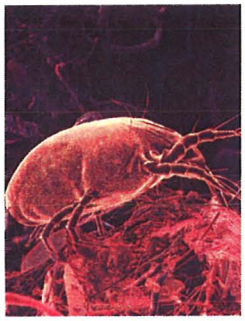
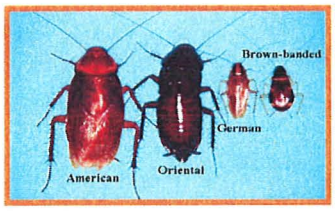
Treatment of Allergic Asthma: Environmental Interventions or Immunomodulation?





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Introduction

Asthma is an important health problem worldwide. It is the most common chronic illness in children and adolescents and it is the leading cause of hospitalization among children less than 15 years of age. This disorder has almost doubled in prevalence since 1980 and now affects approximately 8-10% of the population of the United States. However, as demonstrated in a recent health survey, prevalence rates in our city may be even greater. Survey results indicated that the prevalence of asthma in Dallas County may be as high as 14.8% [1]. While various factors are thought to contribute to the increase in asthma prevalence, these factors will not be the subject of this Grand Rounds. Rather, its focus will be on the pathophysiology of the disease and on treatment strategies, specifically environmental control interventions and immunomodulatory agents and approaches.

Pathophysiology

Asthma is a complex disease with many clinical phenotypes. In appropriately sensitized individuals, it is characterized by two types of airway responses, an early, transient response that occurs 15 to 20 minutes after an allergen exposure and a late, more prolonged response that occurs 4 to 6 hours later. While many concepts regarding disease pathogenesis have been proposed over the years (Table 1), it has become clear that IgE-mediated mast cell and/or basophil degranulation and their resultant inflammatory mediators are key events in the early asthmatic response [2]. Moreover, our current belief that asthma is a chronic inflammatory disorder was derived from the finding that airways of asthmatic individuals are filled with eosinophils, macrophages and lymphocytes and that steroids are an efficacious treatment modality. If left unchecked, chronic inflammation may lead to structural alterations and airway remodeling.

Table 1. Evolving concepts of asthma pathogenesis (From Elias et al., reference 2)

• A primary abnormality of airway-myocyte hyperresponsiveness
• Autonomic dysfunction with exaggerated activity of cholinergic or tachykinin pathways
• IgE-mediated mast cell/basophil degranulation
• Complex T lymphocyte-mediated airway inflammation
• Airway remodeling

From autopsy evaluations done on patients with fatal asthma, it became clear that inflammation is an important component of asthma. Airways from these patients are infiltrated with neutrophils, eosinophils and degranulated mast cells. In addition, there is sub-basement membrane thickening, occlusion of the bronchial lumen by

mucus, hyperplasia and hypertrophy of bronchial smooth muscle and hyperplasia of goblet cells [3]. Initially, it was thought that these findings were specific for fatal asthma only. However, more recently, it has been demonstrated from bronchial-biopsy specimens that even persons with mild disease have substantial inflammation (Figure 1).

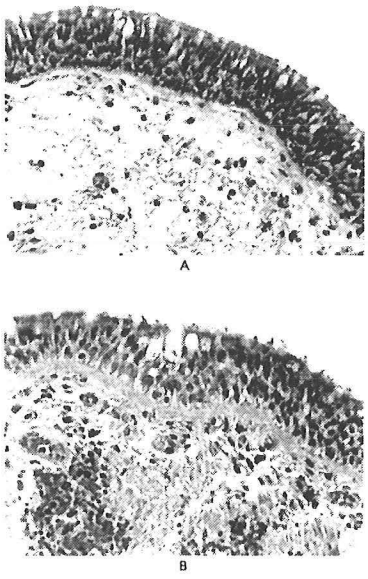

Figure 1. Bronchial mucosal specimen from a person without asthma (Panel A) and a person with mild asthma (Panel B). In the subject without asthma, the epithelium is intact, there is no sub-basement membrane thickening and there is no cellular infiltrate. In the patient with mild asthma, there is goblet-cell hyperplasia, sub-basement membrane thickening, collagen deposition in the submucosa and a prominant cellular infiltrate. (From Busse and Lemanske, reference 3).

The Role of Allergy in Asthma

When the immune system encounters an antigen, an antigen-specific antibody or cellular responses ensues. The type of response that is generated is greatly dependent upon the types of CD4+ T lymphocytes that accumulate at the site of antigen deposition. In mice, and to a lesser extent in humans, it has been demonstrated that CD4+ T lymphocytes can be distinguished by their cytokine profiles. Th1 lymphocytes generate IFN-γ, IL-2 and lymphotoxin, while Th2 lymphocytes generate IL-4, IL-5, IL-9, IL-13 and IL-10. Another group of T cells, termed T regulatory cells and Th3 cells produce IL-10 and TGF-β, respectively.

Both Th1 and Th2 lymphocytes are derived from a common precursor cell. Polarization towards one phenotype or the other is dependent upon signals encountered in the microenvironment. A most important player in this regard is the dendritic cell. In the presence of specific transcription factors (STAT-1 and T-bet) and CD8+α+ dendritic cells and/or IL-12, IL-18 or IFN-γ, differentiation occurs along the Th1 pathway. In contrast, in the presence of alternative signal transducing factors (STAT-6/GATA-3/NF-ATc/c-maf) and CD8α- dendritic cells and/or IL-4, differentiation occurs along the Th2 pathway (Figure 2). While Th1 responses play a role in the pathogenesis of rheumatoid arthritis, sarcoidosis and tuberculosis, Th2 responses are important in allergic and antiparasitic responses as well as in asthma.

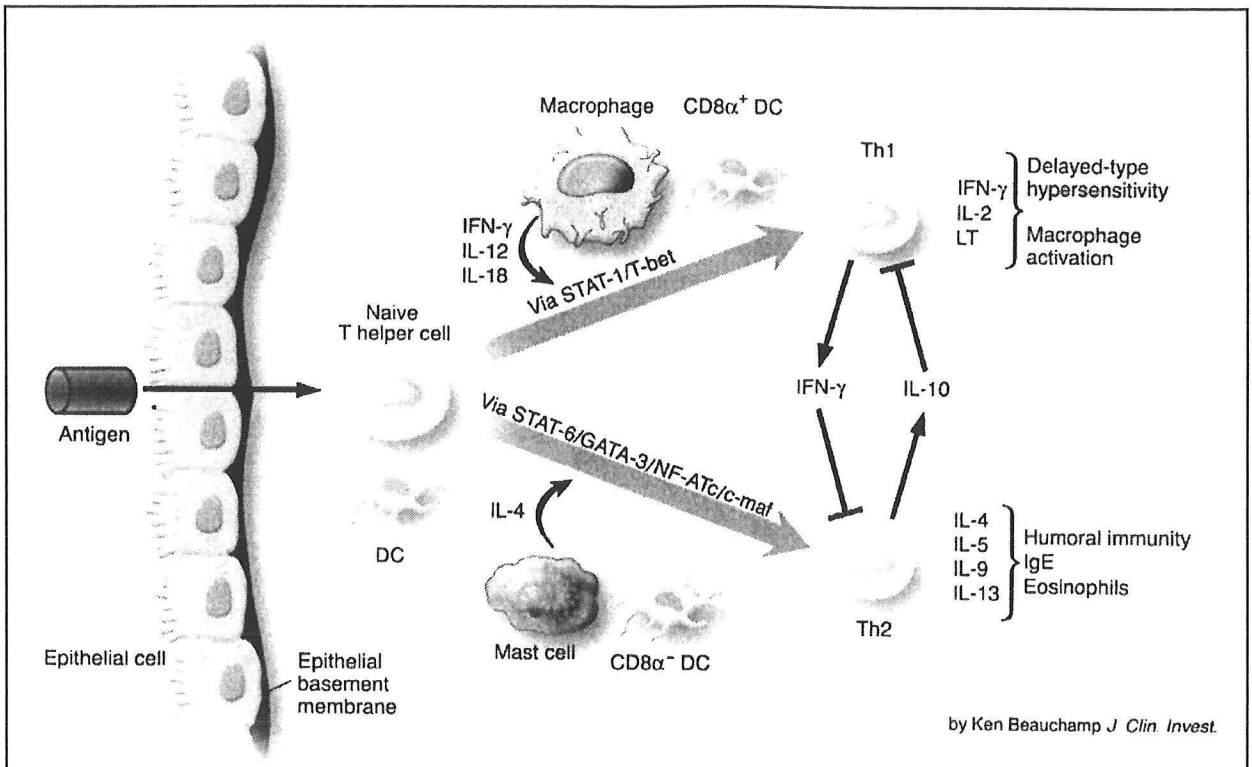

Figure 2. Development of Th2 and Th2 lymphocytes. Antigens enter through the endobronchial tree, cross the epithelial surface, and interact with naive Th cells and DCs. As a result of signals from the surrounding microenvironment, they differentiate into Th1 cells, which produce IFN-γ, IL-2, and lymphotoxin (LT), or Th2 cells, which produce IL-4, IL-5, IL-9, IL-13 and IL-10. (From Elias et al., reference 2).

The importance of allergic sensitization in asthma has been well documented. Many children with asthma have positive skin prick tests to allergens from house dust mites [4], cockroaches [5], pets (especially cat dander) [6] and the fungus, Alternaria [7]. Thus, at least in children, allergic sensitization and asthma appear to go hand in hand. In addition, allergic sensitization may be important in disease persistence. It has been shown that sensitization to Alternaria in 6 year-old children with asthma is associated with a significantly reduced frequency of disease remission by age 11 (9% in children who were sensitized versus 39% in children who were not sensitized) [7].

