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54 Immunopathogenesis of Asthma

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Wheezing in childhood has become progressively more common as a cause for visits to physicians, emergency rooms, or hospital.[1–3] Some of the increase may reflect misdiagnoses, overanxious parents, or shortage of breath in unfit children. However, the large majority of children receiving treatment have objective evidence of asthma: audible wheezing on chest examination, reversible changes in expiratory flow, or bronchial hyperreactivity (BHR). A large proportion of these children also have indirect evidence of inflammation, which includes elevated exhaled nitric oxide (NO), lowered pH of lung condensate, and peripheral blood eosinophilia, as well as evidence of allergic sensitization.[4–7] The general acceptance that asthma is an inflammatory disease came partly from biopsy studies but, more significantly, from the evidence that steroid treatment is effective, and the reversibility of BHR with prolonged allergen avoidance.[8,9] The fact that lung inflammation and attacks of asthma can be caused by allergen exposure is undoubted. Many children are aware of acute episodes related to visiting a house with an animal. In addition, bronchial challenge can induce both eosinophil infiltration of the lungs and prolonged increases in BHR as well as acute changes in forced expiratory volume in 1 second (FEV_1). Indeed, the only consistent method of inducing "inflammation" in the lungs is to put allergen into the lungs of an allergic subject. However, bronchial challenge or segmental challenge is not the same as natural exposure. Not only is the quantity of allergen inhaled much greater, but the number of particles and the size of particles is dramatically different. The natural form of exposure to allergens is as a relatively small number of particles that are 2 to 20 μm in diameter. These are inhaled over prolonged periods (i.e., months or all year round). Only a small proportion of naturally occurring attacks of asthma appear to be directly related to increased exposure. It appears more likely that allergen exposure plays a chronic role in maintaining bronchial inflammation and reactivity.

Although many different foreign proteins can give rise to sensitization, a select group dominates the epidemiology of asthma. This group includes mites, cat, dog, cockroach, and the fungus *Alternaria*. The main characteristic of these protein sources may be the fact that exposure is perennial. However, recent evidence suggests that the allergens are not equal; either the properties of the protein or the nature of the particles may influence the immune response sufficiently to influence both the prevalence and titer of immunoglobulin E (IgE) antibody responses.

Understanding the immunopathogenesis of asthma is important intellectually because it has to be taken into account in hypotheses about the increase in asthma. In addition, understanding the immunopathogenesis is important as part of the rationale for allergen-specific treatment and pharmacologic anti-inflammatory treatment. Although short-term increases in allergen exposure are not thought to be an important precipitant of acute episodes of asthma, there is a very strong association between immediate hypersensitivity and acute episodes. In part, this may reflect the increased BHR associated with elevated IgE and IgE antibodies. More significant may be recent evidence that the impact of rhinovirus infections on the lungs is strongly related to elevated IgE and elevated IgE antibodies.[10,11]

THE RELATIONSHIP BETWEEN ALLERGENS, ALLERGEN SENSITIZATION, AND ASTHMA

The evidence that allergens play a causal role in asthma comes from a wide variety of experiments (Box 54-1).[12] However, the primary evidence concerns the association between sensitization and asthma. These studies are case control, population based, and prospective, but in all cases the evidence for sensitization comes from measurement of IgE antibodies or immediate responses to skin testing. Although the implication of these studies is that allergen entering the lungs plays an important role in lung inflammation, only a minority of studies show a clear dose response between exposure and asthma symptoms. On the other hand, there are no studies showing a relationship between inhaled allergens and asthma in nonallergic individuals. The most likely explanation of dose-response data (i.e., lack of simple dose response to relationship) comes from (1) the effect of sensitization, (2) the inaccuracy of the measurements of allergen exposure, (3) differences between allergen sources, and (4) the fact that most acute episodes, and probably most episodes of wheezing, are triggered by one of the many nonspecific factors that can contribute to symptoms (Fig. 54-1).

THE ALLERGENS ASSOCIATED WITH ASTHMA

Dozens if not hundreds of sources of allergens have been associated with asthma. However, there are only a few that are common enough to play a role in epidemiologic studies, and most of these are either perennial indoor allergens or have a long season (Table 54-1). The first studies used "house dust" to skin test, but because it was impossible to define what was in the extract, it was difficult to take the results seriously.[13] The discovery or definition of house dust mites was a critical event in understanding the pathogenesis of asthma. Voorhorst and Spieksmah identified *Dermatophagoides pteronyssinus* in dust and developed skin test reagents. It rapidly became obvious that dust mites were an extraordinarily important cause of sensitization in all countries where the humidity was high enough to support their growth.[9,14] The reasons why dust mites are so important are still not clear. It could reflect their presence in bedding; the nature of the particles that become airborne; the biochemical/immunologic nature of the allergens; or some other factor present in the particles (e.g., endotoxin).[15,16]

BOX 54-1 Hill's Criteria for Causality and the Evidence Supporting a Causal Link between Mite Allergen Exposure of a Sensitive Person and the Development of Asthma

1. The strength of the association is large and has been supported by:
   A. Population studies
   B. Control studies
   C. Prospective studies
2. Repeated observations in different populations have consistent findings: Europe, United States, Australia, New Zealand, and Japan.
3. A cause leads to a specific effect: asthma is the only lung disease that has been associated with sensitivity to inhalant allergens.
4. A cause precedes an effect.
5. There is a dose-response gradient: good evidence for dust mite and cockroach allergens.
6. There is experimental evidence from:
   A. Avoidance studies
   B. Challenge studies
7. The mechanism is biologically plausible.

