

The role of indoor allergens in asthma

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Introduction

The recent NHLBI guidelines on the treatment of asthma included a clear statement about the importance of identifying causes of asthma and of recommending avoidance measures where appropriate or possible. This recommendation was based on several different developments over the last fifteen years:

- i) The association between sensitization to foreign proteins or allergens has become very well accepted. From studies in many parts of the world, it is clear that this association is with indoor allergens rather than with pollens. Indeed, the data have reached a point where it is almost certain that indoor allergens are an important cause of asthma (1, 2, 3). As a corollary of this, it seems extremely likely that changes in houses during the period 1940-1970 have been an important contributing cause of the increased prevalence, morbidity, and mortality from asthma.
- ii) Conclusive evidence has been presented that asthma is an inflammatory disease of the bronchi, with a characteristic form of inflammation that includes eosinophils, mast cells, and T cells. Furthermore, it is clear that inhalation of allergens or local challenge of the bronchi of *allergic* individuals can produce both physiological changes in the lung typical of asthma and an inflammation that is very similar to that of naturally occurring asthma (4-6).
- iii) Since 1980, there have been rapid increases in

our understanding of the major indoor allergens. Following the purification of *Der p* 1, there followed the purification, cloning, and development of monoclonal antibodies to a large series of indoor allergens, particularly those from dust mites, cats, dogs, and cockroaches. The development of monoclonal antibodies and assays has made it possible to measure exposure and to evaluate quantitatively measures proposed to control exposure (2, 7-10).

The result has been an almost complete change in our understanding of the role of allergens in asthma. In particular, it is clear that allergens can produce inflammatory change in the lungs and that chronic exposure is likely to be an important cause of both inflammation and the associated bronchial hyper-reactivity. Perhaps the strongest evidence for this comes from avoidance studies where it has been shown by several different groups that prolonged reduction of exposure to allergens can not only reduce symptoms of asthma but can decrease non-specific bronchial reactivity (11-16). Overall, the conclusion is that indoor allergen exposure is the commonest cause of inflammation of the lungs and that reducing exposure should be a central part of the management.

The Association between Sensitization and Asthma

That patients could be allergic to autologous house dust was well known prior to 1964; however,

it was difficult to evaluate the information in the absence of any method of measuring the contents of house dust either in an extract or in a house. When the importance of dust mites as a source of allergen in the house dust was established by Spijksma and Voorhorst, it became possible both to create mite extracts and to count mites in house dust (17). The original studies in the Netherlands demonstrated the high prevalence of mite sensitization among children with asthma. Shortly after that, Morrisson Smith reported that mite sensitization among school children in Birmingham, U.K. was strongly associated with asthma, and suggested that increased levels of mites were a cause of the increase in prevalence of asthma between 1960 and 1970 (18).

Since 1970 the association between mite sensitization and asthma has been reported from many different parts of the world (3, 19). In fact, it may be easier to focus on those areas where mite sensitization does not appear to be associated with asthma. These include parts of the southwestern United States, inland Australia, Briançon in the Alps, and northern Sweden (20–22).

In each of these areas it appears likely that the houses are too dry for mite growth, though it is possible that temperature also plays a role. In some areas, mite sensitization is by far the most important association with asthma, apparently contributing to between 65% and 90% of cases among children and young adults. Typical examples are the south of England (18, 23), New Zealand (24), Japan (25), Sao Paulo, Brazil (26), Denmark (27), coastal Australia (20), and Marseilles (12, 21). However, there are many areas where other allergens are of major importance. Thus, in inner city United States, repeated studies have demonstrated the importance of cockroach sensitization, particularly among low income families (28–31). In some of these areas, sensitization to cats and/or dogs is also correlated with asthma, and this appears in general to be dependent on the presence of indoor pets. A particularly clear example is the dominance of cat or dog sensitization among asthmatics in Los Alamos, New Mexico. In that town ~75% of the families have a pet which is kept indoors. By contrast, the levels of mite and cockroach allergens are low or very low, i.e., less than 5% of the houses have significant mite or cockroach exposure (32).