These findings, taken together, suggest that, early in childhood, a cytokine imbalance occurs that promotes the development of IgE antibodies and it appears that allergens in the local environment dictate the specificity of the antibodies generated [3]. Moreover, other studies have shown that allergic sensitization to certain allergens may increase the risk of asthma-associated morbidity [5]. Thus, it is no wonder that, in addition to optimal medical therapy, asthma management approaches should, not only seek to reduce allergen exposures, but also focus upon the development of

immunomodulatory strategies for reducing asthma-associated morbidity.

Environmental Interventions in the Management of Allergic Asthma

Among other factors (poverty, poor compliance with anti-inflammatory therapy), exposure to indoor allergens (dust mite, cockroach, and pet allergens) has been related to asthma severity [8]. Thus, if allergen exposures in the home contribute to asthma-associated morbidity, then reducing these exposures should be integrated into all asthma management programs. However, before moving on, there are two important questions that must be addressed. First, can allergen levels be effectively reduced in the home and, second, if reduction can be achieved, is there disease improvement?

House Dust Mites - High altitude studies

The significance of house dust mites in asthma was first recognized in the early 20th century by Kern [9] who advised his asthmatic patients to avoid dust exposure. However, the first real experiments were not done until a few years later when van Leeuwen [10] demonstrated improvement in asthma symptoms when patients were moved from their homes to a dust free "climate chamber". At about the same time, it was being recognized that patients with asthma who moved to Davos, Switzerland and other sanatoria often improved dramatically [11]. These early studies thus set the stage for the further, more critical, exploration into the relationship between dust mites and asthma.

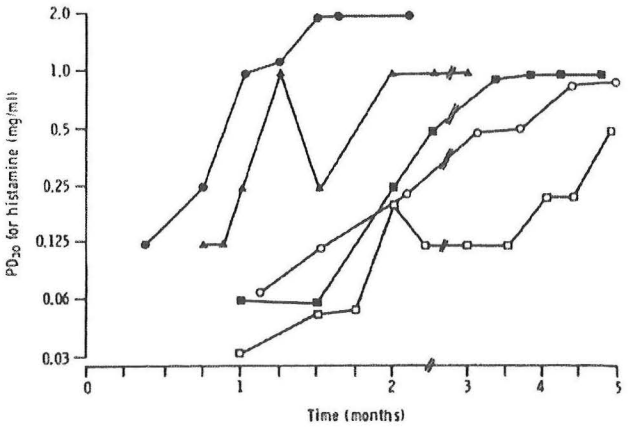

Figure 3. Time course of changes in bronchial reactivity to histamine in five patients showing eight-fold or greater increase in PD_{30} (From Platts-Mills et al., reference 13).

In addition to clinical improvement, dust mite-allergic individuals have been found to have decreased bronchial hyperreactivity (BHR), not only when moved to sanatoria [12], but also when moved to allergen-free hospital rooms. Platts-Mills and colleagues [13] demonstrated that dust mite-allergic patients who lived in hospital rooms for 2 months or more had improved asthma symptoms and early morning peak expiratory flow (PEFR) values. Moreover, 7 of 9 patients achieved a reduction in anti-asthma treatment and 5 of these same patients showed an eightfold or greater increase in the concentration of histamine

necessary to provoke a 30% fall in FEV_1 (PD30) (Figure 3).

Subsequently, Peroni and colleagues [14] corroborated and extended the above findings. This group looked at, not only the effects of reduced dust mite allergen exposure on nonspecific BHR, but also the effects of allergen reduction on dust mite-specific BHR. They evaluated two groups of dust mite-allergic asthmatic children living at high altitude for 9 months. In the first group of children, both total and dust mite-specific IgE levels significantly decreased after 3 months and they remained decreased during the entire 9-month period. However, 3 months after returning to sea level, total IgE levels returned to baseline. In addition, the mean percentage fall in PEFR after exercise testing improved after 3 and 9 months, but it deteriorated once the children resumed living at home. Similarly, the methacholine PD_{20}-FEV_1 improved during the 9 month high-altitude period but returned to baseline levels when the children returned home (Table 2). In a second group of patients, there was a significant increase in dust mite PD_{20}-FEV_1 after both 6 and 9 months at high altitude (Table 3).

Table 2. Summary of results of the first study (From Peroni et al., reference 14)

	October (n=22)	January (n=22)	June (n=22)	September (n=14)
Total IgE (IU/ml)	886 ± 800	585 ± 434	463 ± 350	877 ± 701
Dpt-specific IgE (IU/ml)	35.0 ± 6.6	33.2 ± 6.8	29.6 ± 6.7	25.6 ± 8.5
PEFR decrease after exercise, %	27.8 ± 20.8	18.8 ± 15.9	14.2 ± 12.5	27.9 ± 12.1
Methacholine challenge PD_{20}-FEV_1, ug/ml	124 ± 213	463 ± 612	589 ± 664	140 ± 125

Dpt = *Dermatophagoides pteronyssinus*

Table 3. Summary of results of the second study (From Peroni et al., reference 14)

	October (n=23)	March (n=23)	June (n=23)
Dpt PD_{20}-FEV_1 AUR/ml	47.86 ± 2.81	95.49 ± 3.31	117.4 ± 2.81

AUR = activity units by RAST

These findings extend those of Platts-Mills et al. [13]. A close correlation was demonstrated between prolonged allergen avoidance and a decrease in BHR in two groups of children with asthma. The beneficial effect was observed both with dust mite-specific bronchial challenge as well as with nonspecific challenges (exercise, methacholine). BHR improved significantly after 3 months and further improved after 6 and 9 months indicating that improvement was associated with length of allergen

avoidance. In addition, both total and dust mite-specific IgE levels dropped significantly. However, while BHR and total IgE levels returned to baseline after 3 months of exposure to home allergens, dust mite-specific IgE levels remained decreased. The authors hypothesized that the latter finding may have been due to relatively limited exposure to dust mite allergen during the summer months after the children had returned home. While the dust mite levels were sufficient to enhance BHR, they were not sufficient to raise dust mite-specific IgE levels. Another possibility is that the relapse in BHR and total IgE was due to exposure to allergens other than dust mite.

During an extended stay at high altitude, other factors may contribute to a reduction in BHR. There is less air pollution and, in this particular study, there was no exposure to cigarette smoke, which is an indoor irritant that is known to enhance BHR and increase the incidence of lower respiratory infections. Thus, while dust mite avoidance most likely contributed significantly to disease improvement, avoidance of other allergens and irritants may have contributed as well.

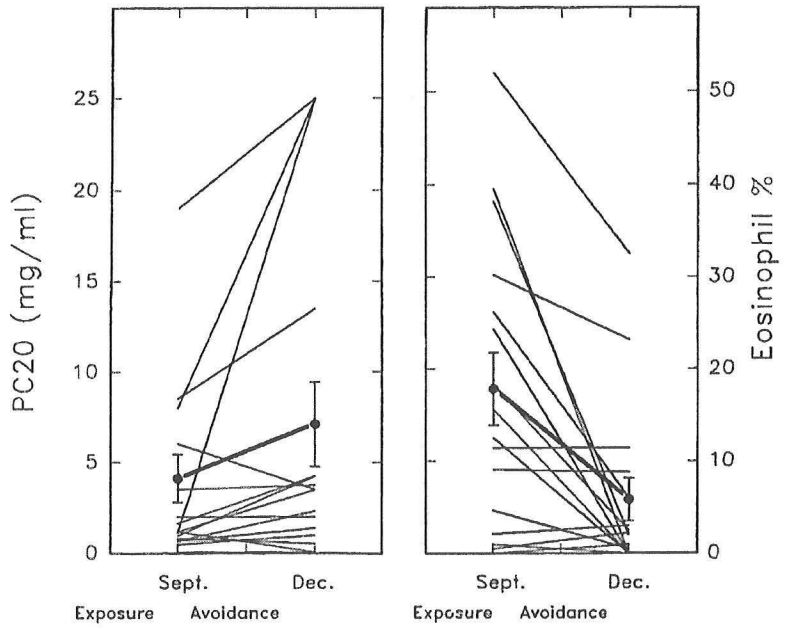

Figure 4. PC_{20} and sputum eosinophils before and after allergen avoidance. Thick lines shown changes in the study population which are expressed as means ± SEM. (From Piacentini et al., reference 15).

In addition to decreasing BHR, two additional studies have demonstrated that inflammatory markers also decrease in dust mite-allergic asthmatic individuals when they are moved to high altitudes for long periods. In 1996, Piacentini and colleagues [15] showed that, after 3 months of living in an Alpine environment, asthmatic children allergic to dust mites demonstrated, not only a significant decrease in nonspecific BHR, but also a decrease in sputum eosinophilia (Figure 4). The study was conducted out of the pollen season so that there would be no interference with these allergens in pollen-sensitized individuals and none of the children had had a respiratory infection in the month preceding the study.

More recently, Grootendorst and colleagues [16] demonstrated, using a controlled, parallel-group design, that 20 weeks of high altitude avoidance leads to sustained benefits in clinical and inflammatory markers of asthma over and above what is demonstrated with high dose inhaled corticosteroids (ICS). Eighteen adolescents with moderate to severe persistent asthma participated. Each was receiving 500-2000 µg ICS daily and each had established dust mite allergy. Despite high-dose ICS, the patients were not optimally controlled. During the 6 months prior to the study, each had had one or more of the following: 1) more than 1 missed school day due to asthma; 2) 1 or more unscheduled clinic visit for asthma; or 3) a short course of prednisolone and/or a hospital admission for asthma.

