Advances in environmental and occupational disorders 2006

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In 2006, there continued to be significant contributions to the Journal in the area of environmental and occupational allergy. In addition to very strong clinical observations, there were a number of studies that examined the effect of environmental agents on cellular and molecular processes in allergy, and molecular approaches were also used in investigations of allergen structure and biology. The Journal also received a number of very strong epidemiologic studies examining several aspects of environmental and occupational allergy. Thus, this particular area of our specialty thrives as a result of clinical, mechanistic, epidemiologic, and translational observations. This article reviews a number of these papers presented in the Journal in 2006. (J Allergy Clin Immunol 2007;119:1127-32.)

Key words: *Hygiene hypothesis, endotoxin, dendritic cell, Toll receptors, air pollution, allergens, fungi, occupational, indoor exposures, exposure reduction*

Abbreviations used
BMI: Body mass index
DC: Dendritic cell
SEB: *Staphylococcus aureus* enterotoxin B
TLR: Toll-like receptor
TMA: Trimellitic anhydride

The hygiene hypothesis continues to be a subject of great interest to researchers in our field, as commented on by Liu and Leung[1] in their editorial and by Shaub et al[2] and von Hertzen and Haahtela[3] in their review articles. As reviewed in these articles (and as is well known to Journal readers), the hygiene hypothesis is based on the idea that exposure to viruses, bacteria, or their products in early life stimulates immune response (largely innate immune response) such that acquired immunity is skewed away from development of IgE responses to environmental and food allergens. However, it is becoming increasingly evident that the interaction of microbial agents, the activation of innate immune responses, and the ultimate effect of these stimuli on allergic phenotypes are very complex and are influenced by route of exposure, age of the exposed individuals, genetic make-up of the individual, duration of exposure, and dose of microbial products (which may be environmental endotoxin levels, frequency of infection, degree of colonization of the gastrointestinal tract by commensal organisms, and so forth). It has been argued that decreased exposure to microbial products because of decreased infections, use of antibiotics, and decreased exposure to commensal environmental saprophytes (which are colonized in the gut after contact with soil) because of urbanization and recent changes in lifestyle have all contributed to increases in allergic disease.

There were a number of studies and reviews examining the biology that underlies the hygiene hypothesis. In an animal study, Gerhold et al[4] found that prenatal exposure to endotoxin (via aerosol LPS challenge of pregnant mice) coupled with postnatal LPS exposure was associated with decreased IgE response to ovalbumin sensitization and development of eosinophilic inflammation. Similar observations were made by Wang and McCusker[5] using a model of LPS and allergen exposure in the neonatal period. Taylor et al[6] examined the ability of Toll-like receptor (TLR)–2 ligands (heat-killed *Staphylococcus aureus*, staphylococcal lipoteichoic acid, and the synthetic lipoprotein Pam3CSK4) to modulate responses of PBMCs of volunteers with and without allergy to house dust mite and found that the TLR2 ligands decreased allergen-induced IL-5 and IL-13 production in cells from volunteers with allergy. Thivierge et al[7] examined the effect of TLR3 and TLR4 agonists (polycytidylic acid and LPS) on expression of cysteinyl-leukotriene (cys-LT) receptors on dendritic cells (DCs) derived from stimulation of mononuclear cells and found that LPS resulted in decreased Cys-LT receptor expression.

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Interestingly, Mandron et al[8] reported that human monocyte-derived DCs stimulated with *S aureus* enterotoxin B (SEB) secreted high levels of IL-2 and could drive polarization of naive T cells into the T_H2 subset. They used TLR2 stably transfected human embryonic kidney 293 cells to confirm that SEB induced TLR2 signaling and then found that neutralizing of anti-TLR2 antibodies blocked the effect of SEB on DCs. Taken together, these reports indicate that innate immune stimuli modulate acquired immune responses, although the effect on T_H2 type immune responses appears to be ligand-specific. Thus, the interaction of innate and acquired immunity is very complex. This is further outlined in excellent reviews by Kaisho and Akira[9] and Horner.[10] These reviews examine Toll receptor biology and signal transduction and the potential use of Toll ligands in mitigation of allergic disease. However, the paradox by which LPS exposure has been shown to both decrease development of allergic responses and (at lower doses) be essential for development of atopy in animal models was also discussed, demonstrating the vast amount that remains unclear about innate immune modulation of atopy.

