree of hypersensitivity, and patients on β-blockers.[82] No specific stratification data were provided that confirm these subsets of patients were the ones who had the higher incidences of systemic reactions.

Greenberg et al[29] prospectively compiled data on systemic reactions to IT in all patients given such treatment at four centers. The dose was "the maximum tolerated or clinically effective" dose, and both rhinitis and asthma patients were included. They noted the occurrence of objective systemic reactions in 39 of 628 patients (6.2%) who had received 20,588 injections (0.19% reactions per injection). This group also found a higher risk of systemic reactions in patients receiving IT containing only pollen antigens ($P<0.001$). They found no association between injections given during a pollinating or nonpollinating season, and there was no difference in risk if the injections were given at increasing doses or at maintenance doses. They also noted that 38% of the reactions occurred

between 35 minutes and 6 hours after the injection.[29] Furthermore, there was a statistically higher incidence of delayed reactions in women.

Vervloet and coworkers[94] evaluated the safety of IT by having 64 French allergists complete questionnaires on 19,739 patients given IT over a 6-month period. They reported systemic reactions in only 0.1% of treated patients. Furthermore, consistent with the findings of Greenberg already mentioned, the risk of a reaction was twice as great in patients treated with pollen extracts. Asthma, rhinitis, and urticaria typified 80% of these systemic reactions. The most common causes of adverse reactions were "excessive doses of antigen, improper timing of treatment, or incorrect technique of injection."[94]

As allergen preparations used in IT are altered to reduce the risks of systemic reactions, as is the case with polymerized allergens, the risks of such therapy can be reduced dramatically.[28]

MECHANISMS OF IMMUNOTHERAPY

Many theories have been proposed to explain the mechanism of IT's effect on asthma. There are several well-described alterations in the immune system after a course of IT, but determining a causal link with clinical improvement by correlating a given effect with a clinical goal is difficult.

The oldest and most often cited theory of IT's effect on asthma is that of anti-allergen–blocking antibody. This theory suggests that by injecting the offending allergen into patients with IgE to that antigen, other classes of antibodies like IgG and IgA will be produced in concentrations far larger than those of IgE. Then when the patient is later exposed to these allergenic epitopes, these sites will be bound primarily by the more abundant IgG or IgA and the IgE on mast cells will not be bound in significant concentrations.

In an ingenious study by Behrens et al,[5] rabbits previously unexposed to *Alternaria alternata* and passively immunized with anti-*Alternaria* IgE developed both an immediate and a late asthmatic response to aerosolized *Alternaria*. Similar rabbits given both anti-*Alternaria* IgE and IgG had a blunting of the late asthmatic response directly proportionate to the ratio of IgG to IgE. Rabbits receiving only anti-*Alternaria* IgG had neither immediate nor late asthmatic responses.[5] Lichtenstein et al[43] reported a correlation between increases in serum anti-ragweed IgG and clinical improvement in rhinitis symptoms in patients treated with IT ($P<0.02$). However, the results were "not perfect and measurement of IgG antibodies does not predict whether any one patient will do well."[43] Some investigators have shown an increased production of IgA in addition to IgG in secretions of patients treated with IT, but its significance, if any, in asthma has yet to be determined.[67]

Whether or not this observed increase in IgG is a true mechanism of the amelioration of patients' symptoms remains in question. Poulsen et al,[69] using guinea pigs "inbred for their ability to develop respiratory

anaphylaxis to experimental antigens" had "notably reduced symptoms in groups treated with . . . IT," yet showed no correlation between clinical response and IgG synthesis. IgG_4 ordinarily represents only about 4% of total IgG, but may compose more than 95% of the IgG specific for a given antigen after IT.[30] IgG_4 is unique in its inability to cross-link two antigen molecules and its inability to bind and activate C1 in the complement cascade.[30] In fact, IgG_4 can block complement activation by IgG_1 by competitively binding antigenic determinants on phospholipid A.[30] Djurup[18] noted that the response to IT is primarily IgG_1 and IgG_4, with the IgG_1 production dominating early in a course of IT and IgG_4 found later in the course of treatment. He also observed that "a too early or too pronounced IgG_4-dominated Ab response seems to indicate a poor clinical outcome of IT . . ."[18] Nakagawa and de Weck[56] observed that "IgE antibody-mediated basophil degranulation could be inhibited by passive sensitization with allergen-specific IgG_4 antibodies in bee venom allergy." In separate studies, Nakagawa et al[57] and Tsai et al[86] independently observed an increase in IgG_4 levels after IT; in the latter study, an increase in IgG_4 after IT correlated with clinical improvement.