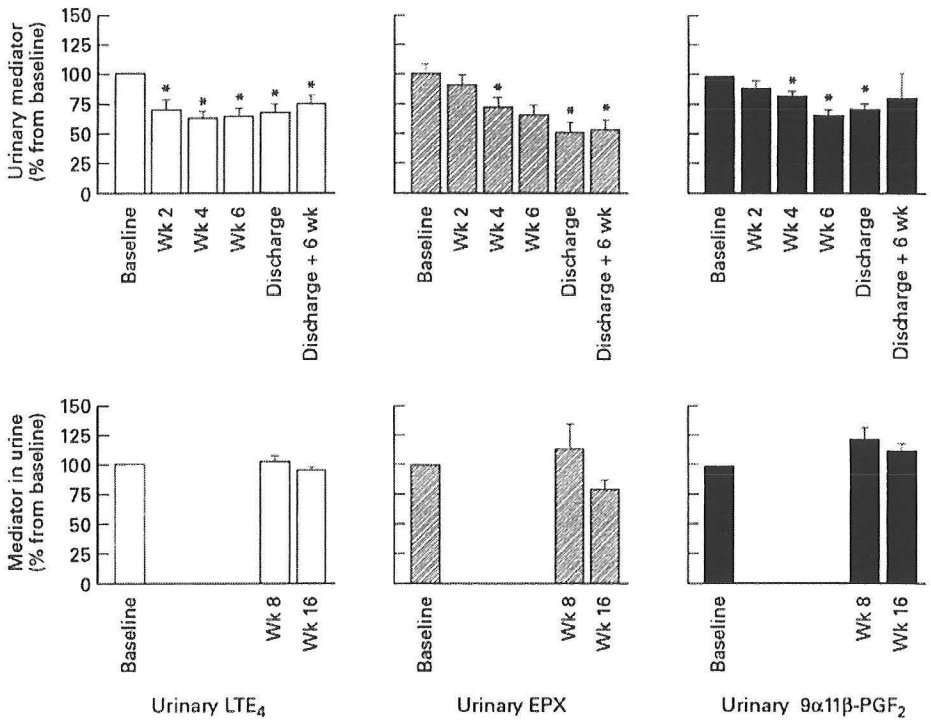

Figure 5. Mean (SEM) changes, expressed as percentage from baseline, in urinary LTE4, EPX, and 9α11β-PGF_2 during the 16-week study in the high altitude group (upper panel) and control group (lower panel) (From Grootendorst et al., reference 16).

For the 10 adolescents who lived at high altitude, BHR and urinary levels of eosinophil protein X (U-EPX), leukotriene E_4 (U-LTE_4) and 9α11β prostaglandin F_2 (U-9α11β-PGF_2) improved significantly while levels of the same urinary mediators did not change significantly from baseline in the 8 individuals in the control group (Figure 5). This decrease in urinary inflammatory markers was accompanied by a concomitant decrease in both blood and sputum eosinophils as well as a decrease in BHR.

Several points can be gleaned from these results. First, the data indicate that

maximal clinical benefit and maximal suppression of airway inflammation in persistent asthma cannot be achieved by high-dose ICS as long as pro-inflammatory stimulation is present. This finding lends support to the current hypothesis that there are important molecular interactions between transcription factors and steroids in which elevated levels of the former, during exposure to pro-inflammatory stimuli, inhibit steroid efficacy [16, 17]. Second, because antigen-specific T cells are less activated at high altitudes due to the absence of dust mite allergen, there is reduced cytokine and chemokine secretion and thus, reduced levels of inflammatory markers in the urine. Taken together, these results indicate that optimal asthma control can be achieved only through combining ICS therapy with allergen avoidance.

Each of these studies demonstrated that dust-mite allergic patients with asthma become markedly improved if they move to dust-free environments. In addition to demonstrating a reduction in medication requirements, they also showed that BHR as well as inflammatory markers of disease may be reduced as well. While these studies have added credence to the belief that allergen avoidance is important in the treatment of asthma, they did not address a critical question. Can effective allergen avoidance be achieved in homes using measures that are flexible to suit individual needs and that are cost effective?

Aerodynamic properties of indoor allergens

Table 4. Aerodynamic properties of indoor allergens (From Custovic et al., reference 8)

Allergen	Particle size	Airborne level	
Mite: *Der p/Der f* Cockroach: *Bla g* 1, *Bla g* 2	Predominantly large particles > 10 µm	Undisturbed: Undetectable with conventional assays	Disturbed: Detectable after vigorous disturbance. Levels settle down within 15-30 minutes
Cat: *Fel d* 1 Dog: *Can f* 1	Large particles > 5 µm (75%) Smaller particles < 5 µm (25%)	Homes with animal: Detectable in all homes. Levels 4-5 times higher with animal in room.	Homes without animals: Detectable in significant proportion of the homes even without artificial disturbance

Before initiating any type of environmental allergen intervention in the home, it is important to understand the aerodynamics of allergen-bearing particles. The aerodynamic properties of the most relevant indoor allergens, dust mite, cat, dog and

cockroach, differ markedly [8]. Dust mite and cockroach allergens are associated with large particles (>10μm in diameter) and thus, they are detectable in the air only after a vigorous disturbance. In contrast, cat and dog allergens (*Fel d* 1 and *Can f* 1, respectively) are often associated with small particles (<5 μm in diameter) and these allergens are commonly found in the air of homes with pets and in many homes without pets (Table 4).

The differences in the aerodynamic characteristics of indoor allergens underlie the different clinical presentations of allergic asthma. Dust mite and cockroach-allergic individuals usually are not aware of a temporal relationship between allergen exposure and asthma symptoms, because the exposure is low-grade and chronic. In contrast, most cat- and dog-allergic patients are aware of their allergy and develop symptoms within minutes upon entering a home with a cat or dog.

House Dust Mites - Home intervention studies

The most effective dust mite-avoidance measure is to place mite-impermeable covers over the mattress and pillows [18]. However, while this is an effective dust mite reduction method, it is important to demonstrate that the use of mattress and pillow encasements and other dust avoidance techniques leads to, not only a reduction in allergen levels, but also a reduction in asthma symptoms.

One of the first controlled studies to demonstrate improvement in asthmatic individuals after implementation of dust mite allergen control strategies was performed by Walshaw and Evans [19]. They enrolled 38 dust mite-allergic adult asthmatic patients in a prospective dust mite avoidance study. While the patients in the experimental group instituted rigorous house dust mite eradication strategies that included mattress and pillow encasements, weekly bed linen washing and removal of bedroom carpeting, the control group did not alter their housecleaning habits. This latter group was told that the study was being done to examine changes in house dust mite levels with the seasons. Baseline clinical data (symptoms, spirometry, BHR) was obtained on both groups of patients at the beginning of the study and then at 4-month intervals thereafter for one year. Dust samples were collected from the mattress, bedroom and lounge floors at the same time intervals for determination of dust mite levels.

Eighteen dust mite-allergic patients were randomly assigned to the experimental group while 20 dust mite-allergic patients were assigned to the control group. Both groups of patients were matched for age, gender, social class, length of disease, dust mite levels, respiratory function and medication use.

Dermatophygoides pteronyssinus was the most common mite found in all homes. More mites were found in the beds than on the floor and mite levels were related to relative humidity. In addition, while dust mite levels fell significantly on the mattresses (and the bedroom floor) in the experimental group, the control group had no change in dust mite levels in the bed (or on the floor).

With respect to clinical manifestations, patients in the experimental group demonstrated marked improvement in several parameters compared to the control group over the course of the study: 1) FEV_1/FVC; 2) nonspecific BHR; 3) inhaled bronchodilator use; and 4) ICS use. Symptom scores also improved in the experimental group while they did not change in the control group. Thus, for the first time, this study demonstrated that adult asthmatic patients can carry out effective dust mite mitigation strategies in their homes, that these measures cause sustained decreases in allergen levels and that dust mite-allergic patients demonstrate both subjective and objective disease improvement with implementation of these measures.

Subsequently, Ehnert and colleagues [20] demonstrated that mite-sensitive children with asthma improve significantly when effective dust mite mitigation strategies are implemented in the home. Twenty-four dust mite allergic asthmatic children with mild to moderate asthma were studied along with two elimination procedures: the covering of mattresses and pillows with polyurethane-coated encasings in combination with treatment of carpets with tannic acid and, second, the treatment of mattresses and carpets with benzyl benzoate (BB).