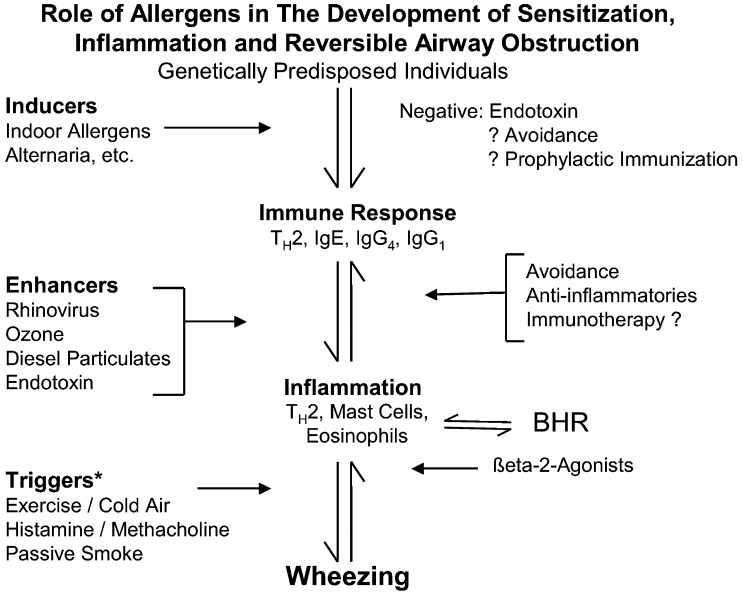
The other allergens that appear to play an important role in asthma include cats, dogs, rodents, and cockroaches, all of which are predominantly inside the house. Although pollens are an important source of sensitization and can cause asthma, seasonal asthma is generally less severe and is often not consistent from one year to the next. Sensitization to fungi is also observed in children with asthma. However, there are great problems with the consistency of the fungal extracts, and there is no consistent method for measuring mold allergens indoors. The only molds that are thought to play an important role in childhood asthma are *Alternaria* and *Aspergillus*.[17,18]

The obvious common feature of the allergens listed in Table 54-1 is that they are perennial. While in most cases this means indoor, it may not be true for the fungi. Inhalation of dust mite and cockroach allergens is thought to be largely in the patients' house. For many years it was assumed that all significant exposure to the indoor allergens occurred at home. This concept has had to be revised, because it is now clear that significant exposure to cat and mite allergens can and does occur outside the child's home. For cat and dog, significant allergen is present in schools and also most houses that do not have a cat. Furthermore, there is extensive evidence that the quantities found away from animals are sufficient to sensitize.[19,20] Indeed, in a recent study, 80% of the children who were skin test positive to cat allergen had never lived in a house with a cat. The message is that preventing primary exposure to animal dander is not possible. Dust mite allergens are not widely distributed away from the sites of mite growth, but children may get high exposure in daycare centers or in Granny's house.[21] The effects of exposure to mite outside the child's house for a week or two, or of exposure in daycare 3 days a week, are not known. However, one explanation of the lack of success of primary avoidance studies is that sensitization can occur outside the house. Some of the recent studies suggest that avoidance measures at home can prevent the lung effects of sensitization even if they cannot prevent sensitization.[21]

The importance of cockroaches as a source of allergen in the United States has become obvious.[5,22] Most of the published data relate to cockroach-derived allergens in the patients' home or own bedroom.[23] On the other hand, it is well recognized that many children spend time living in the houses of friends or relatives, and this is particularly common among children in the cities. The implication is that exposure outside the child's normal home could be relevant to both sensitization and ongoing symptoms.

■ ALLERGEN PROTEINS

Over the past 20 years, a large number of proteins have been identified and cloned. In many cases the proteins show sequence



■ **FIGURE 54-1.** The immune response to allergens requires exposure, but the time course and the dose response are variable. On its own, this response is asymptomatic. Continued exposure to allergen gives rise to inflammation, and this response can be enhanced by diesel particulates, endotoxin, or rhinovirus infection. Inflammation is not necessarily associated with symptoms, but most of the patients have increased BHR, so that bronchospasm can easily be triggered.

■ **TABLE 54-1.** Properties of indoor allergens: 2005

Source	Airborne Particles	Size	Allergen		Function/Homology
Dust mite	Feces	10–40 μm	Der p 1	25 kd	Cysteine protease
Dermatophagoides pteronyssinus			Der p 2	13 kd	Epididymal protein
German cockroach	Frass saliva	>5 μm	Bla g 2	36 kd	Aspartic protease
Blattella germanica			Bla g 5	23 kd	GST
Cat			Fel d 1	36 kd	Uteroglobin
Felis domesticus	Dander particles				
Dog		2–15 μm	Can f 1	21 kd	Lipocalin
Canis familiaris					
Mouse	Urine on bedding, etc.		Mus m 1	22 kd	MUP
Mus domesticus		2–20 μm			
Rat			Rat n 1	19 kd	Pheromone binding
Rattus norwegicus					
Grass	Pollen	30 μm	Lol p 1	29 kd	Cysteine proteinase

For details of properties of allergens, see www.allergen.org.