The results from New Mexico not only demonstrate that cat and/or dog exposure can be a major association with asthma, but also strengthen the view that houses which are dry do not support sufficient mites to sensitize children. Taken together, the data suggest that in most parts of the developed world the dominant association with asthma is to indoor allergens, and that in each area

the most important allergens will be those that are present in high concentrations in the houses.

The Quantitative Relationship between Sensitization and Exposure

Given the conclusion that different allergens are important in different communities, it is clear that there must be a level *below* which sensitization is unlikely (3, 19). Thus, the concentration of cat allergen present in the houses in inner city Atlanta is too low to sensitize most of the population (31). Similarly, the concentrations of mite allergen or cockroach allergen in Los Alamos or inland Australia are too low to cause sensitization (32); that is, the children raised in those areas do not develop IgE antibodies to those proteins. For mite allergen exposure, there is more extensive data which directly bears on the threshold concentration. Thus, results from Denmark, Germany, England, the United States, and southern France all support the view that 2 µg of group I mite allergen per gram of dust is a concentration below which sensitization is unlikely (3, 19). There are several features of the threshold which are important:

- i) The level is the concentration of mite allergen in reservoir dust and is thus not a direct measurement of exposure, but can be taken as an *index of exposure* (currently, airborne measurements of exposure are too difficult for epidemiological surveys and are difficult to repeat) (7, 33, 34).
- ii) The threshold is for genetically atopic individuals. Several of the critical studies have been restricted to children of atopic families or asthmatics (3, 23, 35). At higher levels of exposure, more people will become sensitized, perhaps up to about 40% of the total population.
- iii) Although thresholds have been suggested for other allergens, the evidence is generally less complete. For the cat allergen *Fel d I*, a threshold level of 8 µg/g of dust has been proposed. However, the form in which cat allergen becomes airborne is very different from that of the dust mite. (Cat allergen is on smaller particles which remain airborne longer). Therefore it is unlikely that the relationship between reservoir levels and airborne allergen levels is the same for cat allergen as for mite allergens. In addition, cat allergen is “stickier” than mite allergen, and is found in houses which do not have a cat. In a town where indoor cats are common, almost all the houses have cat allergen in the dust, and it is a real question whether concentrations between 1 µg and 8 µg/g of dust are sufficient to cause sensitization (32).

- iv) The relevance of these thresholds to avoidance measures recommended for symptomatic asthmatics is not clear because sensitization is not reversible (Fig. 1) and the quantitative relationship between exposure and symptoms is much more complex. On the other hand, we believe that the thresholds are highly relevant to the design of studies intended to prevent sensitization in the first place.

The Relationship between Exposure to Indoor Allergens and Asthma

If sensitization to indoor allergens is strongly associated with asthma, and sensitization is quantitatively related to exposure, it is logical to think that asthma is directly related to exposure. Indeed, the theory is that continued exposure of an allergic patient to allergen will give rise to bronchial inflammation and asthma (Fig. 1). However, this relationship is clearly not simple. Many sensitized individuals never have any symptoms and have minimal or no bronchial hyper-reactivity despite continued exposure. On the other hand, some patients have continued severe symptoms despite living in a house with relatively low levels of allergen. Currently the best explanation is that the quantity of allergen necessary to cause bronchial hyperreactivity (BHR) and symptoms in an allergic individual is very variable. Since in most communities ~50% or more of the allergic individuals do not develop asthma, we assume that the level of allergen necessary to cause asthma is

on average higher than the level necessary to sensitize, i.e. ~10 µg group I allergen per gram. However, there are a minority of allergic individuals who will develop symptomatic BHR with much less exposure, and others who would require very high exposure, e.g. ~100 µg group I allergen per g of dust. It is difficult to discuss the difference between allergic patients who develop asthma and those who do not because there are too many unknown factors. For example, we do not know how much allergen enters the lung and whether there are differences dependent on breathing patterns or even anatomy. Similarly, although there are many different pathways by which allergen exposure could trigger inflammation, we do not understand the relative contributions of different pathways. Equally, we have almost no idea about the healing mechanisms that lead to progressive decreases of BHR after allergen exposure is reduced (13, 36). What is clear is that the "threshold" value of 10 µg group I mite allergen per gram of dust is not a threshold in a normally accepted meaning of the word. This value is better seen as a concentration above which most mite-allergic individuals who are going to develop symptoms will have done so.

