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Changing concepts of allergic disease: The attempt to keep up with real changes in lifestyles

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In the past 100 years, changes have occurred in the outdoor environment and in houses that have contributed to the increased prevalence of hay fever and asthma. Much evidence indicates that exposure to indoor allergens is an important cause of asthma. Changes in housing that have contributed to the increased prevalence and severity of asthma include increased temperature, decreased ventilation, and permanent carpeting. In addition to these changes, geographic differences in allergens, deficiencies in cleanliness, poor health care, passive smoke, and lack of exercise also contribute to the increase in severity of asthma that

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J Allergy Clin Immunol 1996;98:S297-306

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0091-6749/96 \$5.00 + 0 1/0/68332

has occurred. The management of asthma includes controlling exposure to indoor allergens and seeking additional treatable causes of asthma (e.g., fungal allergens). Changes will continue to occur, and physicians who treat allergic diseases should become involved in the design of houses to limit exposure. Many questions regarding allergen measurement and control remain. (J Allergy Clin Immunol 1996;98:S297-306.)

Key words: Allergens, asthma, causation, dust mite, exposure, hay fever, housing, outdoor environment, sensitization

Hay fever was first described in the 1820s, but the disease was not common. The cause of hay fever was not clarified until the 1870s, when Blackley,¹ studying grass, and Wyman,² studying ragweed, proved that it was related to pollen exposure. By 1900, hay fever was epidemic, and the prevalence probably continued to increase until 1960, when the incidence among young adults approached 25%.^{3,4} The problem is to understand why the occurrence of a disease such as hay fever should increase so dramatically. It has been suggested that improved health of the community with decreased helminth infections or increased air pollution contributed. The most likely explanation in England is that, before the reform of the Corn Laws in 1847, very little hay was grown; consequently, grass pollen levels were much lower. During the next 50 years, increased importation of wheat from southern Russia directly contributed to the collapse of English wheat production. This change was followed by dramatic increases in the number of milking cows and in hay production. Indeed, over the last quarter of the 19th century, the area of England under grass increased by 3.5 million acres. Similarly, in the United States, it is possible that an increase in ragweed pollen occurred as large sections of the Midwest were cultivated.

In the current century, a series of changes in the design and management of houses appear to be responsible for major changes in allergic disease. Perhaps the first change was the introduction of carpeting as a permanent fixture. Before 1930, carpets were never left down, and they were regularly beaten. In the United States, carpets were unusual in housing of low-income families, and they were put in storage from May to October in middle- or upper-class houses. Thus Edith Wharton⁵ wrote in 1905 in *The House of Mirth* that Mrs. Peniston was "as much aghast as if she has been accused of leaving her carpets down all summer or of disobeying one of the equally cardinal rules of good housekeeping." Carpets were picked up probably because it was recognized that houses became musty. After 1930, the vacuum cleaner was introduced. Vacuum cleaner salespeople then and now convinced the public that carpets can be cleaned while on the floor, which is only partly true.

The next major change was an increase in the temperature of houses, particularly in bedrooms. In some parts of the United States (e.g., New England), bedrooms probably were heated from the early part of

the 1900s. Before 1960 in the United Kingdom, most bedrooms had no heating, and the temperatures were little more than 5° F above the outside temperature. Indeed, during the 1950s, one of the authors slept in bedrooms in which the temperature regularly went below freezing level. These temperatures completely inhibit the growth of dust mites and cockroaches. Analysis of house dust samples from the turn of the century demonstrated the presence of storage mites but not pyroglyphid mites (M. Colloff, personal communication). As the use of central heating increased, it became obvious that many houses were losing large quantities of heat through leakage of warm air. This led to campaigns to decrease energy waste by decreasing ventilation through double glazing, tightly sealed doors, and closing ventilation bricks. These highly successful measures have led to many houses having ventilation rates as low as 0.2 to 0.3 air changes/hr. Although the objective was to decrease fuel costs, the main effects were increased humidity, increased accumulation of particles within the house, and a further increase in temperature.⁶⁻⁸