There were a number of research reports this year that examined the effect of exposure to environmental endotoxin and other innate immune stimuli and development of atopy. Douwes et al[11] examined a cohort of children born to 855 women recruited during the second trimester of pregnancy. By using dust samples collected for 696 subjects, they observed that there was an inverse relationship between levels of endotoxin, 1-3 β-glucans, and extracellular polysaccharides from the genera *Penicillium* and *Aspergillus* found in house dust and doctor-diagnosed asthma. There was also a modest effect observed in a subset of this cohort between extracellular polysaccharides from the genera *Penicillium* and *Aspergillus* and serum IgE. Campo et al[12] examined a cohort of 532 children in Cincinnati and found that dog ownership coupled with increased endotoxin exposure was linked to decreased wheezing in infancy. A study by Perkin and Strachan[13] examined the occurrence of asthma and atopy in a cohort of 4767 children by questionnaire and a subset of 879 children who underwent skin testing and had environmental endotoxin levels assessed as well as assessment of consumption of unpasteurized milk. They observed that farm children had decreased airway allergic diseases and that drinking unpasteurized milk (in either farm or nonfarm children) was associated with decreased atopy as well as increased circulating IFN-γ levels. Ege et al[14] also examined a subset of children from the Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style study and found that maternal exposure during pregnancy to environmental microbial products enhanced gene expression for CD14, TLR2, and TLR4 in mRNA from blood samples of children and decreased the occurrence of allergic disease. Together, these observations support the hygiene hypothesis.

However, there were reports suggesting that endotoxin exposure might also increase atopic disease or wheeze in children, and that other lifestyle factors might affect response to endotoxin. Gillispie et al[15] examined the relationship between environmental endotoxin exposure at 3 months of age and subsequent expression of allergic symptoms at 15 months of age in a cohort of 881 children in New Zealand, and found that endotoxin was associated with increased airway and skin symptoms. Tavernier et al[16] examined dampness and endotoxin levels in homes and found that increased endotoxin levels were predictive of asthma. Perzanowski et al[17] also examined the relationship between environmental endotoxin levels in homes from 301 Dominican and African American inner-city study participants with occurrence of wheeze and eczema. Children in homes with higher endotoxin concentration were less likely to have eczema at age 1 year, but more likely to wheeze at age 2 years, with these associations stronger among children with a maternal history of asthma.

Williams et al[18] examined the effect of the C-260T single nucleotide polymorphism for the CD14 gene promoter on the effect of environmental endotoxin exposure on serum IgE levels in 517 adults, reporting that with lower levels of endotoxin exposure, the CC genotype was associated with higher IgE levels, whereas with higher levels of endotoxin exposure, TT individuals had the highest IgE levels. Radon and Schulze[19] examined the relationship among obesity (body mass index [BMI] $\geq$ 30), early life rural location, and asthma in a questionnaire study of 1861 adults and found that although early life rural life was associated with decreased asthma in nonobese persons (compared with the reference group of nonrural normal weight respondents), the protective effect of rural lifestyle was lost if obesity was present. Alexis and Peden[20] also examined the relationship of BMI to inflammatory response to inhaled endotoxin in volunteers with asthma and normal volunteers, and found a strong correlation between inflammatory response to LPS and BMI in volunteers with asthma, but not in volunteers without asthma. Together, these studies highlight the complexity of the biology associated with the hygiene hypothesis and effect of a variety of factors in modulating innate and acquired immune interactions (Table I).

