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The past year has seen a welcome increase in the number of articles published in the Journal on environmental and occupational disorders. Some of the major themes have been risk factors for allergic sensitization, the measurement and containment of domestic allergens (especially cockroach but also house dust mite), and risk factors for occupational allergy and asthma. Some important articles were also presented on mechanisms of occupational and environmental asthma. (J Allergy Clin Immunol 2004;113:1161-6.)

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RISK FACTORS FOR ALLERGIC SENSITIZATION AND DISEASE

During our professional lifetimes, we have seen a dramatic and progressive increase in the number of people affected by allergic disease. Although much has been learned about the genetic basis of susceptibility, it remains generally accepted that such a rapid rise in allergic sensitization within a single generation must be the result of changes in the environment.

A key theme in current thinking is the hygiene hypothesis. One component of this is the concept that IgE may have evolved as a defense against parasitic infection. Some further support for this idea came from Cooper et al,¹ who reported a reduced risk of atopy among

Abbreviations used

HDM: House dust mite

MMP: Matrix metalloprotease

school-age children infected with *Ascaris* or *Ancylostoma* in a rural area of Ecuador. Both current infection with these parasites and the presence of serologic markers of chronic infection were independent protective factors against atopy.

We do not really understand what determines how and why someone who is sensitized develops clinical disease. Not surprisingly, asymptomatic sensitization is a predictor of subsequent disease, as confirmed by Bodtger et al² in respect of birch pollen allergy. Moreover, a negative conjunctival provocation test was a reliable predictor that the subject would not go on to develop clinical symptoms within 3 years. This finding suggests that a significant proportion of subjects who consider themselves to be asymptomatic are in fact already at a stage at which their eyes are sensitive to allergen, even if they have not yet realized that they are sensitized. Another interesting ecologic observation from last year is the identification of an association between cigarette smoking and contact allergy.³ Previous studies of smoking as a risk factor for allergic disease have focused on airways disease, especially occupational asthma, in which smoking is clearly a cofactor for sensitization to certain chemicals, such as acid anhydrides.⁴ However, when all other known risk factors were taken into consideration, this new study found a 3-fold increase in contact allergy to nickel in subjects who had smoked more than 15 pack-years. It is not immediately clear what mechanism might underpin this link, but it surely adds to the catalogue of ills that are to be blamed on tobacco.

Another unsuspected risk may be posed by airborne soybean dust in agricultural areas. Soybean dust caused a series of outbreaks of asthma in Barcelona in the 1980s, and there is a considerable level of sensitization in the general population, not least among those with peanut allergy, because soya and peanut share common allergens. It is therefore interesting to note that soya was detected in a series of air samples obtained in rural Southern Ontario, especially during the autumn harvesting and processing season.⁵ Perhaps we should add soya to the range of potential causes to be considered in patients with fall asthma.

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In 2002, we had an article on fire ants and last year saw a further report on this new and tiresome hazard. Caplan et al⁶ reported that allergen-specific IgE antibodies for fire ants were 1.7 times more common in Georgia than antibodies to other potential causes of anaphylaxis such as peanut or yellow jacket. It is not clear whether imported fire ants will continue to spread across the United States, but if they do, it seems that a substantial number of people may become sensitized and hence run a risk of anaphylaxis. Biological containment may offer the best chance of controlling the ants, but allergists need to start working now on strategies to deal with sensitized individuals, including the development of appropriate vaccines for immunotherapy.

DOMESTIC ALLERGENS

Exposure to airborne allergens remains a major focus for research, in both epidemiology and therapy. Among these, HDM is still the most important allergen in terms of the proportion of the population sensitized. Although we recognize that HDMs produce a large number of biologically relevant allergens, we still rely heavily on measurements of Der p 1 and Der f 1 to assess domestic exposure and the efficacy of allergen avoidance strategies. Weber et al⁷ reported on a new HDM allergen implicated in dogs and human beings. Although many of us who treat human beings may not realize it, dogs also become sensitized to HDM and can develop a debilitating and disfiguring form of allergic eczema. This is interesting as an example of how inhalant allergens can also cause atopic dermatitis, but having identified the relevant allergen, Weber et al⁷ went on to show that this novel allergen is also recognized by human allergic sera. At 60 kD, this allergen (Der f 18) is considerably larger than most of the other major HDM allergens recognized by atopic sera. Further work is needed to establish how important Der f 18 is in the big picture.