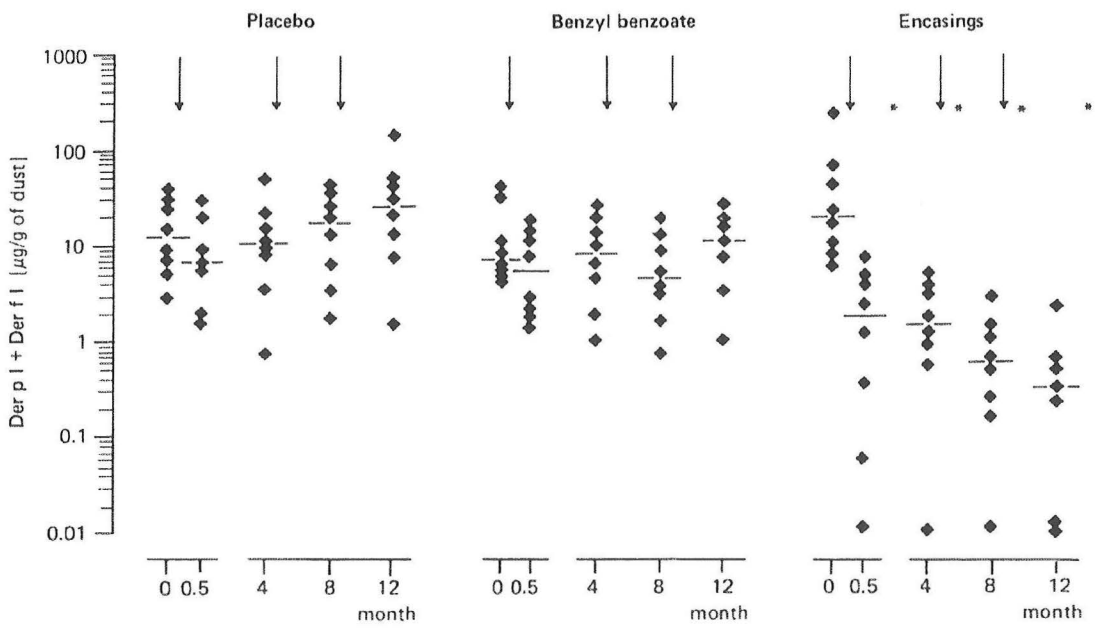

Figure 6. Mite-allergen levels in three groups before and after treatment (arrows); *p<0.05; bars, median values (From Ehnert et al., reference 20)

While BB and placebo treatments did not lead to significant reductions in mite allergen levels, there was a marked decrease in mite allergen levels on mattresses that had been encased by polyurethane covers ($p<0.005$; Figure 6). For all mattresses, levels below that which has been associated with symptomatic asthma (10 µg/g) were achieved [21]. In addition, in both the encasement group in which carpets were treated

with tannic acid and in the BB-treated group (carpets treated as well as mattresses), there was a trend towards mite allergen reduction on the bedroom floor.

When BHR was evaluated in the patients in each of the three groups, only those in the encasement group demonstrated a marked improvement. In the placebo group, the median value for PC_{20} decreased from 0.5 mg/ml histamine on day 0 to 0.27 mg/ml at month 12 (NS) and in the BB treated group, BHR essentially stayed the same. In contrast to these two groups, the PC_{20} for the encasement group steadily increased up to month 8 and then declined slightly in month 12. At months 8 and 12, the increase in PC_{20} was statistically significant compared to that of day 0 ($p<0.05$) (Figure 7).

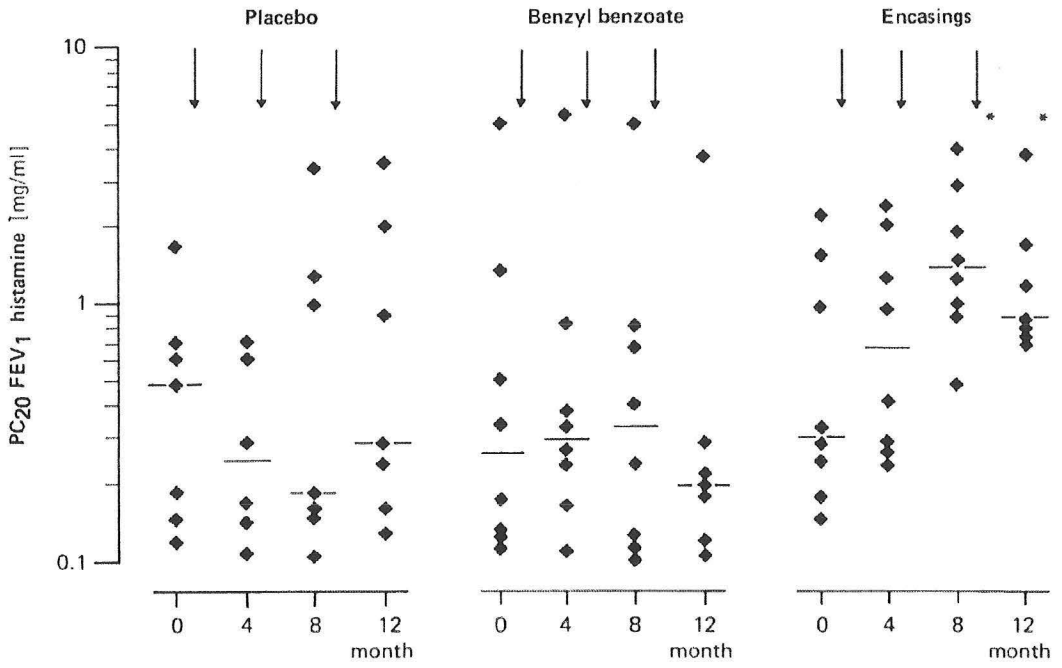

Figure 7. BHR (PC_{20} of histamine) in three groups before and after treatment (arrows); *p<0.05; bars, median values (From Ehnert et al., reference 20).

Thus, as had been previously demonstrated in adults, significant reduction of dust mite allergen levels can be achieved in children's bedrooms using polyurethane-covered encasings for bedding and mattresses and this reduction is associated with decreased BHR.

Recently a meta-analysis was performed to determine whether patients with asthma who are sensitive to dust mites benefit from dust mite control interventions. The meta-analysis included randomized controlled trials that investigated the effects on asthma patients of chemical or physical measures, or both, to control dust mites [22]. All subjects had asthma and were dust mite-allergic. Main outcome measures were the number of patients whose allergic symptoms improved, improvement in asthma

symptoms and improvement in PEFR. Twenty three studies were included (6: chemical measures; 13: physical measures; 4: combined). Altogether, 41/113 patients who received treatment interventions improved compared to 38/117 in the control groups (OR 1.20, 95% confidence interval 0.66 to 2.18). The authors thus concluded that current chemical and physical methods that are aimed at reducing exposure to allergens from house dust mites are ineffective and cannot be recommended as prophylactic treatment for dust mite-allergic asthmatics.

After its publication, there were many "letters to the editor" criticizing one or more aspects of the above study. Cloosterman and van Schayck [23] pointed out that some of the included studies did not achieve sufficient reductions in dust mite levels to be clinically relevant. Platts-Mills and colleagues [24] also reiterated the important point that some of the studies used dust mite control approaches that are known to be ineffective, for example, carpet vacuuming, acaricidal foams and high efficiency particulate air (HEPA) air cleaners. In fact, in 12 of the 23 studies evaluated, decreased dust mite allergen levels were not even demonstrated, and in five studies it was not even determined whether exposure to dust mite allergen had changed! Moreover, only two outcomes were included in the calculations (symptoms and morning PEFR) while these were not the primary outcomes of the successful studies.

To conclude this section on the role of dust mite interventions in asthma, the recommendations from the current asthma management guidelines will be summarized. An NIH Expert Panel [25] reviewed the various studies on dust mite mitigation strategies and asthma, and it concluded that the data are convincing. Dust mite-allergic individuals with asthma improve significantly when effective dust mite mitigation strategies are implemented. Thus, these strategies should be incorporated into the asthma management programs of all dust mite-allergic asthmatic patients.

Cockroach allergen - Home intervention studies

In 1997, Rosenstreich et al. [5] demonstrated that asthmatic children who are allergic to cockroaches and who are exposed to high levels of cockroach allergen in homes have higher hospitalization rates for asthma, more unscheduled visits for asthma and more missed school days and symptoms than asthmatic children who are either not cockroach-allergic or not exposed. Because of the association between cockroach allergy and exposure to asthma-associated morbidity, strategies aimed at reducing cockroach allergen continue to be explored. While it is known that cockroach levels can be reduced successfully with pesticides, it is not always the case that allergen levels drop as well.

Cockroach allergy is particularly important among families living in poverty in American cities [11, 26]. Unfortunately, however, effective control of these insects in apartments and infested houses is quite difficult. The allergen is unevenly distributed in homes and large reservoirs of allergen can accumulate and persist even after the cockroaches have been exterminated [27]. Thus, cockroach interventions must be

multifaceted and must include killing of the insects and subsequent removal of the accumulated allergen.

In 1996, Sarpong and colleagues [28] evaluated cockroach allergen levels in an urban dormitory that was chronically infested with German cockroaches and that underwent semiannual extermination. Dust samples were collected from floors of both bedrooms and kitchens in the dormitory and were analyzed for one of the major cockroach allergens, *Bla g* 2. Floor samples ranged from undetectable (one sample) to 31.0 U/g (median 4.0 U/g). Sixty-seven percent of the floor samples contained *Bla g* 2 levels that were higher than 2 U/g, the cutoff value that has been associated with asthma disease activity [26].

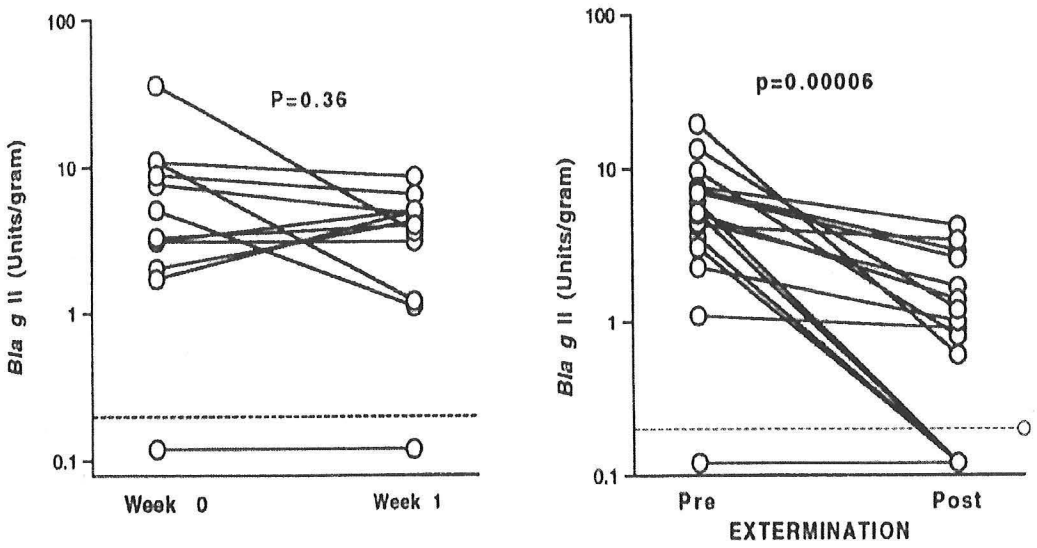

Figure 8. Concentrations of *Bla g* 2 in dust collected from the floors of kitchens and bedrooms on two occasions 1 week apart (Left). **Concentrations of *Bla g* 2 in dust collected from the floors of kitchens and bedrooms during the 2 weeks before extermination and during the 2 weeks afterward** (Right) (From Sarpong et al., reference 28).