homology with other proteins that have a defined function (e.g., proteinases, transport proteins, and profilins).[24,25] It is important to remember that sequence homology does not define function: enzymic activity in particular can be completely lost with minor changes in structure.[26] On the other hand, the mite allergen Der p1 is a cysteine protease, and can act on many proteins including CD-25 and CD-23.[25] Although this protein can cleave biologically relevant surface antigens and can open up tight junctions in vitro, it is much more difficult to establish that these activities are relevant to its allergenicity.[24] Certainly, enzymic activity is not a necessary property of allergens since many major allergens are not enzymes (e.g., Fel d 1, Der p 2, Bla g 2). The recent evidence about mechanisms of tolerance to cat allergens suggest that the structure of the allergen is significant. However, it is not clear whether this reflects the primary structure, the tertiary structure, or the biologic properties of the allergens. The allergen proteins do have some physical properties in common. In particular, the molecular weight is generally between 15 and 40 kd. In addition, the proteins are almost all freely soluble in aqueous solution and are antigenically foreign. Thus, the simple view had been that all proteins that were soluble and were inhaled could give rise to an IgE antibody response in children and thus could become an allergen. In the past 5 years it has become clear that all allergens are not "created equal."

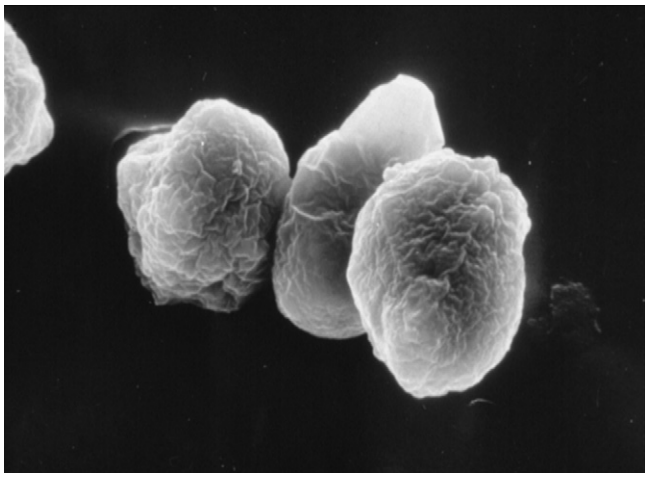
■ AIRBORNE PARTICLES CARRYING FOREIGN PROTEINS, RELEVANCE TO EXPOSURE, AND DEPOSITION IN THE CHEST

The saturated vapor pressure of molecules the size of allergens is close to zero. Thus, airborne exposure to allergens is only in the form of particles, and these are dramatically different from one source to another. In the outdoor air, most particles can be identified under a microscope (e.g., pollen grains and fungal spores). Most areas have regular counts of pollen grains and mold spores reported to the public. By contrast, the particles on which mite, cat, dog, and cockroach allergens become airborne cannot be reliably identified microscopically (Fig. 54-2). Because of this, the science of indoor allergens is dependent on sensitive assays for the major allergens (see Table 54-1). The situation is made more difficult because the particles that have been defined for two of the major indoor allergens are only airborne transiently after disturbance. Airborne behavior, particle size, and allergen content have been estimated for many allergens (Table 54-2).

The aerodynamic size of particles not only defines the speed at which the particles fall in still air (i.e., indoors) but is also relevant to the deposition of particles in the respiratory tract. Traditionally, it was considered that particles larger than 5 μm in diameter were "nonrespirable." However, that term came out of research in the mining industry, and "nonrespirable" meant that particles would not reach the alveoli. For many inorganic particles, it is thought that deposition in the alveoli causes the maximum damage. By contrast, larger particles can reach the tracheobronchial tree. Here the situation is complex because the size of particles is inversely related to the proportion of the particles that enters the lungs; on the other hand, the quantity of allergen per particle increases by the cube of the diameter. Thus, although only 5% of particles of 20 μm in diameter enter the lungs, this may be a more effective method of delivering protein to the bronchi. For a particle of 1 μm, approximately 30% will enter the lungs, but the volume and thus the quantity of protein is only 0.05% of a particle of 20 μm. Thus, although mite fecal particles and pollen grains are large, they may be an effective method of delivering allergen to the lungs, particularly during quiet mouth breathing.

Although mold spores are generally considered to be "outdoor" allergens, indoor exposure may also be relevant because of the long periods of time spent indoors—on average, 23 hours per day. Thus, 200 spores/m^3 indoors may be more significant than 2000 spores/m^3 outdoors. And, again, particle size may be important. Strikingly, *Alternaria* spores are larger than most other fungal spores and have been associated strongly with asthma in the Southwest and Midwest of the United States.[17,18] Mold spores are different from pollen grains, mite fecal particles, cat dander, or cockroach debris in that they have a firm outer surface that is designed to resist desiccation. As a result, they do not release proteins rapidly. Indeed, some of the major allergens of *Aspergillus* are not expressed until the spores germinate. The importance of these differences in particles can be appreciated by comparing (1) mite fecal particles, (2) cat dander, and (3) *Aspergillus* spores (see Table 54-2).