Another proposed explanation of IT's effect in asthmatic patients is based on a reduction in the amount of specific IgE produced. Of the more than 50 studies on IT and asthma we evaluated, 20 studies measured anti-allergen IgE levels. Six studies identified a significant increase in anti-allergen IgE,[4, 10, 20, 31, 88, 92] and two studies showed a significant decrease.[3, 39] In 12 studies, no significant change occurred.[6, 8, 9, 11, 32, 33, 38, 61, 63, 81, 93, 96] None of these 20 studies made mention of any significant correlation between the fluctuation of IgE levels and clinical status.

IT also has been shown to decrease the lymphoproliferative response to allergen. Gatien et al[25] found an increase in T lymphocyte proliferation, measured by ^{3}H-thymidine incorporation, when Amb a 1 (AgE) sensitive patients' T lymphocytes were exposed to Amb a 1, but not when nonsensitive patients' T lymphocytes were cultured with Amb a 1. Specific IT markedly decreased the T cell response in the Amb a 1–sensitive T cells at high Amb a 1 concentrations and "virtually abolished the response at low AgE (Amb a 1) concentrations."[25] Hsieh[35] showed decreased production of IL-2 and IL-2 receptors after IT for 2 to 3 years. Other investigators have shown an increase in T suppressor cell activity after IT.[34, 76]

IT also decreases HRF production. Alam et al[2] observed lymphocytes from asthmatic patients that produced a HRF, especially following specific allergen stimulation. IT resulted in a significant reduction of this lymphocyte-produced HRF in response to allergen stimulation. Liao et al[42] determined that monocytes of asthmatic children "produced a much greater HRF activity, either spontaneously or after stimulation, than did those of normal children." Furthermore, they reported, "the spontaneous HRF activity decreased significantly in good responders [children with a good clinical response to IT], whereas that of poor responders increased."[42] Consistent with these findings, Wang and Hsieh[97] observed lower production of histamine by mononuclear cells in asthmatic children treated with IT versus asthmatic children not treated with IT.[97]

IT affects the immune system in other ways, and the significance of these effects is still being investigated. Leukotriene C_4 levels in the supernatant of mononuclear cells and polymorphonuclear cells stimulated with a calcium ionophore were significantly lower in IT-treated patients than in untreated patients ($P<0.05$).[97] The same treated patients also were noted to have increased levels of prostaglandin E_2 when their mononuclear and polynuclear cells were stimulated with allergen ($P<0.01$).[97] Rak and Lowhagen et al[71] measured serum concentrations of eosinophil cationic protein in patients with birch pollen allergy. During the birch pollen season, patients who were not treated with IT had significantly increased levels of eosinophilic cationic protein, but patients who received IT did not. It also was observed that eosinophilic cationic protein concentrations correlated very well with histamine sensitivity assessed by bronchial provocation tests ($P<0.001$).[71] Rak and Bjornson et al[72] reported increased eosinophils in bronchoalveolar lavage fluid in patients with birch pollen allergy and asthma during a birch pollen season in untreated patients compared to patients treated with IT ($P<0.01$). Similarly, the concentrations of eosinophil and neutrophil chemotactic activities were higher in the non–IT-treated group than in the IT-treated group.

SUMMARY

The management of asthma begins with an understanding of triggers of asthma for a given patient. In patients who suffer from asthma worsened by airborne allergens, avoidance of those allergens should be used when possible. Although medications should be used to control asthma symptoms, there is a growing body of data supporting a role for IT, particularly in patients in whom aeroallergens are associated with increased respiratory symptoms. IT remains our only immunomodulator as a method for reducing disease activity. As with any treatment, there are differences in outcomes depending on the patient, the physician's expertise and experience, the extracts used, the doses reached, and other factors such as concomitant respiratory infections that can exacerbate a patient's asthma. We conclude that high-dose IT has a role in the treatment of asthma, particularly for patients in whom pollens, dust mites, and molds are important triggers.