While routine vacuum cleaning did not significantly alter allergen concentrations taken a week apart (Figure 8, left graph), extermination followed by extensive cleaning did lead to significantly decreased *Bla g* 2 levels in dust samples collected 2 weeks later (Figure 8, right graph). Before extermination, cockroach allergen levels ranged from undetectable (one sample) to 19.6 U/g (median 5.2 U/g). After extermination and cleaning, *Bla g* 2 was undetectable in 6 of 12 samples and the highest level was 4.2 U/g (median 0.95 U/g; 85% reduction). Thus, this study demonstrated, for the first time, that extermination and cleaning can lead to significantly reduced cockroach allergen levels in an inner city dormitory. However, it remained to be seen if this level of reduction could be achieved in inner city homes.

In 1999, Eggleston and colleagues [29] examined the effect of professional pest control and home cleaning on cockroach infestation and allergen concentrations in settled dust samples from the kitchens, bedrooms and TV rooms of inner city homes. Thirteen homes in Baltimore received a professional cleaning with vacuuming and thorough kitchen cleaning. Pest control technicians then applied abamectin gel to the kitchen and to a limited extent to the rest of the home and cleaning was repeated. Technicians visited monthly from month 2 to month 8 to inspect, collect dust samples and place passive cockroach traps. Both cockroach allergen levels as well as cockroach numbers were determined before and after extermination. The number of cockroaches collected in passive traps decreased rapidly in 11 homes but complete extermination was achieved in 7 homes only. *Bla g* 1 levels also decreased in all areas of the house with extermination (93% in kitchens, 77% in TV rooms and 74% in bedrooms). However, at 8 months, levels still remained well above the threshold level (2 U/g) known to elicit asthma symptoms.

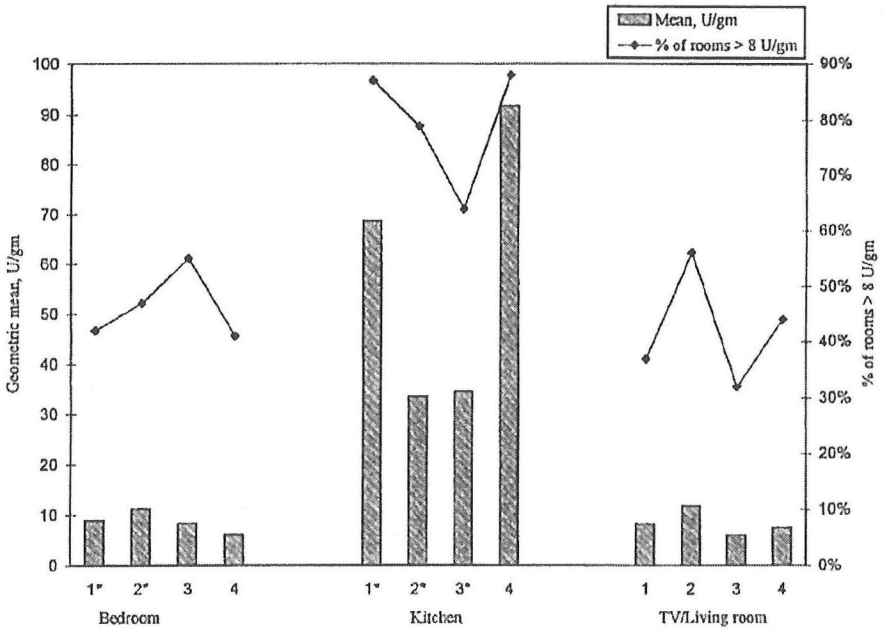

Figure 9. Levels of *Bla g* 1 by room (visits 1 to 4). Bedroom: P<0.05 for visit 1 vs visit 2; kitchen: P<0.05 for visit 1 vs visit 2; P<0.05 for visit 1 vs visit 3 (From Gergen et al., reference 30).

As part of the National Cooperative Inner City Asthma Study (NCICAS), 265 of 331 families with asthmatic children who had positive skin test responses to cockroach allergen consented to a professional home extermination with 2 applications of a cockroach insecticide (abamectin) combined with cleaning and directed education [30]. On a random sample of 48 homes that underwent cockroach extermination (2 extermination visits 1 month apart), *Bla g* 1 levels were measured in settled dust from the kitchen, bedroom, and TV/living room prior to extermination and then again at 2, 6 and 12 months after extermination. As shown in Figure 9, in the kitchen, the geometric mean level of *Bla g* 1 decreased relative to preextermination levels at the 2- and 6-month visits. However, by the 12-month visit, the allergen burden had returned to and even exceeded preextermination levels. In the

bedroom and TV/living room, there were no statistically significant changes in *Bla g* 1 levels after extermination.

While this study demonstrates that cockroach allergen levels can be reduced significantly in kitchens of inner city homes, the reduced levels were still well above those reported to cause respiratory symptoms in asthmatic individuals. Moreover, the reduction was only transient. Several factors may have contributed to these findings. First, the majority of the family dwellings were multi-family dwellings. Reinfestation from other apartments could have occurred soon after extermination. Also, because the levels of cockroach allergen seen in this study were quite high, more extensive cleaning/abatement practices over longer periods of time may be required to decrease allergen levels in homes with high reservoirs of allergen to levels that do not elicit symptoms in sensitized individuals.

In a recent report from the Institute of Medicine [31], the existing information regarding cockroach allergen mitigation was summarized. First, it was stated that there is sufficient evidence of an association between the implementation of intensive cockroach allergen intervention strategies and short-term reduction of cockroach allergen levels. However, in order to be effective, strategies must include both removal of the allergen from reservoirs as well as control of sources. Second, there is still insufficient evidence to determine whether or not there is an association between cockroach reduction interventions and improvement in symptoms or lung function in cockroach-sensitized asthma patients.

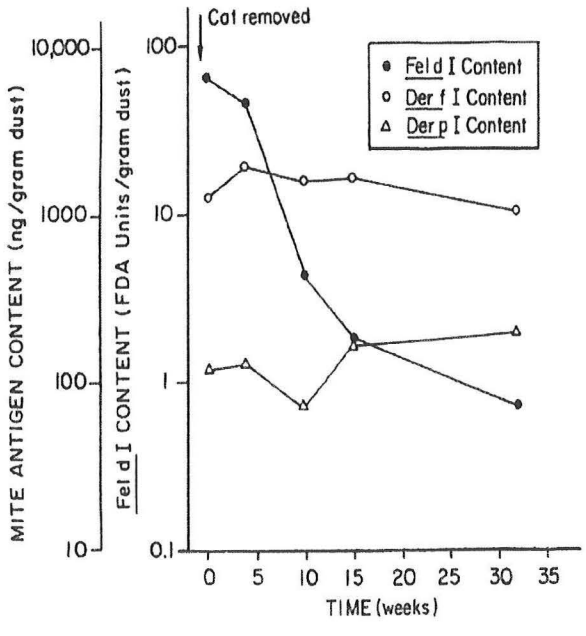

Figure 10. Median content of *Fel d* 1, *Der p* 1 and *Der f* 1 after cat removal (From Wood et al, reference 32).

Pet allergen - Home intervention studies

It seems very simple. The best way to avoid dog or cat exposure is to not have one in the home. However, many pet-sensitized individuals refuse to give up their pet dog or cat. For this reason, it is important to determine if there are any effective allergen reduction strategies for pet-sensitized asthmatic individuals.

In 1989, Wood and colleagues [32], evaluated the effect of cat removal on cat-allergen content in the home. Serial dust samples were collected from 15 homes during a 9- to 43-week period after cat removal and *Fel*

d 1 (major cat allergen) levels were determined. Baseline *Fel d* 1 concentrations ranged from 7.8 U/g to 488 U/g. After cat removal, levels fell gradually over time. By 23 weeks, median *Fel d* 1 levels reached the same level as that found in homes without cats (Figure 10).

These results indicate that removal of a cat from the home environment is an effective means by which to decrease cat-allergen levels. However, it takes many weeks for levels to drop to those found in control homes. Moreover, this allergen-reduction strategy reduction is not often accepted by pet owners.

Subsequent studies evaluated the effectiveness of other strategies in decreasing cat allergen levels. In 1991, deBlay and colleagues [33] found that airborne cat allergen levels can be markedly reduced by combining several different strategies: serial cat washing, reducing furnishings, vacuum cleaning and air filtration. Wood et al. [34] then went on to evaluate the effectiveness of air filtration alone using a high-efficiency particulate air (HEPA) cleaner on cat-induced asthma and rhinitis. Thirty-five cat-allergic subjects who were living with one or more cats were studied in a double-blind placebo-controlled trial. After a month baseline period, patients' rooms were equipped with an active or placebo air cleaner for the following 3 months. Evaluations included monthly measurements of cat-allergen levels, symptom scores, PEFR measurements, medication scores and monthly spirometry and methacholine challenges before and after the study. While airborne cat-allergen levels were significantly decreased in the active-filter group as compared to the placebo group, no differences were detected in settled dust samples, nasal symptom scores, chest symptom scores, sleep disturbance, PEFR or rescue medication use. Thus, the authors concluded that despite reduction of airborne *Fel d* 1 levels using a HEPA filter, levels remain sufficiently high to induce significant allergic inflammation in both the upper and lower airway.