Another important step was the introduction in about 1960 of cool-wash detergents. Detergents were tested for their ability to kill bacteria but not for their ability to control mite growth. In fact, when bedding is washed at ≤90° F, the detergent actually may protect live mites, presumably because of its salt content.^{9,10} Mites are killed only when washed at 130° F or dried for 1 hour at 140° F. A further change in behavior has been the increasing amount of time spent indoors. Recent estimates from the United States suggest that average adults spend <5% of their time outdoors, with the majority of time spent in their own homes.^{11,12}

Another, possibly relevant change of a completely different kind was the introduction of penicillin in 1942 by Florey and Chain. Initially, the penicillins, which were relatively crude and often injected, were associated with an epidemic of anaphylactic penicillin allergy. During the past 20 years, either the change from injected to oral antibiotic agents or the improved purity of preparations has resulted in a marked decrease in severe reactions to penicillin and probably a decrease in sensitization. On the other hand, oral antibiotic use has continued to increase such that courses of oral broad-spectrum antibiotics are now a normal accompaniment of life, and children are treated increasingly casually with antibiotics. The potential for antibiotics to encourage the devel-

TABLE I. Major indoor allergens

Source	Allergen	Molecular weight (kd)	Function	Sequence	Assay
Animals					
<i>Felis domesticus</i> (cat)	Fel d 1		Uteroglobulin	PCR	mAb
<i>Canis familiaris</i> (dog)	Can f 1	25	—	cDNA	mAb
<i>Mus musculus</i> (mouse)	Mus m 1	19	Pheromone	cDNA	—
Insects					
<i>Blattella germanica</i> (German cockroach)	Bla g 1	28	Unknown	Protein	—
	Bla g 2	36	Aspartic protease	cDNA	mAb
	Bla g 4	21	Calycin	cDNA	—
<i>Periplaneta americana</i> (American cockroach)	Per a 1	20-25	—	—	—
House dust mites					
<i>Dermatophagoides</i> spp	Group 1*	25	Cysteine protease	cDNA	mAb
	Group 2†	14	—	—	—
<i>Euroglyphus maynei</i>	Eur m 1	25	—	PCR	—
<i>Blomia tropicalis</i>	Blo t 5	14	—	cDNA	—
Fungi					
<i>Aspergillus fumigatus</i>	Asp f 1	18	Cytotoxin	cDNA	mAb
<i>Alternaria alternata</i>	Alt a 1	32	—	—	mAb

cDNA, Complementary DNA; mAb, monoclonal antibody-based two-site assay; PCR, polymerase chain reaction.

*Der p 1 and Der f 1.

†Der p 2 and Der f 2.

opment of resistant organisms is well recognized. Studies of resistance normally focus on pathogens associated with infections such as pneumonia.

In addition, some patients with diseases such as chronic sinusitis have recurrent "infections" that are only partially responsive to antibiotics. Symptoms of sinusitis are extremely common, and until recently, the disease was attributed to structural abnormalities and/or allergy leading to recurrent infection of blocked sinuses. However, it is clear that inflammation of the sinuses extends to the ethmoid sinuses, which are not blocked; that inflammation often recurs after surgery, despite apparent relief of blockage of the osteomeatal complex; and that the inflammation is characterized by eosinophils, suggesting an immune response of the T_{H2} type.¹³⁻¹⁶ This type of T-cell response is not considered typical of responses to bacterial infection. Analysis of the causes of sinusitis would require identifying the antigens "driving" this inflammation, and the repeated partial response to antibiotics suggests that a bacterial cause should still be considered. Whether sinusitis has become more common is not clear; however, it is possible that repeated partial treatment with antibiotics leads to antibiotic-resistant colonization with aerobic bacteria and favors an immune response of the T_{H2} type.

EPIDEMIOLOGY OF ASTHMA

The recent focus on increased mortality due to asthma has tended to divert attention from the long-term increased prevalence of asthma.¹⁷ Several published de-

scriptions indicate that asthma was relatively uncommon in the 19th century. Smith et al.¹⁸ made a strong case for a significant increase in asthma between 1960 and 1969 in Birmingham, England. Similarly, Burney¹⁹ demonstrated a continuing increase in asthma prevalence to 1985, and remarkable increases between 1960 and 1986 were reported in Scandinavia.^{20, 21} Reed et al. (personal communication) also found good evidence for a major increase in asthma prevalence in one area of the United States. Overall, it appears that progressive increases in asthma mortality, morbidity, and prevalence have occurred in many parts of the developed world.