AIR POLLUTANTS

Reflecting the continued increase in interest of the effect of environmental pollutants on asthma and allergic processes, the Journal received a number of reports on this topic. Particulate air pollution is an important cause of asthma exacerbation. Using a mouse model, Alessandrini et al[21] found that inhalation exposure to ultrafine carbon particles (<100 nm in diameter) markedly increased airway response to subsequent inhaled allergen as long as 4 days after particle exposure with increases in inflammatory cell influx, as well as in IL-4, IL-5, and IL-13 levels. Nikasinovic et al[22] examined the relationship between ambient air exposure to fine particulates (particle size between 0.5 and 2.5 μm) and nasal eosinophilia in 44 children without allergy and 41 children with allergy over a

TABLE I. Key advances

1. Innate immune stimuli affect acquired immune response via actions on DC function.
2. Innate immune responses may prevent or enhance T_H2 inflammation.
3. Particulate air pollution enhances allergic inflammation.
4. Oxidant stress caused by polyaromatic hydrocarbons from diesel exhaust and tobacco modulates acquired immune response, in part because of actions on DCs.
5. Indoor allergen levels vary depending on climatic and housing factors (HDMs) and pet ownership (cat).
6. Cat washing reduces airborne Fel d 1 levels for only 1 day.
7. Pollen allergens are restricted to a few protein families.
8. Indoor exposure to *Alternaria* antigens is epidemiologically linked to asthma symptoms.
9. The health effects of indoor mold exposure deserve further investigation.
10. Occupational exposure to isocyanates can induce IgE-dependent and non–IgE-dependent asthma.
11. Symptoms attributed to multiple chemical sensitivity do not appear to be a result of the specific chemical, but are provoked when the individual can discern (smell) the active substance on a sham-controlled challenge.

period of 48 hours and found a clear relationship between particulate matter levels and eosinophilia in the children with allergy. Alexis et al[23] examined the effect of inhaled coarse particulate preparations (2.5-10 μm in diameter) made from collected ambient air particles on inflammatory and macrophage responses reflected in sputum samples collected from normal volunteers, and found that these particles could induce increased polymorphonuclear neutrophil influx as well as upregulation of expression of CD14 and MHC class II molecules on macrophages. Interestingly, heat treatment of these particles, which eliminated biological moieties such as endotoxin on the particles, also caused increases in PMN influx, but not changes in macrophage cell surface markers. These studies highlight the potential for inhalation of even inert particles of a variety of sizes to increase airway inflammation as well as the specificity of actions of specific elements of ambient air pollutants on airway immune cells.

Diesel exhaust and tobacco smoke also cause significant effects on airway inflammation, in part because of the effect of oxidant generating polyaromatic hydrocarbons from these products of low-temperature combustion of organic fuels. Using a murine bone marrow–derived DC model and a homogeneous myeloid DC line, Chan et al[24] found that diesel exhaust particles and organic extracts made from these particles induced oxidative stress in DCs, which was associated with decreased ability of LPS to induce CD86, CD54, and I-A(d) expression and IL-12 production in DCs as well as decreased IFN-γ and increased IL-10 induction by antigen-specific T cells. Nuclear factor erythroid derived 2-related factor 2 deficiency abrogated the effect of DC function by diesel exhaust particles. Chang et al[25] examined the effect of diesel exhaust derived polyaromatic hydrocarbon exposure of PBMCs from nonatopic donors and found an increase in T_H2 cytokines and pulmonary and activation-regulated chemokines mediated by IL-13, and a decrease in the T_H1 IFN-γ–induced protein 10 levels selectively at both the protein and mRNA levels, which resulted in enhanced chemotaxis of T_H2 cells by PBMC supernatants. Extending these observations to tobacco smoke in human beings, Diaz-Sanchez et al[26] found that challenge with environmental tobacco smoke on allergen induced changes in IgE, cytokines, and histamine measured in nasal lavage fluid. Together, these results demonstrate that pro-oxidative DEP (and tobacco-derived) chemicals can interfere with T_H1-promoting response pathways in DCs, promoting allergic inflammation. This finding provides increased support for the idea that pollutant induced changes in oxidant stress account for the effect of PAH-containing particulates on allergic inflammation.