Subsequently, van der Heide and colleagues [35] found that intensive air filtration was beneficial in the treatment of pet-allergic asthmatic children. They evaluated the clinical effects of air cleaners in living rooms and bedrooms of 20 asthmatic children sensitized to pet allergens and with an animal at home. Using a double-blind placebo-controlled crossover study design, the effect of air cleaner placement in the living room and bedroom for 3 months was compared to the effect of sham air cleaner placement. After a 3-month intervention period, BHR, as expressed by PC_{20} adenosine, decreased significantly as did peak flow amplitude in the active air filter group. These improvements were associated with the capture of large amounts of cat or dog allergens in the air cleaners in the living room and bed room. The authors concluded that, while air cleaners do not affect dust and allergen reservoirs in carpets and upholstered furniture, they can help reduce levels of airborne pet allergens. They went on to say that there may be several reasons why their study results differed from that of Wood et al. [34]. First, they evaluated children and not adults and it may be that the airways of asthmatic children are more susceptible to intervention measures. Second, the placement of air cleaners in both living rooms and bedrooms may be more efficient in reducing pet allergen exposure than placement in bedrooms alone.

The Institute of Medicine Committee on the Assessment of Asthma and Indoor Air [31] has summarized the data regarding cat and dog allergen mitigation and asthma. The Committee stated that there is sufficient evidence of an association between removal of a cat from the home environment and a slow decrease in the levels of cat allergen in that home. There is also suggestive evidence of an association between cat removal and improvement of lung function in cat-allergic individuals and suggestive evidence of an association between other cat-allergen reduction strategies (e.g. washing the cat, HEPA filter use) and some transient decrease in cat allergen levels in the home. There is not, however, sufficient evidence to determine whether or not there is an association between cat allergen-reduction strategies and improvement in symptoms in cat-allergic asthmatics.

The data for dog allergen is even more limited. There is suggestive evidence of an association between dog removal from the home and reduction of dog allergen levels. However, there is insufficient evidence to determine whether or not there is an association between removal of a dog from the home and improvement in symptoms in dog-allergic asthmatic patients [31].

Summary

At least some environmental strategies aimed at reducing allergen levels have been shown to be effective, and thus they should be implemented in the homes of allergic asthmatic patients when feasible. However, most asthmatics are allergic to more than one allergen and, to date, there have been no published studies evaluating the effectiveness of interventions directed at reducing the levels of multiple allergens. The Inner City Asthma Study was designed to answer just this question. Using a multi-faceted, home-based, comprehensive environmental intervention that was tailored to the specific sensitization and exposure profiles of asthmatic children [36], it sought to determine whether such a strategy leads to reductions in home allergen levels and whether these reductions, if achieved, are associated with decreased asthma morbidity. The results of this study will be published soon.

Immunomodulation Strategies in the Management of Allergic Asthma

While new and improved anti-inflammatory drugs, especially ICS, have resulted in improved outcomes for patients with asthma, their long-term use does not appear to induce a fundamental change in immune responsiveness [37]. In addition, while asthma improvement also has been seen after implementation of environmental control measures, these not only are difficult to implement for long periods, but also, it is not clear if long-term immune alterations are induced with decreased allergen exposure.

As stated previously, specific Th2 cytokines, especially IL-4 and IL-13, play important roles in initiating and perpetuating immune responses in allergic individuals. In addition, another group of cytokines, including IL-12, IL-18 and IFN-γ, help regulate the balance between Th1 and Th2 cells. Currently, specific allergen immunotherapy

(SIT) is the only available treatment that causes marked long-term modulation of allergic reactivity in patients with asthma. This treatment modality has been shown to reduce allergen-induced tissue infiltration by IL-4- and IL-5- mRNA-expressing cells and to increase IL-12 mRNA-expressing cells [37-39]. Although there are other immune modulators that may someday play a role in asthma treatment such as anti-IgE antibodies, cytokine modifiers and DNA vaccines, these are not yet FDA approved. Thus, the major focus of this section will be on the role of SIT in the treatment of asthma. Other immunomodulators will be discussed only briefly.

Specific Allergen Immunotherapy

A recent meta-analysis compared the effects of SIT plus medical treatment with those of SIT alone in patients with asthma [40]. All prospective, randomized, double-blind, placebo-controlled studies of SIT published in English between 1966 and 1998 were identified by a MEDLINE search and were included in the analysis. Data was extracted from 24 studies that involved 962 asthmatic patients who had documented allergy. In all the studies, except for two, SIT to a single allergen was evaluated and the most common allergen examined was dust mite allergen.

Specific allergen immunotherapy was judged to be effective in 17 of 24 (71%) studies, ineffective in 4 (17%) and equivocal in 3 (12%). Both children and adults benefitted (Table 5). It was found that asthma symptoms and pulmonary function were more likely to improve in patients who received SIT than in patients who received placebo (asthma symptoms: OR 2.76, 95% CI 2.22 to 3.42; pulmonary function: OR 2.87, 95% CI 1.82 to 4.52). In addition, allergen-specific BHR improved and medication use decreased in the SIT group (allergen-specific BHR: OR 1.81, 95% CI 1.32 to 2.49; medications: OR 2.00, 95% CI 1.46 to 2.72). The authors thus concluded that SIT is effective for at least some patients with asthma who have documented allergy.

Table 5. Summary of investigators' conclusions concerning effectiveness of specific immunotherapy in controlling asthma symptoms (From Ross et al., reference 40).

	Number (%) of studies			
Age group	**Effective**	**Ineffective**	**Equivocal**	**Total**
Adults	9 (75)	1 (8)	2 (17)	12 (100)
Children	7 (70)	3 (30)	0 (0)	10 (100)
All ages	1 (50)	0 (0)	1 (50)	2 (100)
Total	17 (71)	4 (17)	3 (12)	24 (100)

Recently, physicians and scientists from various parts of the world convened in

Geneva at the World Health Organization (WHO) headquarters to review the science of and indications for allergen immunotherapy [41]. Some of the information presented in the next several sections is taken from this report. In addition, more recent studies evaluating the effectiveness of SIT in asthma have been included.

Immunotherapy for house dust mite allergy

As described in the WHO report [41], in most of the double-blind, placebo-controlled studies of SIT with domestic mite allergen, the threshold dose of allergen required to elicit immediate bronchial obstruction was increased and the late-phase reaction was inhibited after immunotherapy [42-45]. In addition, SIT to dust mite allergen was shown to decrease symptoms and/or the need for asthma medications in some studies, especially those in children [42, 44, 46-50]. In three studies, however, the results were inconclusive [51-53] (Table 6).

Table 6. Double-blind, placebo-controlled studies in mite asthma (From reference 41).

	Patient Number					
Reference	**A**	**P**	**Allergen**	**Duration**	**Symptoms**	**BPT**
Bousquet et al.	20	10	*Der p*	7 weeks		P<0.01
D'Souza et al.	46	45	*Der p*	1 year	P=0.02	Improved
Franco et al.	24	25	*Der p*	15 mo	Improved	
Gaddie et al.	20	25	*Der p*	1 year	NS	
Machiels et al.	24	11	*Der p*	1 year	P<0.001	P<0.05
Marques et al.	16	12	*Der p*	1 year	Improved	
Newton et al.	7	7	*Der f*	15 mo	NS	P<0.005
Olsen et al.	17	6	*Der p* or *Der f*	1 year	P< 0.01	P<0.05
Pauli et al.			*Der p*	1 year	NS	
Pichler et al.	16	14	*Der p* and *Der f*	1 year	P<0.01	P<0.005
van Bever et al.	9	9	*Der p*	1 year		Improved
Warner et al.	27	24	*Der p*	1 year	P<0.01	

BPT: bronchial provocation test with allergen; A: active; P: placebo

In this section, two more recent studies demonstrating the effectiveness of dust

mite allergen immunotherapy in asthma in pediatric populations will be presented.

In 1999, Gruber et al. [54] evaluated the effects of house dust mite immunotherapy on BHR. Inclusion criteria included a clinical diagnosis of asthma, a positive skin prick test to *Der p* and/or *Der f*, a specific IgE RAST to Der p and/or *Der f* greater than RAST class 2, a positive bronchial challenge test with *Der p* and/or *Der f*, a positive bronchial reaction to cold air challenge (CACh) and age $\geq$ 7 years. Thirty one patients were recruited and were randomized to either the SIT or the control group. All subjects were being treated with different combinations of antiasthmatic drugs (disodium cromoglycate, beclomethasone dipropionate, budesonide, salbutamol on demand).

Specific immunotherapy was performed with an alum-adsorbed house dust mite extract. In the first three months, subcutaneous injections were given in weekly incremental doses up to the highest dose of 4 quality assurance units (QAU) of *Der p* and 30 QAU of *Der f*. This maintenance dose was administered every 4 to 6 weeks for 2 years.