The characteristics of the particles carrying allergens dictate not only the total quantity inhaled, but also the speed of release locally and the quantity of allergen released at each site of deposition. Whether these properties contribute to differences of



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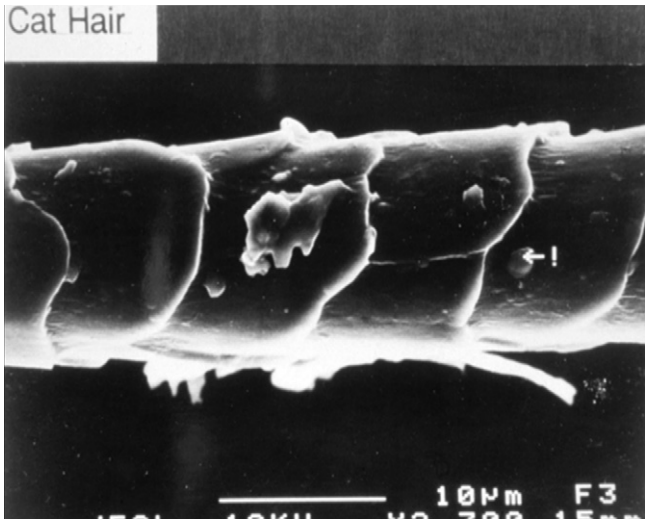

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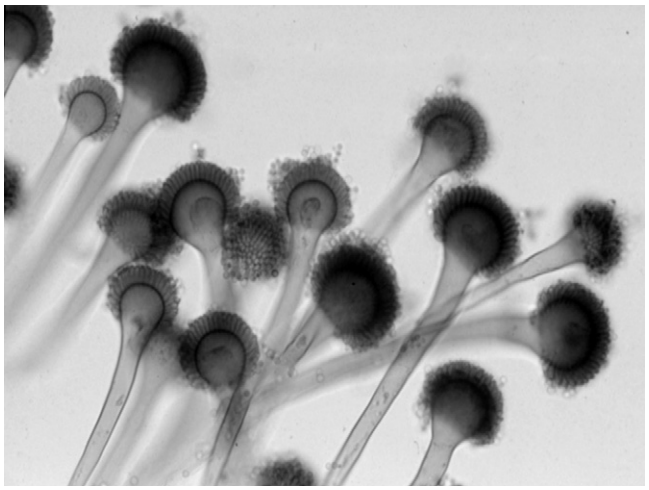


C

■ **FIGURE 54-2. A,** Mite fecal particles seen with scanning electron microscopy, approximate size 25 µm in diameter. **B,** Cat hair showing pattern of hair and dander particles. **C,** *Aspergillus* sporing bodies with multiple spores forming on the endospore.

immune response remains to be determined. However, there are major differences between the allergens that are relevant to (1) the prevalence of sensitization and (2) the nature of symptoms.

■ THE PARADOXICAL EFFECTS OF CAT OWNERSHIP

Children raised in a house with a cat are not at increased risk for sensitization and, indeed, in many studies the presence of a cat in the house leads to a decreased risk for sensitization to cat allergens. This can be seen in case-control studies or by comparing population-based studies.[27–30] The studies on populations show that children raised in countries with the highest percentage of cat ownership have a lower prevalence of skin sensitivity or IgE antibody to cats. This becomes particularly obvious when comparing IgE antibody to cat with IgE antibody to mite.[31] On the other hand, in countries where cat sensitization is the most important correlation with asthma, cat ownership can decrease the risk for asthma.[32]

There are important differences between studies in relation to cat ownership that may reflect differences in dose or timing of exposure. However, there may also be more complex issues of the relationship between different allergens and the concomitant effects of endotoxin exposure.[33,34] There have been three major proposals to explain the cat paradox:

1. That the effect is due to reverse causation (i.e., that allergic families avoid owning cats).
2. That the presence of cats or dogs or both increases levels of bacterial contamination in the house and that this can be measured as endotoxin.[33,34]

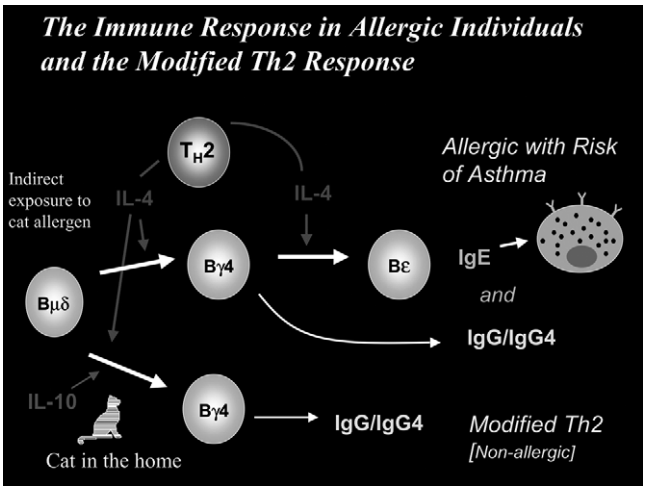
■ **TABLE 54-2.** Contrast between different allergens

	Dust Mites	Cats	Aspergillus
Species	*D. pteronyssinus*	*F. domesticus*	*A. fumigatus*
Particles	Fecal pellets	Dander	Spores
Size	15–30 µm	2–20 µm	1–4 µm
Airborne	10 min post disturbance	Many hours	Fall slowly outdoors
Allergens	Der p 1, Der p 2	Fel d 1	Asp f 1 – Asp f 6
Mass per particle	0.2 ng	0.01 ng	<0.001 ng
Mass inhaled per day	~10 ng	0.5 µg	No estimates