The idea that exposure to dust may exacerbate asthma is very old. The first report of an association between asthma and sensitization to house dust came shortly after the introduction of skin tests.²² However, mites were not recognized at that time, and it was difficult to make sense of a wheal-and-flare response to an unknown house dust atopen. During the past 20 years, there has been a dramatic increase in our understanding of the allergens that make up house dust (Table I). After purification of Fel d 1 in 1973²³ and a major mite allergen, Der p 1, in 1980,²⁴ a wide range of allergens were identified. Monoclonal antibodies and sensitive two-site ELISA assays have been developed for many of the allergens (Table I). In addition, extracts have been standardized so that criteria for skin tests and IgE antibody measurements can be defined.

The epidemiologic evidence for an association between sensitization to indoor allergens and asthma has

TABLE II. Influence of mite concentration in house dust on sensitization and relation to asthma in school children

	Lismore*	Moree*	Los Alamos†
Current asthma (%)	11.3	8.3	6.3
Mite sensitization (%)	28.0	25.0	18.0-6‡
Odds ratio	18	5	1.5
Cat sensitization (%)	5.0	5.0	31.0
Mite allergen ($\mu\text{g/gm}$)	83.0	11.2	0.5

*Data adapted from Peat JK, Tovey E, Mellis CM, Leeder SR, Woolcock AJ. Importance of house dust mite and *Alternaria* allergens in childhood asthma: an epidemiological study in two climatic regions of Australia. Clin Exp Allergy 1993;23:812.

†Data adapted from Sporik et al., Am J Respir Crit Care. In press.

‡Children born in Los Alamos.

come from a wide range of studies, including surveys of clinic populations^{3, 25, 26} and schools, population surveys, and prospective studies.^{17, 27-29} All published epidemiologic studies of children or young adults have shown a clear association between sensitization to indoor allergen (in most cases dust mite) and asthma. However, this association becomes clear only after the age of 2 years, and the association becomes progressively less strong in adults with increasing age.^{27, 30} In children <2 years old, respiratory syncytial virus and environmental tobacco smoke are important factors in acute episodes of wheezing or breathlessness,^{30, 31} but it is not clear that IgE or eosinophils play any significant role.³⁰ In adults with late-onset asthma, IgE levels may not be high, but eosinophilia is characteristic. The presence of eosinophils in the lungs, peripheral blood, and inflamed sinus tissues of patients with intrinsic asthma is one factor that suggests there must be a foreign antigen "causing" the inflammation.¹³⁻¹⁶

When dust mites were first described, Voorhorst et al.²⁵ suggested that 100 mites/gm of dust was a significant level. The finding that the group I mite allergens were predominantly fecal meant that mite counts were only an indirect marker of the quantity of allergen.^{32, 33} Conclusions from studies that evaluated the quantitative relation between mite allergen exposure and sensitization to dust mite allergen in atopic persons included the following: there is a quantitative relation between mite allergen and the prevalence of sensitization, and a group I mite allergen level >2 $\mu\text{g/g}$ of dust increases the likelihood of sensitization.^{11, 34-38} This threshold level was proposed by an International Workshop in 1987 and reaffirmed by a second workshop in 1990.^{34, 39}

In 1990, we published the results of a 10-year prospective study of 68 children living in an area of southern England where most houses have high levels of mite allergen.²⁷ The results suggested that early exposure to high levels of mite allergen was an important factor for sensitization and early onset of wheezing and that con-

trol of exposure in early childhood would be an effective method of decreasing sensitization and reducing asthma prevalence.²⁷ A controlled study by Arshad and Hide⁴⁰ on the Isle of Wight supported the concept of early sensitization. However, it is important to recognize that sensitization also can occur at older ages. This has been particularly obvious among immigrant groups coming to the United States from the Philippines or to the United Kingdom from Hong Kong or eastern Africa. Thus, the correct view probably is that atopic children are predisposed to sensitization at any age, but those exposed to high levels of allergen in their houses during early childhood are particularly at risk for development of asthma.

