

Cockroach Allergens

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Cockroaches produce several potent allergens associated with sensitization and the development of asthma. Many of these allergens have been cloned and produced as biologically active recombinant proteins. Three-dimensional structure and molecular modeling, in addition to studies on the biological functions of these proteins in the cockroach, have provided new insights into the ability of these allergens to cause immunoglobulin E antibody responses. Recent studies have pointed to a potential role of recombinant cockroach allergens for diagnosis and the development of novel therapeutic strategies that may benefit cockroach-allergic patients.

Introduction

During the past three decades, the prevalence of asthma has increased to epidemic proportions in developed countries, and asthma is the most common chronic disease in children. Evidence suggests that events taking place between 2 and 3 years of age might be crucial determinants for the development of asthma. Environmental factors, including allergen exposure, acting early in life, and interacting with specific genes, are key events for the development of the chronic, persistent form of the disease [1–3]. Cockroach allergy has been recognized as an important cause of asthma for more than 30 years [4]. Bernton and Brown [5] were the first to report positive skin tests to cockroach in 44% of 755 allergy clinic patients in New York. Subsequently, many authors recognized that patients with asthma who lived in cities were commonly sensitized to this insect. Kang *et al.* [6] established the causal relationship between cockroach allergy and asthma, by showing early-phase, late-phase, and dual bronchoconstriction following inhalation of cockroach extract by sensitized asthmatic patients. More recently, results of specific inhalation challenges with *Blattella germanica* extract, performed in cockroach-allergic asthmatic patients, revealed that cockroach allergens were capable of inducing a strong inflammatory response in the airways, characterized by the

presence of eosinophils and neutrophils in induced sputum [7]. These studies have clearly demonstrated that asthma caused by cockroaches is antigen-specific and that it is similar to other types of atopic asthma. In the United States, the prevalence of cockroach allergy ranges from 17% to 41% in various studies involving both children and adults [4].

The most common domiciliary species of cockroach are *B. germanica* (German cockroach) and *Periplaneta americana* (American cockroach). *B. germanica* is a small cockroach, approximately $\frac{3}{4}$ " in length, that commonly infests houses in the United States. Kitchens and bathrooms are preferential sites for infestation. *P. americana* is a large cockroach, approximately 2" in length, which infests houses, schools, hospitals, and other large buildings. American cockroaches have less fecundity than German cockroaches and require higher temperatures ($\sim 80^\circ\text{F}$) and humidity for optimal population growth, being the predominant species in tropical countries, including Taiwan and Brazil [4].

Several cockroach allergens have been identified, cloned, sequenced, and produced as recombinant proteins with preserved biological activity during the past 15 years. Recombinant cockroach allergens offer the possibility of improving diagnosis and treatment of patients with cockroach allergy. Cockroach extracts currently available in the United States are highly variable in their protein content and levels of major allergens Bla g 1 and Bla g 2, and are characterized by inconsistent potency [8]. The public impact of cockroach allergy has prompted the selection of cockroach extracts for standardization by the US Food and Drug Administration (FDA), and this process is underway. Well-designed, controlled studies investigating the effect of immunotherapy in the management of cockroach-allergic patients are lacking. Furthermore, strategies for decreasing environmental exposure to cockroach allergens have proven to be difficult to implement. Cockroach allergens may remain detectable in the environment even after successful extermination of cockroach populations.

Exposure and Sensitization to Cockroach Allergens

Cockroach allergy is strongly linked to socioeconomic factors, and it occurs wherever living conditions sustain cockroach infestation [4]. Several studies have demonstrated that most patients sensitized to cockroach were exposed to high levels of cockroach allergens in their

homes, and that cockroach allergy is an important risk factor for emergency department visits for asthma and hospital admissions. Results of the National Cooperative Inner City Asthma Study (NCICAS) have revealed that sensitization and exposure to cockroach allergens are major risk factors for severity of asthma in children from large cities in the United States [9]. More recently, extended evaluation of a large group of children with asthma living in cities across the United States confirmed that cockroach allergen exposure in conjunction with cockroach sensitivity was associated with increased asthma morbidity, and suggested that cockroach allergens have a greater effect on asthma morbidity, compared with mite or pet allergens, among asthmatic children who live in inner-city environments [10••]. Although cockroach infestation and exposure to cockroach allergens have been linked more frequently with living in inner-city environments and having lower income and less education, it has been shown that a significant proportion of middle-class suburban children are exposed to levels of cockroach allergen sufficient to cause sensitization [11]. The most likely explanation for these findings would be passive distribution of cockroach allergens through carriage in shoes or paper products.