3. That high-dose exposure to the cat allergen Fel d 1 (i.e., the presence of a cat in the house) can induce an allergen-specific form of immunologic tolerance.[27,35]

Investigation of the cat paradox has been carried out in countries with different climates, housing conditions, and furnishing. The extremes may be the most instructive. In northern Scandinavia, cat allergen is the most important cause of sensitization and there is virtually no sensitization to mites or cockroaches. Most of the children who become allergic to cats and become asthmatic have never lived in a house with a cat. In this environment, cat ownership leads to decreased allergy, decreased prevalence of asthma, and decreased incidence of asthma.[32,36] By contrast, in an environment with high concentrations of mite allergen in most houses (i.e., the United Kingdom, Australia, New Zealand, or southeastern United States), sensitization to dust mites dominates other forms of sensitization in childhood.[4,6,27,31,37,38] As a result, the presence of a cat has no effect on the prevalence of asthma. In addition, the presence of a cat has no effect on the prevalence of sensitization to dust mite. Thus, cat exposure can induce a specific form of tolerance. The implications of this phenomenon go beyond the relevance of cats in the house:

1. That allergens are distinct not only in their ability to sensitize but also in their ability to tolerize at high dose.
2. That producing IgG and IgG4 antibodies to the cat allergen Fel d 1 does not create a risk for symptoms on exposure to cat allergen; this argues very strongly that IgE antibodies are essential for the response that gives rise to asthma (Fig. 54-3).
3. That the effects of cat ownership cannot be ascribed to a nonspecific effect on sensitization or IgE antibody production, because cat ownership does not decrease IgE antibody to dust mites.



■ **FIGURE 54-3.** The immune response to cat allergens may take a traditional T-helper 2 (Th2) response with immunoglobulin G4 (IgG4) and IgE antibodies. Alternatively, among children living with a cat a significant number produce IgG1 and IgG4 antibodies to Fel d 1 without IgE (modified Th2 response). The T cells are thought to control IgE production both in nonallergic and allergic children. (See Color Plate 40.)

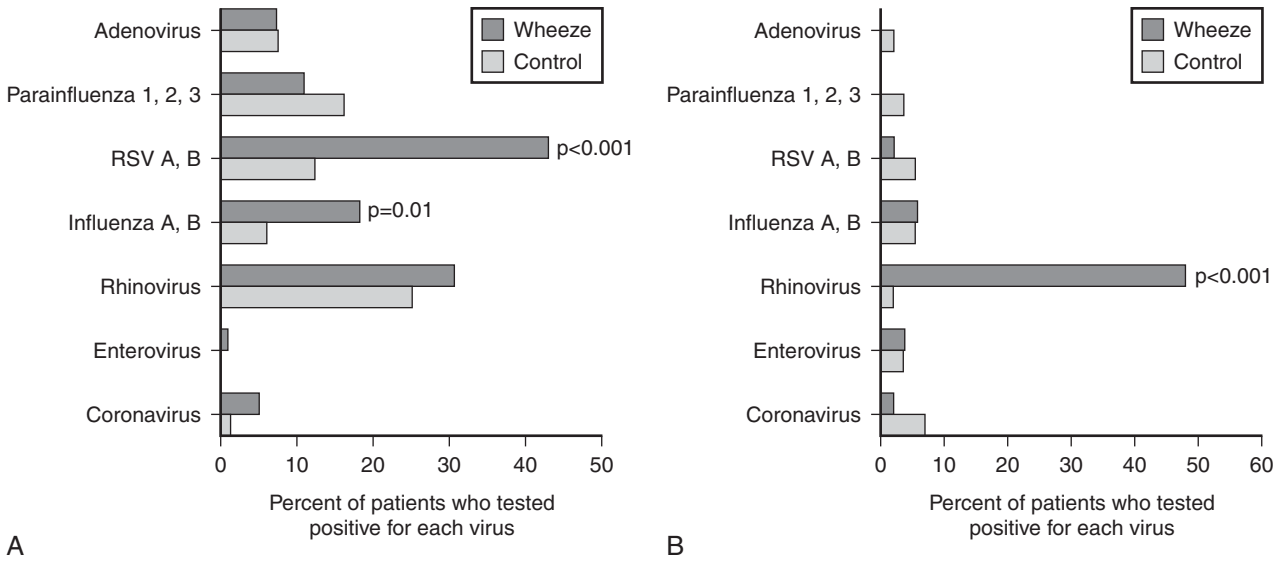
■ RELEVANCE OF DIFFERENT ALLERGENS TO TOTAL SERUM IGE AND THE ASSOCIATED RISK FOR ACUTE ASTHMA

When comparing IgE antibody responses to dust mite and cat, not only is the prevalence of IgE antibody to mite higher, but the titer of IgE antibody to mite can be much higher. In addition, the mean total IgE is higher in some cohorts of children. This raises the question of whether specific IgE responses can increase the total. At present, the evidence is unclear but the prevalence of wheezing children with a total IgE greater than 200 IU/mL is far higher in countries where dust mite is the dominant source of allergens. The relevance of an elevated total IgE is clear from prospective studies, emergency room, and hospitalization data.[5,11] In several different studies, increased risk for acute episodes of asthma can be seen with either total serum IgE or elevated specific IgE antibody greater than 10 IU/mL.