Prevalence of sensitization among school-age children as a function of exposure

In studies of asthma, the highest prevalence of sensitization occurs in children >7 years old and young adults. While it is easier to study children >9 or 10 years old because of decreasing parental concern, younger children are more likely to be in the area or house where they spent their first 2 years. Two prospective studies in areas of high mite allergen have shown a strong correlation between mite sensitization and asthma by 11 to 13 years of age.^{27, 29}

Several different approaches have been developed for studying asthma in school children. It has proved possible to survey school classes and obtain detailed information on sensitization in Australia, the United Kingdom, and the United States.^{17, 28, 41, 42} It is important to realize that asthma is the only chronic disease of childhood where a survey of 500 children would provide sufficient cases to give statistically significant data. A strong correlation between skin sensitization to mites and asthma was established in the first studies from Birmingham, England.¹⁸ Subsequently, an Australian study demonstrated that the association between mite sensitization and asthma was restricted to areas in which most houses had greater than 100 mites/gm of dust (Table II).²⁸ Asthma also was common in the drier inland areas, but it was less severe and was correlated more strongly with sensitization to pollens or molds.^{41, 42} Charpin et al.³⁶ demonstrated a decreased prevalence of mites, sensitization, and asthma in a high-altitude town in France. Determining the prevalence of asthma in a population survey remains a difficult task, confounded by arguments over the definition of the disease.⁴³ Indeed, several groups have reported that single measurements of bronchial hyperresponsiveness are not a reliable indicator of asthma. Nevertheless, symptoms requiring regular treatment, or an association between symptoms and nonspecific bronchial reactivity are commonly used definitions.

In the United States, development of a protocol suitable for a school study has been difficult because of resistance to skin testing or taking blood samples in a school setting. We recently carried out surveys in which a questionnaire and lung-function study completed in

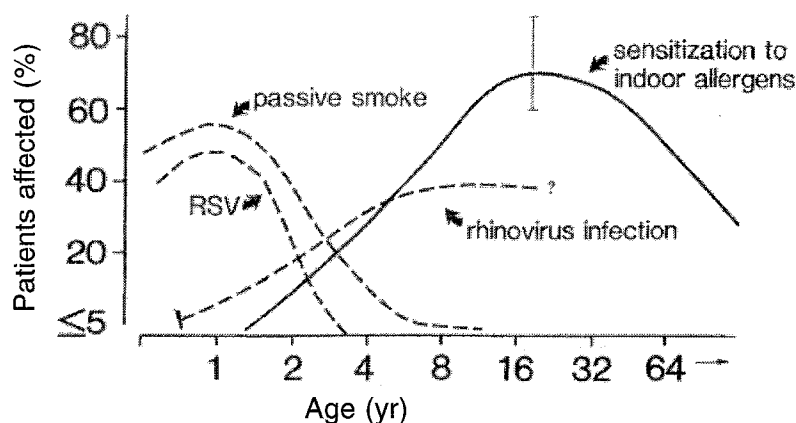


FIG. 1. Risk factors for acute wheezing episodes. RSV, Respiratory syncytial virus.

the school setting were followed by a detailed clinic-setting study of children with a history of asthma and a randomly selected control group of asymptomatic children. Although these studies are still in progress, the findings to date strongly support the conclusions of the Second International Workshop,³⁴ particularly the following: mite sensitization is strongly associated with asthma in areas where most houses contain a group I mite allergen level of ≥ 2 $\mu\text{g/gm}$ of dust; mite and cockroach allergens are not present in houses in the high-altitude environment of Los Alamos, New Mexico, and sensitization to these allergens is not significantly correlated with asthma; and the dominant indoor allergens in dry climates are dog and cat, which is in keeping with studies from northern Scandinavia.^{43, 44}