Although *Dermatophagoides* are the predominant allergenic mites in temperate countries, a wider range of species may be involved in tropical and subtropical areas. A study of cross-reactivity between *Dermatophagoides pteronyssinus* and *Blomia tropicalis* has revealed only limited overlap between the allergens of these 2 mites. This means that even though dual sensitization is common, it is necessary to use extracts of both mites to achieve a full analysis of each patient's sensitivity.⁸ As might be expected, sensitization to HDMs was linked to the level of exposure in a large United Kingdom-based cohort study.⁹ This contrasts with the situation for cat ownership, which was associated with a lower rate of sensitization to cat. Some have interpreted this finding as indicating that cat ownership may protect against cat allergy, although an alternative view would be that subjects who have become sensitized to cat might be less likely to own cats—a form of the healthy worker effect. Indeed, this is supported by evidence from a birth cohort study in southern-central Sweden showing that cat

ownership and cat allergen levels are lower in the homes of mothers who are themselves allergic to cats.¹⁰ Clearly this is something that needs to be taken into consideration in any assessment of the role of domestic animal exposure as a risk factor for allergic sensitization and disease. Nevertheless, a parallel study in Northern Sweden suggests that the negative association observed in Manchester⁹ is consistent, even in a community in which allergic sensitization to cat and dog predominates.¹¹ Northern Sweden is unusual in that it is too cold for HDMs to survive, even in heated buildings, and most pets live indoors. However, despite the absence of HDMs, there are high rates of atopy, with >20% of children 7 to 8 years old and >30% of children 11 to 12 years old affected. This high rate of allergy despite the virtual absence of HDMs should at least raise questions about the likely outcome of any HDM eradication policy.

Although HDMs remain the key domestic allergens in Europe and more prosperous parts of North America, there is increasing evidence that other allergens may be important in lower-income areas of the United States. Most previous work has focused on cockroach allergy, but Perry et al¹² reminded us that rats can also present an allergenic hazard. These authors found detectable rat allergen in dust samples from 33% of inner city homes, whereas 21% of the subjects studied were sensitized to rat allergens, as judged by skin prick tests. Among subjects who were both sensitized and exposed to rat allergens, there were increased rates of hospitalization, unscheduled medical visits, and days of reduced activity compared with unsensitized or unexposed groups. As well as confirming the clinical relevance of rat sensitivity, this article and another reporting on allergen exposure and induction of airways inflammation¹³ add to a growing body of evidence supporting the concept that exposure to relevant allergens is associated with worse clinical symptoms. This being so, why has allergen avoidance not proved more effective in asthma?

Although we have generally regarded cockroach allergy as a problem of lower-income families, a survey of suburban middle class homes in the Baltimore area showed that low levels of cockroach allergens are perhaps more common than previously suspected. Moreover, these low levels of exposure were associated with an increased risk of sensitization to cockroach.¹⁴ Cockroach sensitivity should therefore be considered as a possible allergic trigger, even in middle-class patients. This observation probably applies only to the Eastern seaboard, but it would be interesting to look for evidence of cockroach sensitivity in other areas. Clinical experience in Europe suggests that cockroach sensitization is rare in Europe, except in people who have lived for a time in the United States.