■ THE INTERACTION BETWEEN VIRAL INFECTION AND ALLERGIC RESPONSES IN CHILDREN WITH ACUTE EPISODES OF ASTHMA

Viral infection can be seen as a precipitant of asthma either in a prospective study on wheezing children or in case-control studies in an emergency room or in a hospital.[5,11,39] The results show unequivocally that viral infections are an important precipitant of acute episodes. However, the data for children younger than 3 years is strikingly different from the data on older children. Younger than 3 years, it is possible to identify one or more viruses in a very large proportion of children presenting with, or admitted to hospital with, acute episodes of asthma or bronchiolitis (Fig. 54-4). This includes not only respiratory syncytial virus (RSV), influenza, and coronavirus, but also rhinovirus and the newly described metapneumovirus.[11,40] At this age, the symptomatic children are no more allergic than age-matched children without respiratory symptoms admitted to the same emergency room or hospital. Indeed, in one study the mean total IgE of children admitted to hospital was 8 IU/mL. Among children older than 2 (or 3) years, and also in young adults, the data are completely different because rhinovirus is the only virus that has been shown to be associated with acute episodes and the children are highly allergic.[11,39,40] Indeed, the mean total IgE of children admitted to hospital for asthma 3 to 11 years of age was approximately 330 IU/mL, while the value for controls was approximately 35 IU/mL. Very similar data have been seen from a study in the United Kingdom.[40] The question is how does rhinovirus precipitate acute episodes of wheezing and why is this response so strongly associated with allergy?

Understanding of the mechanisms by which rhinovirus induces acute episodes of asthma in allergic children has been obtained from observational studies or challenge studies. The evidence from emergency room studies is that when the children present, they have elevated peripheral blood and nasal eosinophils, as well as elevated exhaled nitric oxide and lower pH of exhaled condensates.[7,10,11,40] All of these features can be induced to some degree with rhinovirus challenge of a nonsymptomatic asthmatic.[10,41] These studies are done in children using the NIH definition of children (i.e., up to 21 years). However, what is striking is that the response to rhinovirus challenge is much more marked among asthmatics with total IgE of greater than 200 IU/mL.[10] Rhinovirus challenge has been investigated experimentally for approximately 20 years, primarily in nonallergic or nonasthmatic individuals. The results are absolutely clear that this virus does not induce asthma in a



■ **FIGURE 54-4.** Evidence of recent viral infection was obtained from nasal secretions on children admitted to hospital with or without wheezing. The results are shown for children younger than 3 years (**A**) and children age 3–18 (**B**). (From Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP, Erwin EA, Shaker MS, Hellems M, Peerzada J, Hayden FG, Hatley TK, Chamberlain R: Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. J Allergy Clin Immunol 2004;114:239–247, fig 4, p 244.)

nonasthmatic individual. Of course, the rhinovirus is primarily a pathogen of the nose and is an extremely unusual cause of pneumonia. Thus, there are two possible explanations. The first is that rhinovirus does enter the lungs sufficiently to cause increased symptoms and pathology in allergic individuals or second that events in the nose can trigger events in the lungs by a neurologic, cellular, or cytokine-mediated effect. The studies of Dr. Busse's group in Madison have established beyond doubt that a rhinovirus infection can alter response of the lungs to an allergen challenge.[41,42] They have also argued that the virus can be identified in the lung using reverse transcriptase polymerase chain reaction.[43] Surprisingly, repeated nasal allergen challenge prior to rhinovirus challenge did not increase either the severity of the "cold" or the lung response.[44]

Given the apparent effect of total IgE on the risk for asthma and the different effect of some allergens on total IgE, we could ask whether these allergens increase the risk for acute episodes. Preliminary evidence suggests that acute episodes and hospitalization for asthma are less common in countries where the houses do not have dust mite allergens. Equally, those children who make an IgG and IgG4 antibody response without IgE antibody have very low mean levels of total IgE (i.e., ~25 IU/mL) and no associated risk for wheezing.

■ MECHANISMS OF INFLAMMATION IN THE RESPIRATORY TRACT

There is little doubt that inflammation in the lungs contributes to asthma symptoms and to reversible changes in lung function. Indeed, it has been shown that prolonged allergen avoidance, or steroid treatment, can decrease inflammation of the lungs in parallel with improvement of asthma. Thus, both allergen avoidance and steroids can decrease symptoms, improve lung function, and decrease bronchial hyperreactivity (BHR). What is not clear is how much different elements of the predominantly allergen-induced inflammation contribute to BHR or changes in lung function. The most convincing association with symptoms is the presence of peripheral blood eosinophils and the presence of eosinophils in the nose. Given the evidence that eosinophil granule contents (e.g., major basic protein [MBP] or eosinophil cationic protein [ECP]) are toxic to bronchial epithelium, it seemed logical that eosinophils played a major role in the inflammation of asthma. Surprisingly, treatment with anti-interleukin-5 (anti-IL-5), which successfully reduced peripheral blood eosinophil counts, did not improve asthma symptoms.[45] Considerable attention has been focused on the sequence of events that leads to deposition of collagen below the basement membrane in children with asthma. This and other changes have been associated with the term *remodeling*; however, this term should be avoided because it is widely misinterpreted. Remodeling has been used to imply (1) progressive decline in lung function; (2) collagen deposition, increase in goblet cells, and fibroblast activity; and (3) changes in the elasticity of the lung. Unfortunately, there are no clear studies that connect any of the inflammatory changes with decreases in lung function. Furthermore, there is little evidence that progressive decline in lung function is an important feature of asthma in childhood. In most studies those patients who present with lower than average lung function will maintain decreased lung function over long periods of time. In the Childhood Asthma Management Program study there was little evidence for decline in lung function over 4 years. Furthermore, the beneficial effects of inhaled steroids in controlling the disease that were highly significant did not result in any significant difference in lung function 1 month after stopping treatment. Thus, the evidence that inflammatory changes can lead to progressive changes in lung function is not clear, and the term *remodeling* should be avoided. On the other hand, the fact that inhaled steroids provide effective control for mild or moderate asthma argues strongly that inflammation plays an ongoing role in the symptoms. However, steroids have such a wide range of actions that their efficacy does not provide evidence about which part of the inflammatory response is relevant.