Emergency department studies in children and adults

In many areas of the United States, asthma is the leading cause for hospital admission of children, normally by way of the emergency department. Studying random children in the emergency department provides a cross section of moderate to severe asthma, excluding most mild cases, and is not dependent on a measurement of bronchial hyperresponsiveness. We reported a study conducted in inner-city Atlanta that was designed to analyze the relationship of sensitization and indoor allergen exposure to asthma in African-American children.⁴⁵ The results clearly demonstrated that the houses contained high levels of mite and cockroach allergens and that sensitization to those allergens was strongly correlated with asthma. A second study designed to examine the difference between infants and school-age children and the relative effects of viral infection, tobacco smoke, and indoor allergens on sensitization and developing asthma confirmed that sensitization to indoor allergens (predominantly dust mites) does not become relevant to acute attacks of asthma until children are ≥ 2 years old.³⁰ In children > 2 years of age, the most commonly cultured virus was rhinovirus. In children 2 to 16 years of age, the combination of sensitiza-

tion and rhinovirus infection was present in 14 of 76 asthmatic children and 0 of 46 control subjects. Fig. 1 illustrates the conclusions of these pediatric studies.

Several studies identified sensitization to common inhaled allergens as a risk factor for asthma in patients over 15 years of age with acute asthma. In central Virginia, mite, cat, and cockroach sensitization were each significant in relation to acute asthma, whereas sensitization to pollens appeared to be relatively unimportant.⁴⁶ By contrast, asthma attacks peak in May and June in northern California in association with the grass pollen season. As many as 90% of the asthma attacks in patients treated during the grass pollen season at Travis Air Force Base, near Sacramento, California, were related to pollen exposure.⁴⁷ Furthermore, dust obtained from the houses of these patients contained very high levels of the grass pollen allergen Lol p 1,⁴⁷ suggesting that indoor exposure to pollen allergen might represent a significant addition to outdoor exposure. A study conducted in Wilmington, Delaware, found marked differences between city area and suburban housing.⁴⁸ Cat allergen was common in the suburban area, and cat sensitization strongly correlated with asthma in patients from suburban houses. In the poorer city areas, cockroach allergen was present in the houses, and cockroach sensitization strongly correlated with asthma.

The conclusion from these studies is that the correlation between sensitization and asthma is highly specific and reflects allergens present in the homes of patients. However, some aspects of this relation are unclear. First, although occasional studies show that the level of allergen is higher in the houses of patients with asthma,⁴⁹ most studies have found little or no difference between the houses of allergic persons with asthma and comparable houses of persons without asthma in the same neighborhood.^{28, 45, 48} Thus, although in many areas everyone is exposed, only those who are genetically predisposed become sensitized with the associated risk of asthma. Second, most studies of indoor allergen exposure do not specify the time that the relevant exposure

occurred, making it difficult to correlate risk of acute asthma with current exposure. Although mite allergen levels show seasonal variation in some areas, in general this variation is not sufficient to produce marked seasonal "epidemics"³⁸; seasonal differences in the United Kingdom are only modest.⁵⁰ The best evidence for the role of current exposure comes from experiments in which exposure of persons with asthma to indoor allergens is reduced either when these persons change residence or carry out avoidance measures in their houses.^{34, 51} Finally, data suggesting that early exposure is important come from a limited number of studies,^{27, 40} and it is unclear whether early exposure predisposes to sensitization, the development of asthma, or both. Although controlled trials of avoidance from early childhood would clarify this association, they are hard to conduct because many difficult-to-control variables, such as attendance at day-care centers or preschools, and the presence of domestic animals, can provide significant sources of early exposure.

LATE-ONSET ASTHMA

With a clearer definition of the role of indoor allergens in asthma in children and young adults, the definition of intrinsic (or nonextrinsic) asthma also has improved. Patients who have no evidence of sensitization to common inhaled allergens and whose condition does not improve when they are moved into a controlled environment pose a challenge in medical management. Although the prevalence of steroid-dependent asthma is not known, the impression is that it has not decreased. Studies of adults arriving in the emergency department confirm that many patients >30 years of age with severe asthma do not have the common features of extrinsic asthma.^{46, 48} These patients have been enrolled in studies of methotrexate, gold, troleandomycin, azathioprine, and cyclosporine A.⁵²⁻⁵⁴ It is commonly assumed that both steroids and other "antiinflammatory" agents act by suppressing eosinophilic inflammation; however, their use is not dependent on identifying the specific cause of the inflammation.