We have generally assumed that cockroach sensitivity occurs through conventional allergic mechanisms, ie, the induction of sensitizing IgE antibodies. Page et al¹⁵ presented data supporting an alternative, or perhaps we should say an additional, mechanism by which cockroach allergens can cause asthma. When cultured human bronchial epithelial cells were exposed to serine proteases

contained within cockroach extracts, the protease-activated receptor 2 was cleaved. This led to activation of the extracellular signal-regulated kinase and downstream transcription of IL-8. A letter to the Journal reminded us that inhalation of cockroach extracts can cause sputum eosinophilia and neutrophilia in sensitized subjects,¹⁶ but the new data suggest that cockroach proteases may have direct effects on human airways independent of their ability to induce sensitizing antibodies. This theme of allergens having direct effects on inflammatory cells was further pursued by Peake et al,¹⁷ who studied the induction of nitric oxide synthesis in alveolar macrophages exposed to HDM fecal particles. Their data suggest that both Der p 1 and Der p 2 can activate alveolar macrophages independent of any allergic sensitization. This effect was not caused by function of the cysteine protease activity of Der p 1, and neither was it caused by endotoxin contained within the HDM fecal particles.

ALLERGEN AVOIDANCE

On a more practical note, our patients want to know what sort of improvement they could expect if they took steps to reduce their exposure to cockroaches. Arbes et al¹⁸ have provided some groundwork for this by looking at the effectiveness of a structured intervention to reduce cockroach allergen levels in low-income urban housing. The data presented relate to allergen levels rather than to clinical asthma, but this study is an important step on the road toward cockroach allergen avoidance studies.

Avoidance of HDM and cat allergens is based on firmer evidence. Another contribution by Arbes et al¹⁹ reported that clinically significant HDM levels are commonly present in US beds and bedrooms. Several independent risk factors for higher levels of HDM allergens were identified, including ambient humidity, region (northeast worst, west best), low income, older houses, and the presence of children. Although extreme forms of HDM avoidance can improve allergic symptoms, there has been some doubt recently whether the more modest degree of HDM avoidance achievable in the home will be clinically effective. Halken et al²⁰ presented an encouraging study of 60 Danish children with allergic asthma, demonstrating that mattress and pillow encasings can bring about a substantial reduction in HDM exposure and, more importantly, can lead to a reduction in the requirement for inhaled corticosteroids. Some caution is called for by 2 related publications. Mahakittikun et al²¹ pointed out that different encasings vary in their ability to resist colonization by HDMs and that a trade off may have to be made between resistance to colonization and the ability of the encasings to withstand laundering. Arlian et al²² echoed this point with new information on the effectiveness of standard wash cycles and detergents in removing HDM allergens from clothing and bedding. Traditionally, allergists have recommended the use of high-temperature washing to denature HDM allergens. However, many synthetic fabrics must be washed at lower temperatures,

and there is a general desire to economize on domestic energy use. These new data assessed allergen removal in warm (36–38°C) and cold (22–27°C) cycles. Only 84% of Der f 1 was removed by washing in water alone or by using detergent, but as much as 98% of allergen was removed when detergent and bleach were used. Interestingly, at these temperatures, there was significant transfer of live mites from infested to noninfested items during washing.²² The results of this study suggest that HDM avoidance may not be achievable with the fashionable low-temperature washing cycles. This may also contribute to the relative failure of most HDM avoidance strategies to deliver clinical benefits. A study attempting to prevent the onset of childhood asthma in Australia found that HDM avoidance had no effect in preventing onset of asthma or asthma-related symptoms, but it did reduce the use of oral steroids.²³ This result suggests that the avoidance measures used in this study may have dropped the exposure levels below the level that triggers symptoms in patients who have become sensitized, but not low enough to prevent sensitization. In contrast, the same study found a beneficial effect of dietary supplementation with omega-3 fatty acids, which led to a 10% reduction in wheezing, although it had no effect on the prevalence of doctor-diagnosed asthma. A final footnote on allergen avoidance: it has long been known that old-fashioned vacuum cleaners resuspend allergenic dusts rather than removing the guilty particles. Some have suggested that improved filtration systems might be the answer. However, Gore et al²⁴ showed us that personal exposure to cats is actually increased by using vacuum cleaners fitted with modern high-efficiency particle arrest filters. Therefore, it seems that we should continue to emphasize the importance of source control, or perhaps the use of chemical bleaches,²⁵ rather than looking for better dust removal systems.