RELATIONSHIP BETWEEN IMMUNE RESPONSES, INFLAMMATION, AND SYMPTOMS

The primary epidemiologic evidence linking allergens to asthma relates to skin tests or serum IgE antibodies. However, IgE antibody production is T-cell dependent and the immune response to allergens also includes IgG, IgG4, and IgA antibodies. It could be argued that the association with IgE is seen most clearly because this form of sensitization is easy to detect (i.e., radioallergosorbent test [RAST] in vitro or skin tests in vivo). There are many studies, however, in which T-cell responses or IgG antibodies to allergens have been found in nonallergic and nonwheezing children. Thus, there are good reasons to focus on the role of immediate (i.e., IgE-mediated) hypersensitivity. Allergen challenge of the lungs of an allergic subject produces immediate (i.e., within 15 minutes) declines in FEV_1, late responses, eosinophil infiltration, and prolonged increases in BHR. Mast cells can release not only histamine, cystinyl leukotrienes, and platelet activating factor (PAF), but also cytokines including IL-5 and chemokines. There are several recent developments that relate directly to understanding the role of the immune response in inflammation and symptoms:

1. The response of the lungs to intradermal injections of allergen derived peptides that will react directly with T cells.
2. The clinical efficacy of anti-IgE treatment in patients with moderate to severe asthma.
3. The evidence that children who make IgG and IgG4 antibodies to cat allergen without IgE antibodies do not have an increased risk for asthma.

T-CELL PEPTIDE RESPONSES

Although not currently available as a treatment, there is extensive evidence that injections of peptides derived from Fel d 1 can induce a delayed (i.e., within hours) response in the lung and can have a beneficial effect on symptoms.[46,47] These results strongly support the view that T cells in the lung can contribute to the pathology of asthma. However, to date the studies have all been conducted in allergic subjects. Thus, there are two questions: First, are the quantities of peptides reaching the lungs a realistic model of what could happen during natural exposure; and second, how do the T cells get to the lungs? Lymphocytes are recruited to sites of local "inflammation" following the presence of a foreign antigen. Thus, an attractive argument is that in children with IgE antibody, the local deposition of an allergen particle can trigger mast cell degranulation, which leads to the recruitment of a variety of cells, including lymphocytes. Most of these cells are short lived in the tissues. However, T cells recruited to the tissues may persist locally. The presence of T cells in the lungs of allergic patients could explain many features of the chronicity of asthma. However, the hypothesis is that these cells will only accumulate locally in children who already have immediate hypersensitivity.

TREATMENT WITH MONOCLONAL ANTIBODIES TO IMMUNOGLOBULIN E

Injecting polyclonal anti-IgE into the skin produces a wheal and flare reaction in all subjects except the very small number of IgE-deficient patients, most of whom have hypogammaglobulinemia. Thus, treatment with anti-IgE that binds the main epitopes on the epsilon heavy chain is not possible. However, antibodies to the site that binds to the receptor for IgE (Fc-ε-R1) will only bind IgE that is not bound to a mast cell or basophil. Treatment with monoclonal antibodies to IgE would seem to be a logical treatment for allergic disease. However, there are some reasons why it should not succeed. First, other monoclonal antibodies that are in use clinically act on cytokines or interleukins that are present in much smaller quantities. Second, the short half-life of IgE means that these antibodies pass rapidly through the circulation but remain for much longer periods (i.e., up to 6 weeks) on mast cells in the skin. Third, as discussed above, it seems likely that at least part of the inflammatory response in the lungs is mediated by T cells (i.e., not dependent on IgE antibodies). Given the potential problems, the success of anti-IgE treatment in clinical trials has been encouraging.[48] Indeed, some children derive major benefit from this form of treatment. The implication is that IgE antibodies play a role in the persistence of inflammation and BHR in the lungs. This finding is not only significant clinically but also because it provides proof of the concept that IgE antibodies play a direct role in asthma.

A MODIFIED TH2 RESPONSE TO CAT ALLERGEN IS NOT ASSOCIATED WITH SYMPTOMS OF ASTHMA OR INFLAMMATION IN THE LUNGS

Children raised in a house with a cat are less likely to develop IgE antibody to cat allergens, but as many as 50% of these children have made an IgG antibody response to the cat allergen Fel d 1 without IgE antibody.[9,32] What is relevant to the present discussion is that this IgG antibody response on its own does not create a risk for wheezing. Thus, children living in a house with a cat with very high exposure to cat allergen do not develop symptoms unless the immune response includes IgE antibody. Furthermore, the nonallergic subjects mount a T-cell response that is similar to the response observed in allergic children. The implication is that T cells only play a role if there is also an IgE antibody response, which could mean either that the T cells have a subtle difference or that IgE antibody is necessary for T cells to be recruited to the lungs.