INDOOR ALLERGEN EXPOSURE

New methods for assessing indoor allergen exposure have been developed. Single nasal air samples for house dust mite (HDM), cat, and dog allergen exposure was compared with reservoir allergen concentrations obtained from dust samples in patients' homes and subsequently correlated with patient asthma severity. Good correlations were noted for cat and dog but not for HDM allergen. HDM sensitivity and reservoir exposure were associated with increased airway hyperresponsiveness. However, single nasal air samples had no advantage over reservoir dust analysis for measuring exposure in the individual patient with allergic asthma.[27]

Cat allergen levels were assessed in a European multicenter study. Although not having a cat in the home was associated with lower Fel d 1 concentrations in mattresses, high Fel d 1 exposure occurs in communities where cat ownership is common.[28] Cat allergen was also detected in childcare center sandpits, which may be of relevance in cat-sensitive children.[29]

In European homes, large qualitative and quantitative differences in mattress HDM allergen levels were found, which may be explained by geography and housing conditions.[30] Low winter temperatures reduced Der p 1 but not Der f 1. Important factors for high HDM allergen levels included an older mattress, a lower floor level of the bedroom, limited ventilation of the bedroom, and dampness. These factors appear to be particularly true for Der p 1 but not Der f 1. The results suggest regular mattress replacement and improvement in bedroom ventilation in the winter could reduce HDM allergen exposure.

Another multicenter European study demonstrated that the risk for Fel d 1 sensitization increased with exposure in a nonlinear manner.[31] No association was found between

the presence of Der p 1–specific IgE and aeroallergen exposure during early life in 2 of the 3 study centers. The dose-response relationships between allergen exposure and sensitization differ among allergens and may vary among locales.[31]

In children presenting to emergency departments with acute asthma, IgE-binding patterns and the predominant contribution of Der p 1 and Der p 2 were found across a wide range of total IgE titers. IgG antibody titers were lower in children admitted for exacerbations.[32]

The adjusted odds ratio of asthma in adults increases with total IgE in a dose-dependent pattern.[33] IgE antibodies to HDM and mold allergens increase the risk for asthma in adults (ages 21-63 years) not previously diagnosed with asthma. Therefore, atopy is a strong determinant of asthma in adulthood that could be altered by reducing exposure to these allergens.

ALLERGEN EXPOSURE REDUCTION

A multinational study demonstrated that tightly woven mattress covers and plastic prevent HDM penetration; however, nonwoven or loosely woven acaracide-coated and laminated materials do not.[34] Cost effectiveness of home-based interventions to reduce indoor allergens was discussed in correspondence to the Journal[35] and indicated that home visits may not only improve cost effectiveness but also be helpful in intervening against nonallergic issues (eg, injuries in the home).[35,36] In a study examining the duration of airborne Fel d 1 reduction after washing pets, the effect on airborne Fel d 1 levels was short-lived, lasting approximately 1 day after washing the cat.[37]

The studies indicate the need for further evaluation of indoor allergen control methods, the cost effectiveness of reducing sensitization, and expression of respiratory diseases.

ALLERGENS

A major allergen from honeybee venom, Api m 3, is an acid phosphatase. A recombinant allergen has been produced that may be helpful in the diagnosis and treatment of honeybee venom allergy.[38]

The major HDM allergen, Der p 1, is a cysteine protease as shown by crystallography.[39] This protein is a dimer, tightly packed into a double layer, which likely exists in HDM fecal pellets, the natural form of allergen exposure. Production of the fully mature protein may be useful in studying cell surface interactions with the protein and subsequent allergic inflammatory responses.

HDM extracts have been shown to have both T_H2 adjuvant and tolerogenic activities.[40] Mice vaccinated intranasally with both ovalbumin and a house dust extract primed them for T_H2-biased immune and airway hypersensitivity responses. In contrast, low-dose intranasal house dust extract alone was protective via Toll receptors. It should be noted that the studies were not performed with HDM extracts but rather house dust extracts that might contain LPS. In fact, LPS replicated the effects of low-dose intranasal house dust extract treatment.