OUTDOOR ALLERGENS AND ENDOTOXIN

Turning to the outdoor environment, there is widespread concern in the public, in the media, and in government regarding the possible role of air pollution in respiratory health. This level of concern is not mirrored in the articles published in last year's Journal, although 1 article did address the possible mechanism by which diesel exhaust particles may cause or modulate airways inflammation. Diesel exhaust particles increased the airways inflammatory response to ovalbumin in a mouse model of asthma, whether given with or after the ovalbumin challenge.²⁶ Perhaps surprisingly, there was no effect on ovalbumin-specific IgE or T_H2 cytokine production, suggesting that the target cells and molecules underpinning the effect of diesel exhaust may lie elsewhere.

Epidemiologic studies from Bavaria and elsewhere have demonstrated that growing up on a farm is protective against the development of allergy, especially if there is exposure to cows during the first year of life.²⁷ This is 1 of the pieces of evidence that underpins the hygiene

hypothesis. However, it is not clear whether this protection through agricultural exposure is a result of differing patterns of infection or of nonspecific effects of bacteria and their DNA or various endotoxins. It is well established that bacterial DNA motifs (CpG and so forth) can influence the immune response and bias it away from the allergic cytokine pattern.²⁸ Roy et al²⁹ published a study of the endotoxin and bacterial DNA content of dust from barns and homes in various settings, showing that high levels of bacterial DNA are found in barn dusts, followed by rural homes, then farmers' homes, then urban homes. Interestingly, there were also qualitative differences between the dusts from the various locales, with farm dust showing a marked ability to potentiate LPS-induced IL-10 and IL-12 release, whereas bacterial DNA from urban homes did not. In this study, bacterial DNA was closely correlated with endotoxin content. Inhalation of endotoxin (LPS) was shown to increase numbers of sputum neutrophils and the expression of CD14 (the putative receptor for LPS) on airway macrophages, but CD11b expression on sputum and peripheral blood phagocytes was downregulated. Moreover, phagocyte function was reduced in sputum and blood, as judged by the ability of phagocytes to ingest opsonized yeast particles.³⁰

If endotoxin is important as a contributory factor in allergy, we should note that clothing is an important vector for endotoxin. Until now, assessments of environmental endotoxin exposure have generally been based on floor or bedding dust samples. Nam et al³¹ obtained dust samples from indoor clothing of their coworkers and found endotoxin levels as high as those that are found in conventional domestic samples. Although washing reduced the amount of endotoxin on garments, it did not remove it completely. Extremely high levels were seen on garments such as hand-knitted sweaters that were only infrequently washed.

LATEX ALLERGY

Latex is another environmental hazard that can be carried on other materials. Most latex gloves used to be prepared with cornstarch as a lubricant. Unfortunately, cornstarch particles can acquire and carry latex allergens, and hence, we have moved to starch-free gloves in an attempt to minimize respiratory exposure to latex. As an alternative to cornstarch, cotton fluff has been introduced into glove manufacture. However, perhaps not surprisingly, cotton fluff can also serve as a vector for latex allergens. Baur³² presented data showing that cotton fluff is free of latex allergens when it enters the factory but becomes allergenic during the manufacturing process. As well as being a potential hazard for medical staff and patients allergic to latex, the latex-contaminated fluff also appeared to be a significant source of occupational sensitization. Moreover, this study found latex allergens in the water tanks used for cooling the gloves during manufacture, and this might also contribute to the

occupational hazard. Most of the people affected by latex allergy are not the manufacturers but health care workers. Quirce et al³³ described their effort to quantify environmental challenge procedures for the investigation of respiratory latex allergy, whereas Bernstein et al³⁴ reported on the heterogeneity of IgE responses in different groups of health care workers, with a view to developing better diagnostic materials. To complete the picture for latex allergy, Sastre et al³⁵ reported a double-blind, placebo-controlled study of specific immunotherapy for latex allergy using a standardized aluminium hydroxide-absorbed extract. Active treatment led to a 12-fold reduction in skin sensitivity to latex, with associated reductions in response to challenge with latex gloves, although there was no overall effect on asthma symptom or medication scores.