Another line of evidence directly addresses the quantitative role of allergens in causing symptoms, that is, avoidance experiments. During the initial studies on dust mites, Voorhorst reported that many houses in the Netherlands contained ≥500 mites per g of dust and that there were no mites (i.e. <20/g) in Davos in the sanatorium where mite-allergic asthmatic children were sent from the

ETIOLOGY OF BRONCHIAL REACTIVITY IN ADULTS

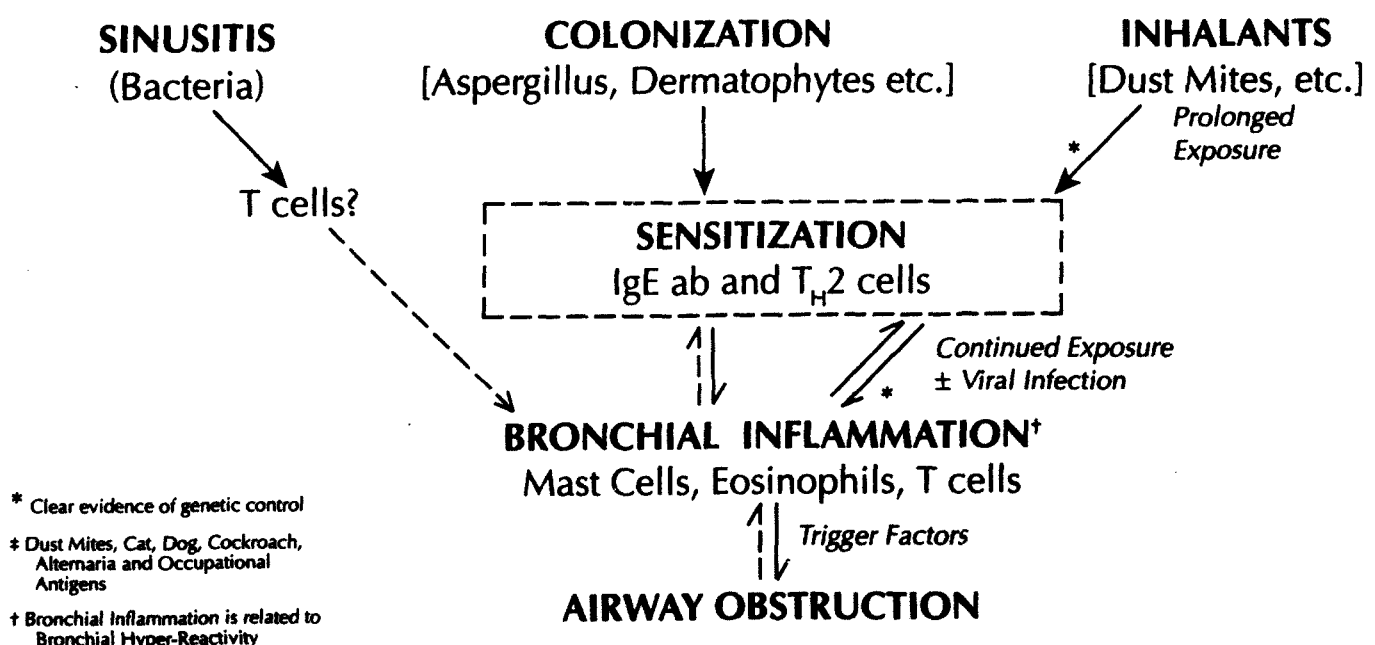


Fig. 1. Etiology of bronchial reactivity in adults. Allergen levels causing sensitization vary between individuals.