The German cockroach allergen, Bla g 6, is a troponin C, calcium-dependent, IgE-binding protein. This allergen may occur in other insects and cause cosensitization or allergenic cross-reactivity.[41]

Further description of the characteristics of pollen allergens has been published. Cortes et al[42] reported that a novel amino peptidase isolated from *Parieteria* alters epithelial integrity and degrades neuropeptides. An excellent review of allergenic proteins from pollens was presented by Radauer and Breiteneder.[43]

FUNGI

Indoor *Alternaria* exposure was examined in US homes. High indoor levels of *Alternaria* antigen increased the odds of occupants having asthma symptoms in the past year.[44] The American Academy of Allergy, Asthma & Immunology position paper on the medical effects of mold exposure[45] generated a significant amount of correspondence.[46-49] It is hoped that further research in the controversial areas will resolve differing viewpoints.

OCCUPATIONAL DISEASES

Several advances in isocyanate-induced asthma appeared. Isocyanate exposure can generate IL-5–positive, CD25-positive, and CD4-positive cells in bronchial mucosa in the absence of Cε and IL-4 mRNA expression.[50] The biophysical state of isocyanates can alter IgE binding *in vitro* (vapor toluene diisocyanate [TDI]-albumin conjugates bound IgE in 44% of patients with TDI-induced asthma vs 17% to liquid TDI-albumin).[51] Isocyanate-specific IgE antibodies are a relatively specific, but not sensitive, marker for isocyanate-induced asthma, and the converse is true for specific IgG (more sensitive, less specific). TDI-IgE levels decline over time after exposure cessation, whereas TDI-IgG does not.[52] Further research on the mechanisms may increase our understanding of the prevention and treatment of this common cause of occupational asthma.

Styrene manufacturing is an increasingly recognized cause of occupational asthma.[53] Further, novel wood allergens in locust wood dust (*Robinia pseudoacia L*) have been detected that appear to be specific and do not show cross-reactivity with other known wood dust allergens.[54]

A new (lateral flow) immunoassay may be of value in assessing exposure levels to fungal α-amylase, an important allergen in the baking industry.[55]

Latex sensitivity is an occupational hazard in healthcare workers that is significantly associated with asthma but is not a risk factor for rhinoconjunctivitis.[56] Healthcare workers have an increased risk for latex sensitization and asthma symptoms when exposed; thus, methods of prevention are needed.[56] Cases of latex allergy induced

by wearing of rubber swim caps were reported, which may be important to swimmers.[57]

An interesting animal model of chemical-induced asthma was reported.[58] Mice sensitized to trimellitic anhydride (TMA) by dermal and intranasal routes, then challenged with TMA exhibited changes in airway function. However, animals dermally sensitized to dinitrochlorobenzene did not show any ventilatory changes. Both compounds induced mixed T_H1 and T_H2 responses, but only TMA induced ventilatory changes. Thus, skin contact (along with respiratory exposure) to certain sensitizers may be important in occupationally induced asthma.

MISCELLANEOUS

An interesting case report appeared of a patient with prolonged elevation of serum tryptase levels caused by idiopathic anaphylaxis.[59] Twenty-six hours after the patient's event, tryptase was still 110 ng/mL. In most cases, tryptase is elevated for only 3 to 4 hours. Codeine is a time-honored antitussive agent. However, in patients with chronic obstructive pulmonary disease, codeine was no more effective than placebo in treating the cough symptom.[60] Last, an important systematic review of the multiple chemical sensitivity syndrome was published.[61] This review of provocation studies in individuals reporting multiple chemical sensitivity suggests that the subjects' symptoms only occur when they can discern between active and sham substances by smell. Thus, the mechanism of action is not specific to the chemical itself but is related to expectations and previous beliefs of the individuals elicited by olfaction-neurologic interactions.

CONCLUSION

The articles outlined demonstrate the effect allergists and immunologists have in understanding and addressing clinical issues caused by environmental and occupational exposures. The increase in understanding of immune effects of environmental agents will not only clarify these issues from a biological perspective but also point the way to new interventions designed with an understanding of these environmental effects on allergic inflammation first identified by allergists interested in environmental influences on allergic disease. We invite investigators to submit results of such studies to the Journal, where they will command the attention of not only allergists and immunologists but also the medical and scientific community at large.

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