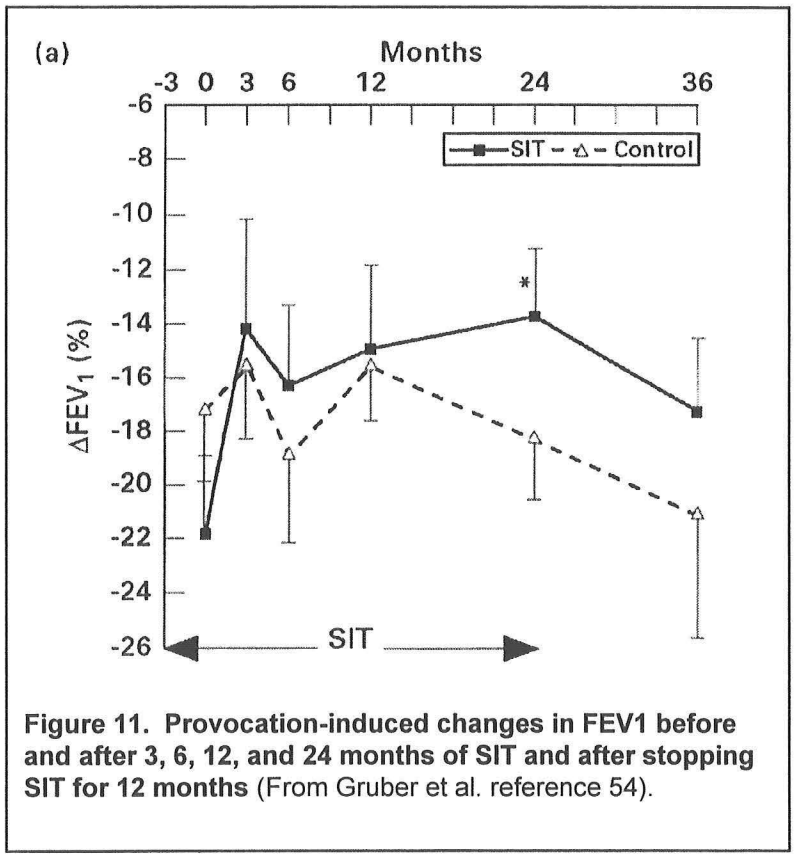

Figure 11. Provocation-induced changes in FEV1 before and after 3, 6, 12, and 24 months of SIT and after stopping SIT for 12 months (From Gruber et al. reference 54).

Initially, 16 patients were assigned to the SIT group and 15 to the control group. Two subjects in the SIT group and three in the control group ultimately withdrew from the study. After the first year of the study, six patients in the SIT group and one patient in the control group had lost their BHR to CACh ($P<0.05$). Moreover, there was a significant reduction in CACh-induced changes in FEV_1 in the SIT group compared to the control group. At the beginning of the study, cold air induced a percent change of -21.8 ($\pm$ 2.7%) in the SIT group. This fell significantly to -13.7 ($\pm$ 2.4%) after the second year. In contrast, in the control group there were no significant improvements in Δ FEV_1 after cold-air challenge over the course of the study (Figure 11). One year after SIT was terminated, there was a tendency of BHR to increase in the SIT-treated group.

These results demonstrate that two years of SIT to dust mite allergen leads to a

reduction of nonspecific BHR in house dust mite-allergic children with asthma. If nonspecific BHR is a marker of inflammation, as has been suggested, these findings suggest that there is a beneficial effect of SIT on asthma pathophysiology. However, since BHR was shown to increase after the cessation of SIT, the authors concluded that a 1-2 year course of SIT may be insufficient for providing a beneficial long-term effect on BHR. They speculated that SIT should be extended to at least 3 years or longer.

A more recent study not only demonstrated a decrease in BHR with dust mite immunotherapy but also it showed that SIT may prevent the development of new sensitizations in monosensitized subjects. Pifferi and colleagues [55] assessed the effects of a three-year period of subcutaneous administration of a standardized preparation of *Der p* on the respiratory health of a group of asthmatic children monosensitized to house dust mite. A randomized clinical trial was performed in which 15 children received SIT for house dust mite and 14 children served as controls. All children were matched for age (mean age: 10 years), allergen sensitization, asthma severity, lung function, and BHR. Over the course of the study, respiratory symptoms and pharmacological and respiratory function parameters were evaluated at regular intervals. Skin prick tests and methacholine challenges were performed at the beginning and the end of the study.

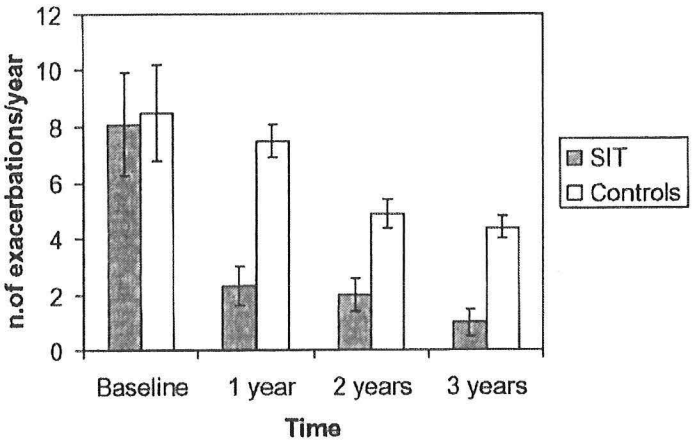

Figure 12. Asthma exacerbations per year in SIT subjects vs. control subjects (From Pifferi et al., reference 55).

Although the SIT subjects demonstrated a trend towards better lung function throughout the three year study period, FEV_1 was not significantly different between the SIT group and the control group at all time points. In contrast, the number of asthma exacerbations significantly decreased in the SIT group compared to the control group. The difference was observed after the first year and it remained significant at the end of the three year period (Figure 12). Salbutamol and systemic steroid use also decreased significantly in the SIT group as opposed to the control group as did nonspecific BHR. Most interestingly, the occurrence of new sensitizations in the SIT-treated group was markedly lower than in the control group (P=0.01). While none of the SIT group developed new sensitivities, five children in the control group developed new skin test

reactions to either pollen or pet dander.

These data further support that SIT is effective in dust mite-allergic patients with asthma. The authors theorized that SIT works by interrupting the chain of events that characterizes allergic disease. It causes a switch in the differentiation of effector cells from a Th2 phenotype to a Th1 phenotype, thus modulating the cytokine response from one that is pro-inflammatory to one that is anti-inflammatory. A decrease in the release in inflammatory mediators could account for both the improved nonspecific BHR that was seen as well as the inhibition of the development of new sensitivities.

Immunotherapy for animal protein allergy

Several double-blind, placebo-controlled studies have demonstrated significant improvement in BHR in patients with cat allergy after SIT [56-61] (Table 7). Both improvement in symptoms as well as reduced medication needs have been seen in cat-allergic patients who underwent SIT. Dog allergen immunotherapy has not been as effective [58, 60].

Table 7. Double-blind, placebo-controlled studies in animal dander asthma (From reference 41).

	Patient number					
Reference	**A**	**P**	**Allergen**	**Duration**	**Symptoms**	**Challenge**
Taylor et. al.	5	5	Cat	3-4 mo.		X 10
Alvarez et al.	14	14	Cat	12 mo.	P<0.001	x 3.4
Haugaard et al.	15	9	Cat, dog	12 mo.	Cat:P<0.01 Dog: NS	Cat: x 4.5 Dog: NS
Ohman et al.	9	8	Cat	4 mo.		X 1.4
Sundin et al.	15	17	Cat, dog	12 mo.	Cat/dog: improved	Cat: x 11 Dog: NS
van Metre et al.	9	13	Cat	12 mo.		X 2.8

While each of the above studies demonstrated that BHR to cat allergen is reduced after SIT, none of them evaluated the response to natural exposure to cat allergen after SIT. Recently, Varney and colleagues [62] performed a double-blind, placebo-controlled study that evaluated the efficacy of SIT with standardized cat dander extract using objective endpoints and simulated "natural" exposure to cats.

Twenty eight adult patients with cat allergy were selected for study. All had

severe cat-induced rhinitis; 13 had clinical asthma and the remainder had experienced cat-induced bronchospasm. While each had a positive skin prick test to cat dander, none of them had other significant allergies. Specific immunotherapy was performed with a standardized preparation of cat dander extract and injections were given twice a week until maintenance was reached and then at four week intervals thereafter.

In addition to demonstrating a reduced PEFR decrease upon cat exposure, patients receiving SIT also had reductions in conjunctival provocation sensitivity and skin test sensitivity to cat extract. Moreover, when patients were assessed by a natural cat exposure challenge (visiting a house in which three cats had lived for over 8 years), only those who had undergone SIT showed a marked reduction in symptoms. This study confirms that SIT with cat dander extract is both safe and effective and leads to protection against simulated domestic exposure to cats as well as improvements in provocation test thresholds.

Immunotherapy for cockroach allergy

Cockroach allergy, in conjunction with high levels of exposure to allergen, has been associated with increased asthma-associated morbidity [5]. Therefore, the most reasonable approach to treating cockroach-allergic asthmatics would be to decrease allergen exposure in their environments. However, as discussed previously, while short-term reduction of allergen levels may be achieved with intensive environmental intervention strategies, prolonged reductions are more difficult to achieve. Another potential approach would be cockroach-specific immunotherapy. However, to date, there has been only one controlled trial of cockroach immunotherapy in patients with asthma.

Kang and colleagues [63] evaluated the effectiveness of SIT in severe perennial asthma in cockroach-allergic patients. Adult subjects were selected from severe perennial asthmatics who demonstrated strong cockroach sensitivity by allergy skin testing (AST), bronchial provocation testing (BPT) or both. All patients required one or more bronchodilators "around the clock" throughout the year for their constant asthma symptoms and each had had multiple emergency department visits and were hospitalized one or more times for asthma in the year preceding the study. Of the 28 patients enrolled, 12 required oral corticosteroid therapy in addition to their bronchodilator medications. There was no mention of inhaled corticosteroid medications.