Netherlands (17). Similarly, Charpin and Vervloet in France have reported the quantitative levels of mite allergen in the sanatorium at Briançon and compared those to the houses of mite-allergic children in Marseilles (21). Finally, we reported that young adults with persistent asthma could lose their bronchial reactivity if they were moved into a hospital-based unit where the mite allergen level was 0.2 µg/g (compared to an average of 13 µg/g in their houses) (13).

These experiments show that a change which includes a >95% reduction in allergen exposure can lead to reductions of symptoms and BHR. This strongly supports the view that ongoing exposure is an important cause not only of sensitization but also of continuing symptoms. However, by no means all BHR is reversible, in some cases, despite prolonged periods of avoidance with minimal symptoms, BHR shows little change. Thus, there can be two questions: to what degree is continued allergen exposure responsible for ongoing symptoms, and is continued allergen exposure necessary for continued BHR?

Perhaps the most confusing aspect of these relationships is the time course. As late as 1980, it was still common to refer to allergens as a trigger factor for asthma. (Many medical textbooks still use the term, but they are never less than 20 years out of date.) The implication was that allergens induce the acute attacks of bronchospasm but are *not* causative. The term "trigger" also implies that this effect is rapid. We now know that much of the inflammatory effect of allergens on the lung is delayed in time course, and that the effect of a single bronchial challenge can last many days or even weeks (36). When the question is asked the other way around, "How long does it take to lose symptoms after stopping or reducing chronic exposure?" the answer is, again, a long time. Even though symptoms may improve within days, decreases in BHR that have been reported from Davos, Briançon, the Dolomites, and London have always taken weeks or months (11–16). Thus, it now seems clear that exposure of an allergic patient to allergen can produce three related effects: acute bronchospasm, prolonged eosinophil-rich inflammation lasting days, and increased BHR which may last weeks. Given the complexity of this effect, it is not surprising that most patients have little understanding of the time relationship between exposure to allergens and their chronic symptoms of asthma. In turn, this means that such direct questions as what causes particular attacks of asthma are almost useless. By contrast, questions designed to identify what substances the patients are *allergic* to may be very helpful.

Interaction between the Effects of Allergen Exposure and Acute Viral Infections

Many patients with asthma describe symptoms suggesting that their attacks are preceded by an upper respiratory tract infection. This gave the impression that viral infections were an important cause of attacks of asthma. Among children under 2 years of age, acute attacks of asthma/ bronchiolitis are commonly precipitated by Respiratory Syncytial Virus (RSV) (37, 38). Some older evidence suggested that influenza virus could also cause transient increases in BHR. By contrast, direct experiments with rhinoviruses have been very disappointing. In general, an experimental infection with rhinovirus does not produce increases in BHR or infiltration of eosinophils into the lung. By contrast, rhinovirus infection can increase sometimes dramatically the inflammatory response to allergen exposure (39). This is a very important finding because it explains how we could have asthma so strongly associated with allergy and nonetheless have many of the acute attacks precipitated by an acute upper respiratory tract infection. Despite many earlier attempts to establish this relationship, it was difficult to get good data showing that naturally occurring acute attacks of asthma were precipitated by viral infection. However, recent studies using better cultures for virus or other techniques have shown that both in children over 2 years old and young adults, viral infection is commonly related to acute attacks of asthma (38, 40, 41). Under 2 years old, most attacks are related to RSV, but this does not appear to be related to allergy or nasal eosinophilia, and in most cases is not a forerunner of chronic asthma (38).