Before considering the causes of nonextrinsic asthma, it is best to define the terminology. The term intrinsic asthma was first used in the 1930s to imply that the source of antigen was intrinsic to the body and was often synonymous with infectious asthma.^{55, 56} Rackemann⁵⁷ was not convinced by the theories about the role of infections and used intrinsic synonymously with idiopathic. Defining the cause of asthma in Rackemann's terminology would make the case "extrinsic." We believe that fungi growing on the body can become allergens in some patients, but these patients also have many features of intrinsic asthma. Therefore, we choose to use the term "intrinsic" in the older sense of the word: that is, nonextrinsic but including situations in which the patient is colonized with yeasts, bacteria, or dermatophytes and has in some way become allergic to the colonizing organisms.

During the 1930s, it was noted that many patients with asthma, rhinitis, and urticaria had dermatophyte infections and had positive immediate hypersensitivity skin-test results to extracts of *Trichophyton* spp.⁵⁸ We confirmed that observation and purified a *Trichophyton tonsurans* allergen, Tri t 1, that binds IgE antibodies.^{59, 60} We also demonstrated that patients with "Trichophyton asthma" improve when they are treated with the antifungal agent fluconazole.⁶¹ The most striking changes in these ongoing studies are decreased bronchial sensitivity to *T. tonsurans* extract, improved well-being and ability to exercise, and decreased steroid requirement.⁶¹ Asthma associated with infection by *Trichophyton* spp is uncommon and may be a disease primarily of hot climates. Nonetheless, it is an important model of intrinsic asthma. If antifungal treatment can reduce the symptoms of asthma in patients who have become allergic to *Trichophyton* spp, other intrinsic or infectious sources of allergens should be sought.

In a well-established form of asthma, *Aspergillus fumigatus* becomes established in the lung. Allergic bronchopulmonary aspergillosis has several features, including lung infiltrates, brown sputum, and serum precipitins, that distinguish it from other forms of intrinsic asthma.^{62, 63} Until recently, the treatment was oral steroids, but the introduction of itraconazole provided an oral antifungal agent active against *Aspergillus*.⁶⁴ Clinical trials in patients colonized with *Aspergillus* currently are underway.

Sensitization to dermatophytes is largely restricted to men; however, intrinsic asthma is as common in women as in men.⁶⁰ It may be that yeast colonization of mucosal surfaces is the equivalent in women of dermatophyte infection, although there is very little objective information about immune responses to yeast. Steroids encourage yeast growth, but whether this colonization encourages sensitization to enzymes derived from the yeast is not known. If so, it is possible that some patients would benefit from long-term oral antifungal treatment.

Another association with intrinsic or severe asthma suggesting that a search for cause is appropriate is that between polyps and intrinsic asthma, although there initially was no etiologic explanation for the association.⁶⁵ More recently, it was shown that nasal polyps are very rich sources of inflammatory mediators and that inflamed sinus tissue and the lungs of persons with asthma have similar characteristics.¹³⁻¹⁶ However, these results do not indicate an etiologic role. Computed tomography scans allow accurate quantitative evaluation of sinus disease, and sinusitis can be scored numerically.¹⁵ Analysis of computed tomography scores showed a highly significant correlation between severity of sinusitis, asthma, and eosinophilia. The strong correlation with eosinophilia suggested that sinusitis rather than asthma was the true source of the eosinophilia.¹⁵ Cultures predominantly grew aerobic bacteria, mainly coagulase-negative *Staphylococcus* organisms. Currently, very