Unlike most of the previous SIT studies that have been discussed, the patients in this study had multiple allergen sensitivities. Thus, unlike the previous studies, they underwent SIT with either all inhalant allergens to which they were sensitive, including cockroach allergen, or all inhalant allergens without cockroach allergen. Initially, 15 subjects were begun on SIT that included cockroach allergen and 13 received SIT with all inhalant allergens except cockroach allergen. In the experimental group, 3 patients were lost to follow-up and one refused to have blood drawn leaving 11 subjects for

evaluation. In the control group, 6 patients were lost to follow-up and 5 were switched to cockroach immunotherapy, because of severe and frequent asthma exacerbations, (they were not included in the analysis) leaving 2 control subjects for evaluation. Duration of SIT was 59.9 months in the cockroach immunotherapy group and 52 months in the control group. Parameters assessed included: basophil histamine release and symptom and medication scores.

During the initial 6 months of SIT, there was no difference between the two groups in the number of asthma exacerbations that required emergency department visits and hospitalization. During the next 6 months, however, most of the control group patients continued to have severe and frequent exacerbations while the cockroach SIT group improved steadily. After the end of the first year, none of the 11 subjects in the experimental group had been hospitalized for asthma and all eight patients in that same group who were on regular oral corticosteroids had been tapered off this medication. Also, patients in the cockroach SIT group had significantly decreased symptom and medication scores ($P<0.01$) after SIT while those in the control group did not.

This study suggests that cockroach immunotherapy may be beneficial for cockroach-allergic asthmatic individuals. However, before any conclusions can be made, double-blind, placebo-controlled trials must be performed. These will not commence until a standardized cockroach allergen extract is made available.

Immunotherapy to multiple allergens

In clinical practice, the majority of allergic asthmatics are sensitized to multiple allergens. However, there is only one double-blind, placebo-controlled trial of multiple-allergen SIT for perennial allergic asthma.

Adkinson and colleagues [64] evaluated the additive benefit of broad spectrum SIT in children receiving medical care for asthma. Children of either sex who were 5 to 12 years of age were eligible to be enrolled if they: 1) had had asthma for more than one year; 2) had used asthma medications daily or bronchodilators 5 to 7 days per week for more than 6 months in the year before the study; 3) had 2 or more positive skin tests; 4) had a total serum IgE level greater than the 95th percentile for their age; and 5) had personal and family histories of atopy. Eligible children were derived in about equal numbers from an inner city population and a suburban population.

For an initial period of 408 ($\pm$ 210) days, children were observed and "stabilized". During this period, children were instructed about how to manage their asthma and were evaluated for allergen sensitivity and compliance with medications. Medications were adjusted using an algorithm in order to achieve and maintain optimal medical therapy. Patients' homes were also visited so that environmental control interventions could be discussed and house dust could be sampled.

Before randomization, one investigator chose up to seven treatment allergens

per child according to the results of skin prick and RAST tests, with a preference given to perennial allergens over seasonal allergens. Treatment mixtures were prepared by combining 1.6 ml of the highest concentration of each allergen with albumin-saline diluent to a total volume of 9.6 ml per treatment vial (if fewer than seven allergens were used) or 11.2 ml, if seven allergens were used. Placebo consisted of caramelized saline containing histamine.

Immunotherapy was given in a blinded fashion by a treatment team and was initiated with 0.1 ml of a 1:1000 dilution of concentrate. Injections were increased weekly in order to reach a target maintenance dose of 0.7 ml of concentrate. Maintenance therapy was given every two weeks for 24 months and then every three weeks until the completion of the study. The primary outcome measure was the amount of medication required to control symptoms and maintain peak flows within acceptable limits. Secondary outcome measures included: daily PEFR, asthma symptom scores, number of days that either oral or inhaled corticosteroids were used and number of clinic visits for asthma. Methacholine challenges were performed before randomization and at six-month intervals thereafter.

A total of 121 children were enrolled. The average age was 9.2 years with 40% of the children being 8.5 years or younger. Fifty-four percent were white and 45% were African-American. At randomization, 43% of the children were in stable condition on corticosteroids (the majority were receiving inhaled corticosteroids only). All remaining children (57%) required daily cromolyn or theophylline, daily inhaled albuterol or both. At baseline the PC_{20} for methacholine was less than 2 mg/ml for all children. The predominant allergen sensitivity was to *Dermatophygoides* mites (in 80% of the children), followed by short ragweed (in 77%) and a mixture of rye-group grasses (69%). The median number of extracts for treatment was 6 (range 2-7). The baseline characteristics between the children in the SIT group and the placebo group were not significantly different.

Children in the SIT group remained in the study for a mean time of 1005 days while those in the control group remained a mean time of 1023 days. Seventy percent of the children in the SIT group and 95% of the children in the control group received the target maintenance dose every two to three weeks for at least 18 months.

Daily medication scores in both groups declined significantly from randomization to the last followup visit ($P<0.001$). Both groups also had significant reductions in symptom scores ($P=0.003$ (placebo); $P=0.02$ (SIT)) and methacholine sensitivity ($P=0.003$ (placebo); $P=0.008$ (SIT)). Neither group had significant changes in PEFR or in emergency department visits and hospitalizations. The SIT group did have a significant reduction in inhaled corticosteroid use ($P<0.001$) while the control group did not.

A subgroup analysis was performed to determine whether certain patient subgroups received benefit from SIT. The study groups were divided according to the

baseline medication score (a reflection of asthma severity), age, total IgE level and number of allergens received. Other variables evaluated included: presence or absence of dust mite sensitivity, use or nonuse of corticosteroids initially, immunotherapy quality, gender and race. Of the variables evaluated, only younger age (<8.5 years) and milder asthma approached significance as factors that suggested a treatment effect favoring SIT. In light of these results, the authors concluded that SIT with multiple allergens for over two years is of no benefit in allergic children with perennial asthma who are receiving appropriate medical therapy.

After the above article was published, there were many "letters to the editor" criticizing one or more aspects of the study. One of the major criticisms was that the panel of allergens used in the skin testing was not presented nor were the sensitivity profiles of the children. Cockroach allergy is an important perennial allergen in the pediatric population of the United States and yet, the prevalence of cockroach sensitivity in this population was not assessed. Because it is difficult to eradicate cockroach allergen, continued exposure to it may explain the lack of efficacy of SIT in these polysensitized patients [65]. In addition, it was pointed out that lack of efficacy may have been at least partially due to dilution or possibly degradation of allergens [66].

Summary

According to the NIH, Expert Panel Report 2, Guidelines for the Diagnosis and Management of Asthma [25], SIT may be considered in the treatment of asthma in the following cases: 1) when there is evidence of a relationship between symptoms and exposure to an unavoidable allergen to which the patient is sensitive; 2) when the patient's symptoms are persistent; and 3) when pharmacologic control of the asthma is difficult. In addition, when considering whether or not an asthmatic patient should receive SIT, results from the studies previously discussed should be considered. First, it appears that individuals who are monosensitized and who undergo therapy with a single allergen are more likely to obtain benefit than those who are polysensitized. Second, it appears that SIT is more effective in those individuals with milder disease [64, 67] and those who are younger (less than 8.5 years of age) [64].

In addition to clinical benefits, SIT has a number of immunomodulatory benefits as well. First, it is known that SIT promotes Th1 type responses in the skin [68], nasal mucosa [69] and peripheral blood [70] and that these effects are associated with clinical improvement. In addition, the clinical and immune-modifying benefits persist even after the discontinuation of SIT [38]. Interestingly, it has also been shown that SIT may prevent the development of new allergen sensitivities in patients with asthma [55, 71]. Moreover, an important study was recently published that demonstrated that allergen immunotherapy in children with rhinoconjunctivitis may prevent the development of asthma [72]. Thus, SIT has broad immunomodulatory effects, at least in children [73]. It alters the Th1/Th2 balance in such a way that clinical benefits persist for years after discontinuation of a therapeutic course of therapy; it may prevent the development of new allergen sensitivities and it may prevent the progression of allergic rhinitis to

asthma.

Novel Immunomodulatory Therapies for Asthma

There are a number of new immunomodulatory therapies for asthma and allergic diseases on the horizon. Since IgE plays a central role in the pathogenesis of allergic diseases, the use of anti-IgE antibodies in the treatment of allergic conditions such as asthma is being explored. Omalizumab (rhuMAb-E25) is a recombinant humanized mAb that recognizes IgE at the same site as the high-affinity IgE receptor. Treatment with this agent leads to a rapid decrease in free IgE concentrations and is associated with attenuation of both the early and late-phase reactions in patients with mild asthma [74]. More recently, Busse and colleagues [75] showed that omalizumab may be effective in patients with severe persistent asthma as well. This group demonstrated that the addition of omalizumab to standard asthma therapy reduces asthma exacerbations and decreases inhaled corticosteroid and rescue medication use in these patients.

Another exciting way to potentially immunomodulate allergic diseases, including asthma, is by treatment with immunostimulatory CpG DNA sequences (CpG vaccines). Bacterial DNA contains a relatively high frequency of unmethylated CpG dinucleotides. In mammalian DNA, these exist at a lower frequency and they are unmethylated [76]. Bacterial CpG DNA has been shown to have an indirect effect on the Th1 immune response by activating the innate immune system to up-regulate cytokine expression (IL-12, IL-18, IFN-γ, INF-α, IFN-β), MHC molecules, and co-stimulatory molecules [76, 77]. In animal models of asthma, CpG DNA has been shown to inhibit Th2 cytokine responses, eosinophilic inflammation and BHR to methacholine [78]. In human studies, it has been shown that the chemical conjugation of CpG DNA to the short ragweed allergen amb a 1 enhances the allergen immunotherapeutic effect by reducing allergenicity and inducing a Th1-biased immune response. Trials using immunostimulatory CpG DNA conjugated with allergen are underway in allergic rhinitis [79]. Trials in allergic asthma are sure to be close behind.

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