Intrinsic Asthma and Sinusitis

As any physician who is involved with the care of severe asthma is well aware, there are many adults whose asthma is not explained by sensitization to common inhaled allergens. Intrinsic asthma has several features that distinguish it from extrinsic asthma, including late onset, severity, association with sinusitis and aspirin sensitivity, and persistent eosinophilia. The term intrinsic was first coined by Cooke, but the more common term in the 1930s was *infectious*. This term implied that patients were infected with bacteria or fungi somewhere in the body and that patients were responding to that "infection." Two recent developments suggest that this concept of infectious asthma should not be rejected. First, it has become clear that some men with late onset and severe asthma have fungal infection of their feet and sensitization of their lungs, nose, and skin to *Trichophyton* extracts (42). In

keeping with the idea that these fungal infections can contribute to their asthma is recent evidence that these patients improve with prolonged anti-fungal treatment using Fluconazole (43). Virtually all of the patients of this kind have chronic sinusitis. While some of the patients are allergic to other allergens, overall there is no correlation between IgE antibodies to mite (or the other indoor allergens) and IgE antibody to *Trichophyton* (42, 43).

The second area where a role for a "commensal" organism has been proposed is in chronic sinusitis. Among patients scheduled for functional endoscopic sinus surgery (FESS), there is a very strong correlation between the severity of sinus disease (on CT scan) and peripheral blood eosinophilia. Among these same patients, the correlation with inhalant allergy was modest, and there was no significant correlation with total serum IgE (45). Culture of the inflamed sinus tissue revealed aerobic bacteria in >95% of cases and coagulase negative staphylococci (CNS) in ~90%. The question is whether an immune response to aerobic bacteria could be responsible for the eosinophilia and the persistent inflammation. Since IgE antibody to CNS has not convincingly been demonstrated, it remains possible that the sinusitis is caused by a T cell response (presumably T_H2) to these bacteria.

What is clear is that inhalant allergy is not a convincing explanation for most of the chronic sinusitis or asthma that is often associated with it. The importance of identifying causes of intrinsic asthma is obvious. However, severe chronic sinusitis appears to be becoming more common, and there are large numbers of patients with disease that is proving very difficult to control either medically or surgically. From the point of view of the present article, the importance is to try to recognize that there are many patients whose asthma is not primarily related to indoor allergen exposure. In the future, we believe that management of these intrinsic asthmatics will also focus on identifying the cause.

Air Pollution: NO, SO₂, Ozone Particulates, Environmental Tobacco Smoke, and Radon

The air that we breathe is contaminated with myriads of particulates and chemicals which are known to or could have an effect on the lung. In some cases, such as Radon, it is safe to say that there is no evidence that this gas, either in houses or in uranium mines, has any short-term effects

on the lungs. On the contrary, ozone seems to have an instant effect on the lung, but probably lacks an inflammatory effect or a causative role in asthma. Indeed, despite considerable effort, there is only modest evidence that any of the major outdoor air pollutants are true allergens. Typically, studies showing an effect of outdoor pollution or vehicle exhaust have reported odds ratios of 1.1 to 1.4 (46, 47). Overall, it seems that the air pollutants do not induce inflammation of the lung experimentally, are only modestly related to asthma, and are not a convincing cause of the increased incidence of asthma that has occurred over the last 30 years (48).

Evaluating the role of tobacco smoke in asthma is complicated because there are many studies with different outcomes. However some aspects are clear. First, there is very good evidence that environmental (or passive) tobacco smoke (ETS) has direct irritant effects on the lungs of children under 4. This is clear from population studies and from evaluation of children presenting to hospital with acute symptoms (38, 49). By contrast, in children over the age of 3 or 4 years, there is very little evidence that ETS has a major effect. Certainly it is very difficult to understand how the Environmental Protection Agency (EPA) in the United States calculated that ETS is responsible for 20,000 new cases of asthma per year. On the other hand, there is good evidence that ETS exposure can trigger bronchospasm in some adults with asthma. Indeed, some intrinsic asthmatics are exquisitely sensitive to ETS and report prolonged symptoms after transient exposure. Nonetheless, in emergency room studies on adults, there appears to be very little difference between the exposure to tobacco smoke of asthmatics and controls (30, 50). Although it seems obvious that active smoke is irritating to the lungs, the evidence for acute effects is rather confusing. Thus in a population survey, it was not clear that there was an increased prevalence of asthma among active smokers. Perhaps more striking still, in a recently reported prospective study, there was no evidence that active smoking had had any effect on symptoms or lung function at the age 24 (51). One possibility is that active smoking has direct irritant effects on some patients and contributes to asthma in these cases, but that the hot smoke has some anti-inflammatory effects in other cases. Thus, the net effect on asthma of active smoking in adults is small. Certainly it is common experience that some active smokers find that their asthma gets worse when they try to give up smoking. Active smoking among men became epidemic during the first world war, and therefore does not appear to correlate in time with the more recent increases in the prevalence of asthma.