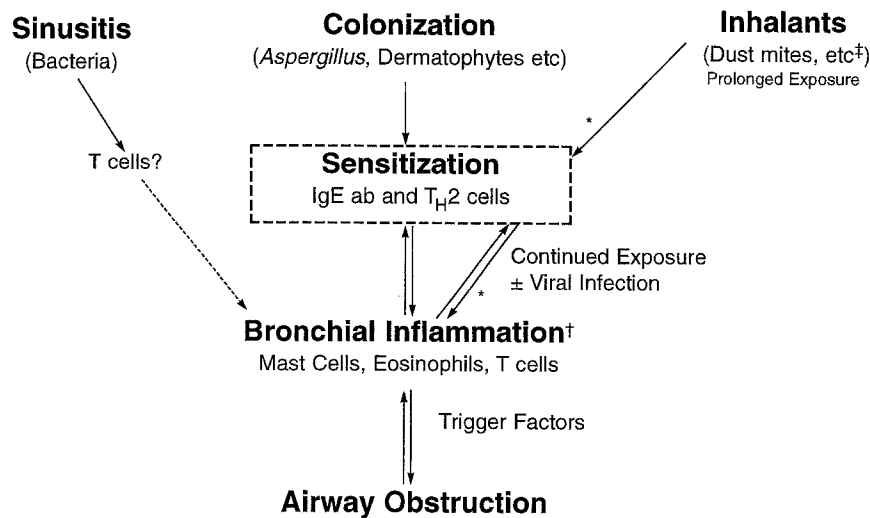


FIG. 2. Cause of bronchial reactivity in adults. *ab*, Antibodies. *Clear evidence of genetic control. †Bronchial inflammation, related to bronchial hyperreactivity. ‡Dust mites, cat, dog, cockroach, *Alternaria* organism, and occupational antigens.

little is known about T-cell responses to these nonpathogenic aerobic bacteria. The clinical course of these cases is marked by repeated partial responses to antibiotics, which is in keeping with the fact that coagulase-negative *Staphylococcus* organisms and other common aerobic bacteria develop broad antibiotic resistance. Coagulase-negative *Staphylococcus* bacteria isolated from patients with asthma are different from those isolated from healthy persons. Thus, the hypothesis is that in patients with chronic sinusitis, a form of sensitivity develops to common aerobic bacteria and is characterized by T_H2 responses and eosinophilia. The reason that antibiotics cannot cure this condition is bacterial resistance and inflammation favoring recurrence.

CAUSATION

The evidence is strong that dust mite exposure is causally related to sensitization and asthma.^{51, 66} Evidence is less complete for other inhalants, but it seems clear that cat, dog, cockroach, and fungal exposure are causally related to asthma. In addition, it is clear that the different geographic patterns of sensitization to indoor allergens reflect levels of allergens found in houses, just as outdoor sensitization reflects geographic distribution of pollens. One of the arguments favoring causation is the evidence that bronchial provocation induces both acute bronchospasm and a delayed response that includes inflammatory mediators and eosinophil infiltration typical of asthma.⁶⁷⁻⁶⁹ However, natural exposure to many allergens and especially to dust mite and pollens is very different from the conditions of bronchial provocation. Mite fecal particles and grass pollen grains usually are $\geq 10 \mu\text{m}$ in diameter, which is several hundredfold larger in volume than nebulized droplets, and have an allergen content an estimated several thousandfold

higher, at 0.2 ng Der p 1/fecal particle versus 10^{-6} ng/droplet.⁷⁰

On the other hand, larger particles require disturbance to become airborne, and a smaller percentage of inhaled particles enters the lung. Experimental studies suggest that 5% to 10% of particles 10 to 20 μm in diameter enter the lungs.^{71, 72} However, larger particles may still allow efficient passage of foreign proteins into the lung because of their large volume. Furthermore, allergen concentration at the site of impact of fecal particles (or pollen grains) is much higher than the local concentration achieved by using nebulized droplets in bronchial provocation.⁷⁰ Therefore natural exposure can be viewed as a series of discrete inflammatory events that produce an effect on lung function or bronchial reactivity only if they were continued for days or weeks. Further, allergen exposure can be viewed as a major factor in the development and maintenance of bronchial reactivity rather than as a trigger for bronchospasm (Fig. 2).⁷⁰