Changes in the lungs of children with asthma include a cellular infiltrate, excess mucus production, collagen deposition, and irritability of smooth muscle. The mechanism of this response includes a cascade of leukotrienes, prostaglandins, cytokines, and chemokines. Many of these have been identified as potential targets for treatment. However, given the number of molecules identified, it has been difficult to establish their role in the lung response. Many different approaches have been used, including measurement of cytokines, in samples obtained from the lungs, gene expression studies, detailed studies in murine models, and the development of antagonists or monoclonal antibodies suitable for clinical trials. Ultimately, it is clinical trials that provide the most convincing evidence. Thus, the efficacy of leukotriene antagonists strongly supports a role for these molecules in asthma. The results of the studies with anti-IL-4 or IL-4 receptor antagonists have been positive in moderate to severe asthma but were unconvincing in mild persistent asthma. Some years ago, the results with antagonists for PAF were consistently negative. Several other targets have been investigated and abandoned by the pharmaceutical industry. The continuing success of corticosteroids either as a local or a systemic drug may

reflect the fact that they influence the expression of multiple genes as well as dramatically reducing circulating and tissue eosinophils. If, as seems obvious, corticosteroids are clinically effective because they have multiple actions, other agents may need to be combined (e.g., anti-IL-5 and an IL-4 antagonist). However, experiments of that kind would be difficult to carry out as clinical trials.

CONCLUSIONS

The treatment of asthma in children older than 3 years is focused on long-term anti-inflammatory treatment. This strategy recognizes that the large majority of these children have inflammation in their medium and large bronchi, and that this response is a major cause of reversible airflow obstruction. In addition, many or most of these children are allergic to one or more of the allergens that are found in homes in the area where they live. It is well established that inhaling allergen in an allergen challenge can induce an eosinophil-rich cellular infiltrate and prolonged increases in nonspecific BHR. Thus, there is a logical case that inhaling allergens is a cause not only of sensitization but also of the disease. This view is supported by some but not all results of allergen avoidance studies.[9,49] On the other hand, it is difficult to establish a simple dose response between allergen exposure and the prevalence or severity of asthma. However, the complexity of the relationship between allergens and asthma (see Fig. 54-1) would tend to obscure the dose response. Simple relationships between exposure in the patient's home and wheezing could be obscured by (1) genetics, (2) the inaccuracy of floor dust assays as a measurement of inhaled exposure, (3) exposure to "indoor" allergens in buildings other than the child's home, and (4) tolerance to allergens at high dose.

Virus infection plays an important role in bronchiolitis/wheezing/asthma throughout childhood. In children younger than 3 years, many different viruses can induce bronchiolitis. At this age, RSV, influenza, metapneumovirus, and rhinovirus may all play a role. The major defined risk factor for viral-induced wheezing episodes in children younger than 3 years is small lung size at birth, and at this age, allergy does not play a significant role. Many of the children who have early viral-induced episodes will go on to have persistent asthma. However, early episodes are common, and it is not clear whether the early infections influence the subsequent development of allergy or persistence of asthma. After age 3 years, the role of viral infections changes completely. Presumably, because of lung growth, viral infection of nonallergic children is no longer a cause of emergency room or hospital visits. At this age, the only virus that appears to play an important role is rhinovirus, and this effect is only seen in allergic children. More significantly, these children are not simply skin test positive, but they have major elevations of total serum IgE (geometric mean value for 53 children age 3–18 years was 390 IU/mL).[11] This result is consistent with other studies and suggests that conditions that increase total IgE could be a risk factor for severe episodes of asthma.

Elevated total IgE is strongly associated with asthma. Burrows and colleagues[50] reported that the higher the total IgE, the greater the prevalence of asthma. It has been clearly shown that total IgE is strongly influenced by genetics; however, recent studies suggest that some allergens can contribute more than others. In particular, dust mite, cockroach, grass pollens, and the fungus *Alternaria* have been shown to induce high-titer IgE antibody (i.e., 10 IU/mL) and in some instances to increase total serum IgE. In contrast, with cat and dog allergens, not only are positive skin tests less common, but the titer of IgE antibody is generally lower. Thus, some allergens, but not others, can increase total IgE to a level that is associated with acute episodes. This effect may contribute to the higher prevalence and severity of asthma in some communities (e.g., New Zealand, United Kingdom, and the North American inner city) compared with others (e.g., Scandinavia).

The relevance of immunopathogenesis to treatment can be seen in three ways. First, controlling the inflammatory response has become a mainstay of treatment using inhaled steroids, leukotriene antagonists, and, in a small number of cases, anti-IgE. Second, allergen-specific treatment using avoidance or immunotherapy can influence inflammation in the lungs. Third, some future approaches to therapy could focus on altering the immune response using peptides or recombinant molecules that can influence T-cell responses and IgE antibody production. Given the complexity of the immune response to allergens and its relationship to symptoms, it is no surprise that analysis of the genetics of asthma has provided inconsistent results. Presumably, environmental effects related to both the time course and the dose of different allergens as well as the modulating effects of endotoxin exposure can alter the association with different genes. In addition, the effects of many different changes in lifestyle may also influence these relationships. The implication is that we should focus on interpreting and altering the inflammatory response to the environment.

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