Advances in environmental and occupational disorders in 2013

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In this review of articles published in the *Journal* in 2013, we report on the significant advances in environmental and occupational disorders. Research advances have led to the identification and defined the structure and function of several major allergens. A meta-analysis confirmed the importance of mold exposure in patients with allergic rhinitis, and a new immunologic classification of aspergillosis emerged. Insights into the role of diesel exhaust particles in patients with severe asthma were clarified. Improvements in stinging insect allergy diagnostics were reported. Genetic, immunologic, and biomarker studies advanced the understanding of adverse drug reactions. New practice parameters for cockroach allergen control were presented. The pathologic role of viruses and bacterial agents in patients with asthma and chronic obstructive pulmonary disease were further defined. An excellent review of allergen bronchoprovocation testing was reported. The roles of bronchoprovocation and bronchodilator responsiveness in asthma diagnosis were further clarified. A biomarker for neutrophilic asthma was identified. Therapeutic advances in asthma research include the inhibition of IL-13 by lebrikizumab, use of montelukast in asthmatic smokers, and a thorough review of bronchial thermoplasty in patients with severe asthma. Lastly, maternal asthma was linked to a number of adverse neonatal outcomes. (J Allergy Clin Immunol 2014;133:1265-9.)

Key words: *Allergens, fungi, venoms, adverse drug reactions, viral infections, asthma, bronchoprovocation*

Abbreviations used

BT:	Bronchial thermoplasty
CF:	Cystic fibrosis
COPD:	Chronic obstructive pulmonary disease
DEP:	Diesel exhaust particle
DRESS:	Drug reaction (rash) with eosinophilia and systemic symptoms
GM:	Galactomannan
HDM:	House dust mite
HRV:	Human rhinovirus
NTHi:	Nontypeable *Haemophilus influenzae*
OR:	Odds ratio
RT-PCR:	Real-time PCR
TLR:	Toll-like receptor

In this review of articles published in the *Journal* in 2013, we will address advances in our knowledge of a number of environmental and occupational disorders that include allergens, fungi, irritants, venoms, and drugs (summarized in Table I). We also examine the role of infectious agents in patients with respiratory disease and advances in diagnostic techniques and biomarkers for asthma. Finally, we will address improved methods of therapy for asthma, which include pharmacotherapy, bronchial thermoplasty (BT), and environmental allergen control measures (summarized in Table II).

ENVIRONMENTAL FACTORS AND ALLERGIC DISEASE

Allergens

The keeping of indoor mammals as indoor pets is a common activity in many parts of the world. Rabbits have become increasingly popular pets in recent years. Unfortunately, sensitization to pet allergens is responsible for a significant burden of allergic respiratory disease. Although several important rabbit allergens have been identified, Hilger et al[1] identified, isolated, and characterized a novel major rabbit allergen termed Ory c3. This molecule is a lipophilin that belongs to the secretory globulin protein family similar to the major cat allergen Fel d 1. However, no IgE cross-reactivity between Ory c 3 and Fel d 1 was detected. The identification and characterization of this new allergen will aid in the diagnostic testing for rabbit allergen sensitization and assays for its detection in environmental samples.

Research on the structure of allergens can enhance our understanding of their function, mechanisms of sensitization, and assessment of exposure. Mueller et al[2] determined the structure of the major cockroach allergen Bla g 1 using x-ray crystallography, mass spectrometry, and nuclear magnetic resonance spectrometry. These studies revealed the ability of Bla g 1 to bind hydrophobic ligands (lipids), which can potentially act as adjuvants for allergic sensitization. Because assays for environmental assessment of Bla g 1 have been expressed in arbitrary units, this new information can lead to assays expressed in absolute units. Such assays can be used to better compare assessment of exposure to different allergenic proteins.

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Sensitization to house dust mites (HDMs) is a significant cause of allergic respiratory disease. Ruebsaet et al[3] reported on the effects of the major HDM allergen Der p 1 on regulatory T cells. T cells from HDM-sensitive children stimulated *in vitro* with Der p 1 generated a population of forkhead box protein 3–positive $GATA3^+$ cells, whereas $CD4^+$ cells from non–HDM-sensitive children did not. These forkhead box protein 3–positive $GATA3^+$ cells suppressed proliferation of other T cells and T_H1-associated cytokines but not T_H2 cytokines. Therefore these cells might contribute to the polarization and amplification of T_H2 responses in sensitized subjects rather than suppressing these responses.

Fungi and irritants

Home dampness and indoor mold growth have been associated with asthma and other respiratory symptoms, but data linking these exposures to rhinitis have been lacking. Jaakkola et al[4] conducted a systemic review and performed a meta-analysis of published literature, which showed that exposure to indoor dampness was associated with an increased risk for rhinitis. Mold odor was associated with an increased risk for rhinitis (odds ratio [OR], 2.18 [95% CI, 1.76-2.71]; absolute risk, 1.87 [95% CI, 0.95-3.68]). Although visible mold increased the risk for rhinitis (OR, 1.82 [95% CI, 1.56-2.12]; absolute risk, 1.51 [95% CI, 1.39-1.64]) and rhinoconjunctivitis (OR, 1.66 [95% CI, 1.27-2.18]). Thus controlling indoor dampness and subsequent mold growth might reduce the burden of rhinitis.