References

1. Aas K: Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. Acta Paediatr Scand 60:264, 1971
2. Alam R, Rozniecki J, Salmaj K: A mononuclear cell derived histamine releasing factor (HRF) in asthmatic patients. Histamine release from basophils in vitro. Ann Allergy 53:66, 1984
3. Armentia A, Martin-Santos JM, Quintero A, et al: Bakers' asthma: prevalence and evaluation of immunotherapy with a wheat flour extract. Ann Allergy 65:265, 1990
4. Assem ESK, McAllen MK: Changes in challenge tests following hyposensitization with mite extract. Clin Allergy 3:161, 1973
5. Behrens BL, Clark RAF, Marsh W, et al: Modulation of the late asthmatic response by antigen-specific immunoglobulin G in an animal model. Am Rev Respir Dis 130:1134, 1984
6. Bertelsen A, Andersen JB, Christensen J, et al: Immunotherapy with dog and cat extracts in children. Allergy 44:330, 1989
7. Boulet LP, Cartier A, Thomson NC, et al: Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. J Allergy Clin Immunol 71:399, 1983
8. Bousquet J, Calvayrac P, Guerin B, et al: Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. In vivo and in vitro parameters after a short course of treatment. J Allergy Clin Immunol 76:734, 1985
9. Bousquet J, Hejjaoui A, Clauzel A, et al: Specific immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Prediction of efficacy of immunotherapy. J Allergy Clin Immunol 82:971, 1988
10. Bousquet J, Maasch HJ, Hejjaoui A, et al: Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. J Allergy Clin Immunol 84:546, 1989
11. British Thoracic Association Mite Allergy Subcommittee of the Research Committee: A trial of house dust mite extract in bronchial asthma. Br J Dis Chest 73:260, 1979
12. Bruce CA, Norman PS, Rosenthal RR, et al: The role of ragweed pollen in autumnal asthma. J Allergy Clin Immunol 59:449, 1977
13. Bruce CA, Rosenthal RR, Lichtenstein LM, et al: Quantitative inhalation bronchial challenge in ragweed hay fever patients: A comparison with ragweed-allergic asthmatics. J Allergy Clin Immunol 56:331, 1975
14. Cantani A, Businco E, Benincori N, et al: A three year controlled study in children with polinosis treated with immunotherapy. Ann Allergy 53:79, 1984
15. Cartier A, Thompson NC, Frith PA, et al: Allergen induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. J Allergy Clin Immunol 70:170, 1982
16. Citron KM, Frankland AW, Sinclair JD: Inhalation tests of bronchial hypersensitivity in pollen asthma. Thorax 13:229, 1958
17. Cockcroft DW: The bronchial late response in the pathogenesis of asthma and its modulation by therapy. Ann Allergy 55:857, 1985
18. Djurup R: The subclass, nature and clinical significance of the IgG antibody response in patients undergoing allergen-specific immunotherapy. Allergy 40:469, 1985
19. Dreborg S, Agrell B, Foucard T, et al: A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. Clinical results. Allergy 41:131, 1986
20. D'Souza MF, Pepys J, Wells ID, et al: Hyposensitization with *Dermatophagoides pteronyssinus* in house dust allergy: a controlled study of clinical and immunologic effects. Clin Allergy 3:177, 1973
21. Forgacs P, Swan AV: Treatment of house dust allergy. A report from the research committee of the British Tuberculosis Association. Br Med J 3:774, 1968
22. Formgren H, Lanner A, Linholm N, et al: Effects of immunotherapy on specific and nonspecific sensitivity of the airways [abstr]. J Allergy Clin Immunol 73:140, 1984
23. Frankland AW, Augustin R: Prophylaxis of summer hay-fever and asthma. A controlled trial comparing crude grass-pollen extracts with the isolated main protein component. Lancet 1:1055, 1954
24. Gaddie J, Skinner C, Palmer KNV: Hyposensitisation with house dust mite vaccine in bronchial asthma. Br Med J 2:561, 1976
25. Gatien JG, Merler E, Colten HR: Allergy to ragweed antigen E: effect of specific immunotherapy on the reactivity of human T lymphocytes in vitro. Clin Immunol Immunopathol 4:32, 1975