The arguments for causality by other possible antigens are different. In cases of occupational allergens, the temporal relation as well as improvement after exposure is stopped may be convincing evidence. For some seasonal allergens such as grass pollen and *Alternaria* organisms, a temporal relation also may be convincing evidence for a causal relation.^{47, 73} By contrast, the only convincing evidence for dermatophytes, yeasts, dietary factors, and possibly bacterial antigens in sinusitis is efficacy of treatment, making it essential to determine whether antifungal treatment or antibiotics can improve the symptoms of asthma or reduce steroid requirements. Allergens of *Aspergillus* and *Trichophyton* organisms are the only intrinsic allergens for which there is evidence of efficacy for specific treatments.^{61, 64}

CONCLUSIONS

Our understanding of the pathophysiologic bases of diseases and their treatment is changing rapidly. However, changes in habit or lifestyle, such as reductions in cigarette smoking and dairy-product consumption, also have changed the prevalence or severity of some diseases. Allergic diseases, both hay fever and asthma, have undergone major changes in prevalence in response to changes in the outdoor environment and in our houses. Given the overwhelming evidence that indoor allergen exposure is an important cause of asthma, the increased prevalence and severity of asthma is at least in part a direct consequence of changes in houses. In developed countries the role of housing has increased because people spend more time indoors. The dominant changes in housing have been in temperature, ventilation, and carpeting. However, it has been suggested that there has been a decline in cleanliness standards in the United States in association with both parents' working outside of the home.⁷⁴ Allergy once was considered a privilege of the affluent; now, asthma is equally common in poor populations.²¹ There are some clear differences in patterns of sensitization (e.g., cockroach sensitization in inner-city areas in the United States) that directly reflect housing conditions. However, it is likely that many other factors, including poor health care, passive smoke, and lack of exercise contribute to the severity of asthma among poor families.

Given the dramatic changes that have taken place during the past 50 years, it seems inevitable that change will continue. Isaac Asimov's⁷⁵ description in *Caves of Steel* envisages a future society living entirely indoors in defined conditions and eating a diet restricted to varieties of yeast. Without accelerating this type of "progress," some control of exposure should be part of the management of asthma. The objective in controlling exposure to many toxins (e.g., radon, formaldehyde, and asbestos) is to establish threshold values or a maximum tolerated dose, values below which the risk of exposure is negligible. However, high-level exposure to these toxins is considered equally toxic to the whole population. The problem with establishing thresholds for allergens is that they are not inherently toxic, so that thresholds have a very different meaning. For two thirds of the population, the major indoor allergens produce no symptoms, and there is probably no toxic dose. Thus thresholds are relevant only to genetically atopic persons.

It is also important to ask whether any level of allergen exposure can produce tolerance or desensitization. Theoretically, high-dose tolerance could prevent or reduce antibody response. In addition, repeated exposure could cause local desensitization of the lungs or nose. There does not appear to be a dose for dust mite allergens that is too high for sensitization or asthma.^{11, 27, 66} However, levels of some animal allergens (e.g., Fel d 1, Can f 1, and Rat n 1) can be very high, and airborne exposure consists of a much larger number of small particles.^{7, 76} If natural exposure to animal aller-

gens sometimes gave rise to desensitization, it would add a new element to the argument for avoidance. It may be that cat allergen levels between 1 and 8 $\mu\text{g/gm}$ dust are sufficient to sensitize atopic persons. Because this allergen level commonly is present in houses without a cat (the allergen is thought to be carried in from neighboring houses with a cat), simple removal of the cat may have only limited effects for some persons. The evidence that washing cats is beneficial is preliminary; however, it is standard practice in many warm climates to wash dogs. The question is whether a given reduction in exposure would be sufficient to change both symptoms in allergic persons and the risk of sensitization. It is highly likely that the quantitative changes necessary to achieve these two effects are different.

Allergists have attempted to keep up with the pace of change in the outside world and in housing. In the past 20 years, the monitoring of indoor exposure has improved greatly. It is possible to change the design of houses to control symptoms and to reduce the prevalence of allergic disease. Change will continue and will alter the spectrum of allergens associated with asthma. In the next 10 years, the objective of physicians who treat patients with allergic diseases should be active involvement in the design of houses (e.g., flooring, heating, ventilation, and furniture). Although many aspects of allergen measurement and control remain inadequate (especially in relation to fungal allergens), physicians are in a position to change from a reactive to a proactive mode.

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