RISK FACTORS FOR OCCUPATIONAL ALLERGY

Several articles in last year's Journal reviewed risk factors for occupational rhinitis and asthma. Rodier et al³⁶ reported on a high incidence of occupational rhinitis among new recruits to animal laboratories. Higher rates of allergy were found in subjects who were already sensitized to other allergens such as grass pollen. Nguyen et al³⁷ raised the question of which type of sensitization comes first. Among subjects who became sensitized to occupational allergens, a high proportion also developed sensitization to ordinary aeroallergens, which had not been present at the initial assessment. If correct, this finding suggests that retrospective analysis of atopic status in people who develop occupational asthma may give a false impression that they had pre-existing allergy.

Another article described an HLA association for the development of allergy to rats.³⁸ The authors suggested that we should look for similar associations with allergies to other animals. However, not all occupational allergies are associated with general atopy. A review of employees at a natural dye factory found that 48% had become sensitized to carmine, and 18% had occupational asthma,³⁹ but there was no association between occupational sensitization and sensitivity to other aeroallergens.

Isocyanates remain the most important single cause of occupational asthma worldwide. Conventional wisdom is that higher concentrations of isocyanates represent a higher risk than lower-level exposures. Lemièrre et al⁴⁰ stirred up some controversy in their report that, gram for gram, low levels of isocyanate exposure are at least as likely, if not more likely, to induce bronchoconstriction as higher levels. The mechanism of isocyanate-induced asthma remains something of an enigma. Unlike sensitivity to high-molecular-weight allergens or some low-molecular-weight allergens such as acid anhydrides, sensitivity to isocyanates does not appear to involve IgE. Serologic tests have proved elusive, and it is common to find isolated late-phase responses in inhalation challenges. This has suggested the possibility that isocyanate asthma

may be driven by T-cell recognition of isocyanates or isocyanate derivatives. Wisniewski et al⁴¹ reported that $\gamma\delta$ T cells proliferated *in vitro* when T-cell lines were exposed to hexamethylene di-isocyanate. These cell lines produced IFN- γ but no IL-5 or IL-13 when stimulated. This observation is in line with previous, but controversial, studies of IFN- γ in asthma.⁴² Although it is clear that the T_H2 cytokine pattern can explain preferential IgE synthesis, it is much less clear that the T_H2 hypothesis can explain asthma.

Another area of current interest in asthma biology is the role of matrix metalloproteases (MMPs) and how they may interact with cytokines in the expression of allergic inflammation.⁴³ Lee et al⁴⁴ tested the effects of a matrix metalloprotease inhibitor in their animal model of toluene diisocyanate asthma and demonstrated that inhibition of MMP activity abrogated the increased expression of IL-1 β , IL-4 and TNF- α that is normally induced by toluene di-isocyanate. In addition, inhibition of MMPs led to reduced recruitment of inflammatory cells and reduced expression of relevant adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1). These studies confirm the view that occupational asthma is a valuable model in which to test the various hypotheses proposed for allergy and asthma.⁴⁵ They should encourage us to do further work on the mechanisms of occupational asthma and to apply the results to our understanding of ordinary atopic disease. In this and many other aspects, environmental and occupational disorders have much to teach us. The year 2003 was a bumper year for studies in this area in the Journal, with a 4-fold increase in published articles. It seems unlikely that we will be able to sustain this rate of growth, but the editors remain open to the best work in this area, and we look forward to publishing another excellent crop of articles on environmental and occupational disorders in 2004.

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