Aspergillus fumigatus complicates the clinical course of cystic fibrosis (CF) in adults and children. Baxter et al[5] sought to better classify the spectrum of *Aspergillus* species sensitization in adults with CF. On the basis of sputum galactomannan (GM) assays and real-time PCR (RT-PCR) for *Aspergillus* species, as well as serum specific IgE and IgG levels, they proposed a new classification of aspergillosis in these patients: class 1, nondiseased (negative sputum GM and RT-PCR results); class 2, positive sputum GM result, RT-PCR result, and increased total and specific IgE and IgG levels to *Aspergillus* species (serologic allergic bronchopulmonary aspergillosis); class 3, negative sputum GM result with or without positive RT-PCR result, and increased specific IgE, but not specific IgG, levels (*Aspergillus* species sensitized); and class 4, positive sputum GM result, positive RT-PCR result, and increased specific IgG, but not specific IgE, level (*Aspergillus* species–induced bronchitis). These classifications might improve phenotyping studies and pathologic evaluation and enhance the management of patients with CF.

Diesel exhaust particles (DEPs) are a contributing factor in allergic rhinitis and asthma. Although the mechanisms are not clearly defined, Brandt et al[6] investigated the role of DEPs in the generation of IL-17A in an animal model and in children with allergic asthma. Mice exposed to DEPs together with HDM allergen had enhanced airway hyperresponsiveness to methacholine and generated a mixed T_H2 and T_H17 response ($IL\text{-}13^+IL\text{-}17^+$ T cells). Neutralization of IL-17A prevented DEP-induced airway hyperresponsiveness. In allergic asthmatic children exposure to high DEP levels was associated with more frequent asthma symptoms over a 12-month period and 6 times higher serum Il-17A levels compared with values seen in those with with low exposure levels. Strategies to abrogate IL-17A might reduce the burden of asthma in patients with allergic asthma exposed to traffic-related air pollution.

Venoms

The diagnosis and treatment of stinging insect reactions can be complicated by the presence of IgE antibodies to cross-reactive carbohydrate determinants on venom glycoproteins. Paper wasps (Polistinae) are common in Europe and North America, where they can cause stinging insect venom–induced anaphylactic reactions. Blank et al[7] demonstrated that *Polistes* species venoms are devoid of cross-reactive carbohydrate determinants, which suggests that serum specific IgE to the venom indicates true sensitivity. However, discriminating between *Polistes* species venom and *Vespula* (yellow jacket) species venom is still difficult because of protein-based cross-reactivity and requires additional testing (eg, IgE inhibition assays).

Currently available *in vitro* diagnostic tests for yellow jacket venom–specific IgE (ImmunoCAP; Phadia, Uppsala, Sweden) might lack sensitivity. Using recombinant Ves V 5 to spike the ImmunoCAP yellow jacket venom assay, Vos et al[8] showed that the sensitivity of the test for specific IgE antibodies increased from approximately 83.4% to 96.8%. These 2 reports indicate significant progress in our ability to more accurately diagnose and tailor specific treatment for systemic reactions to stinging insect venoms.

Adverse drug reactions

Allergists are frequently consulted regarding immunologically mediated hypersensitivity reactions to drugs. These can range from macular rashes to severe systemic reactions, such as drug reaction (rash) with eosinophilia and systemic symptoms (DRESS) syndrome. These reactions involve peptides modified by drugs (haptens) interacting with HLA molecules to activate T cells. Carbamazepine, an antiseizure medication, has been associated with drug rashes and more severe reactions. Previous genetic studies suggest that HLA-B*31:01 and HLA-B*15:02 genotypes predispose to a variety of carbamazepine hypersensitivity reactions. Because carbamazepine is metabolized to more than 30 metabolites in human subjects, Farrell et al[9] studied the immunologic responses to unmetabolized carbamazepine and its halogenated derivatives in T cells from a HLA-B*31:01–positive subjects with DRESS syndrome caused by carbamazepine and a carbamazepine-naive HLA-B*15:02–positive subject. T cells from both subjects demonstrated proliferative responses to unmodified carbamazepine, as well as some of the halogenated derivatives. Thus T-cell activation by carbamazepine does not require metabolism.

In another report Schnyder et al[10] examined the role of HLA-B*57:01 in reactions to abacavir, an antiretroviral drug. Interestingly, abacavir-specific $CD8^+$ cells are detectable in the circulation of abacavir-naive HLA-B*15:01 subjects. To further explore the relationship between abacavir reactions and DLA-B*57:01, abacavir-reactive circulating T cells were evaluated from HLA-B*57:01 HIV-infected patients with hypersensitivity, HLA-B*57:01 HIV-positive patients without abacavir exposure and HLA-B*57:01 HIV abacavir-naive subjects. All were skin patch tested to abacavir. All subjects had circulating abacavir-reactive T cells, but only subjects with abacavir hypersensitivity had positive skin patch test results. These 2 reports enhance our knowledge of adverse immunologically-medicated drug reactions. Further studies of genetic predisposition to drug hypersensitivity will be useful to individualize pharmacotherapy and reduce the risk of adverse drug reactions.