Conclusions

Although there are many different causes of asthma, and many more factors that can contribute to symptoms, it seems likely that one major group of changes is responsible for the extraordinary world-wide increase in asthma that started in 1960. The evidence that sensitization and continuing exposure to indoor allergens is the most important cause of asthma and also the most convincing cause in the increase in asthma comes from many different studies (1). Indeed, the strength of the argument comes from the fact that population studies, studies on patients presenting to hospital, prospective studies, and avoidance studies have given similar results in several different countries. In many areas, the dust mite appears to be the dominant cause of the increase, and it is tempting to attribute increases simply to improved conditions (i.e., increased temperature and humidity) for mite growth. However, increases have occurred in areas where mites are not a convincing explanation. There are a wide range of changes in houses that could have contributed, including increased carpeting, cool wash detergents, increased quantities of upholstered furniture, and possibly decreased standards of housekeeping. However, there are two changes that seem to be the most convincing, and they are interrelated. The first change that started as early as 1950 was the increase in indoor, and in particular, bedroom temperatures. Prior to 1950, it was unusual to heat bedrooms. When mites were first reported in 1964, they were found at highest levels in bedding and mattresses, presumably because this area was kept warm by the body. As indoor temperatures rose, it became obvious that large quantities of energy were being wasted because of ventilation. In an English bedroom in 1950, there was no "energy" inside the bedroom and, consequently, it did not matter how much air exchange took place. Indeed, throughout the 19th and early part of the 20th century, it was considered very important to maintain ventilation, because of the risk of poisoning from coal gas.

In the United States, the campaign to reduce ventilation was federally funded, supposedly to reduce heating costs. In fact, the results of double glazing and increased insulation were progressively higher indoor temperatures *and* very low exchange rates. Today it is not unusual for houses to have air exchange rates as low as 0.2 air changes per hour. Thus, overall, there have been very dramatic changes in temperature and ventilation. The effect of ventilation on indoor humidity depends on the outdoor conditions. Korsgaard in Denmark has shown clearly that simply opening a window for 2

hours per day can reduce indoor humidity sufficiently to inhibit mite growth. Reduced ventilation will also allow the accumulation of small particles in the air, including airborne cat allergen and ETS particles. It is possible, therefore, that there has been a combination of improved conditions for mite and mold growth combined with decreased ventilation, which allows the accumulation of small particles, both those containing allergens and others. Whether these changes are the full explanation for the world-wide increase in asthma in "developed" countries is not possible to say, but they are the most convincing of the explanations that have been proposed. Perhaps it is worth pointing out that over this same period of time another aspect of the cocooning of humans has also accelerated; that is, the progressive increase in the amount of time spent indoors. Humans spend a larger and larger proportion of their time in houses which are progressively warmer and tighter. During this same time, there has been a dramatic increase in the prevalence of asthma, and almost all studies find that the patients with asthma have a very high prevalence of IgE antibodies to indoor allergens. It has been amply demonstrated that inhaling these same allergens can induce the inflammatory changes that are typical of asthma. The conclusions as far as the treatment of asthma are clear. Asthmatics should be evaluated to identify their specific sensitivities and subsequently advised on measures to decrease exposure to the relevant allergens. Equally, we need to reevaluate the design of houses. It seems clear that it is not safe to live in houses which are hot, humid, and full of nests. We need either to reduce temperature, control humidity, or dramatically reduce furnishings. It seems likely that a combination of these measures is the correct approach to reducing sensitization to indoor allergens and the associated epidemic of asthma.

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