A prospective study has demonstrated a significant association between exposure to cockroach allergens in the first 3 months of life and the development of repeated wheeze in the first year, among children from metropolitan Boston [12]. Studies of siblings of the index children participating in the Boston cohort showed that exposure to cockroach allergens early in life was also associated with doctor-diagnosed asthma and recurrent wheezing during a 22-month follow-up period [4]. Children exposed to greater than 2 U/g Bla g 1 or Bla g 2 in the home had a relative risk for incident asthma of 35% and were at risk for recurrent asthmatic wheezing. Early exposure to cockroach was reported to be a risk factor for more severe symptoms of asthma in a multi-ethnic sample of low-income infants younger than 2 years living in Denver [13]. Furthermore, sensitization to German cockroach was shown to be a critical factor for decreased pulmonary function in middle-school children with asthma living in Taiwan [14].

Our studies carried out in Brazil revealed that cockroach allergy is present in 55% of patients with asthma and/or rhinitis who are attending allergy specialty clinics [15]. Cockroach sensitization was also a significant risk factor for wheezing among children 2 to 12 years old who required treatment of acute symptoms at emergency departments [16••]. In this study, respiratory viral infections, particularly those caused by respiratory syncytial virus (RSV), were major risk factors for acute wheezing among children 0 to 2 years old. Prospective follow-up of these infants for 2 years revealed that 52% continued to have repeated episodes of wheezing between 2 and 4 years of age, and this outcome was highly associated with the development of sensitization to indoor allergens [17].

Allergen sensitization, to house dust mites and cockroach in particular, and early exposure to cockroach allergen were strong and independent risk factors for persistence of wheezing among these children living in a subtropical environment. Our results suggest high rates of sensitization to these allergens. In our prospective study [17], 74% and 37.5% of children were exposed to high levels of mite and cockroach allergens in their homes, respectively, similar to other reports from Brazil [18•,19]. Previous studies in our area have shown that daycare centers and schools are sources of significant exposure to mite and cockroach allergens [20], which might also contribute to sensitization, and that exposure to cat and dog allergens has been consistently low, in both homes and schools [18•,20]. Sensitization to pets, which are usually kept outdoors, has been low and not associated with acute wheezing among our patients.

Allergens

Cockroach allergens are derived from several sources, including saliva, fecal material, secretions, cast skins, debris, and dead bodies. Significant amounts of allergen can be recovered from cockroach washings and from the secretory debris that accumulate in jars where cockroaches are kept in the laboratory. Several cockroach allergens, from both *B. germanica* and *P. americana*, have been purified, sequenced, cloned, and produced as recombinant proteins [21].

The first cockroach allergens to be identified, using immunochemistry, were Bla g 1 and Bla g 2. Bla g 1 has an unusual structure consisting of a series of up to seven tandem repeats, each approximately 100 amino acid residues in length, and includes an allergen originally reported as Bla g bd90K [22–24]. Bla g 1 is also the only *B. germanica* allergen that has a structural homologue in *P. americana* (Per a 1). These cross-reactive group 1 cockroach allergens (Bla g 1 and Per a 1) show 30% homology to a mosquito (*Anopheles gambiae*) protein precursor ANG12, which is secreted only in the female insect after a blood meal. This suggests that these allergens may have a digestive function.

Bla g 2 appears to be an especially potent allergen, which elicits immunoglobulin (Ig)E responses in approximately 60% of cockroach-allergic patients, at exposure levels that are 10-fold to 100-fold lower than other common inhalant allergens, such as dust mite and cat. It has been found in cockroach gut tissues, raising the possibility that Bla g 2 could be a digestive enzyme. Molecular cloning techniques determined the amino acid sequence of Bla g 2 and established that it is a 36-kDa protein that shares homology with the family of aspartic proteases [25]. Aspartic proteases catalyze the hydrolysis of a peptide bond using an acid-base mechanism, through a nucleophilic attack by the water molecule, which is polarized by two catalytic aspartic acid (D) residues within the conserved DTG triad. Molecular modeling and assessment

of enzymatic activity by functional assays revealed that Bla g 2 is an inactive aspartic protease, with critical amino acid substitutions around the catalytic residues. Therefore, enzymatic activity does not seem to account for promoting allergenic activity of Bla g 2, as it has been suggested for several mite allergens (Der p 1, Der p 3, Der p 6, and Der p 9) that function as proteolytic enzymes. Primary structure of Bla g 2 is related to groups of inactive mammalian aspartic proteases, known as pregnancy-associated glycoproteins (PAG), which are expressed in the chorion of pregnant females from ungulates, including pig, horse, cow, and sheep. Recently, the crystal structure of Bla g 2 has been solved, providing insights into the structural basis for the allergenic properties of the molecule [26••]. Amino acid substitutions and unusual features of the structure of the active site, including increased distance between the catalytic residues, are likely to explain the absence of enzymatic activity of Bla g 2. In addition, presence of five disulfide bridges and a Zn-binding site increase stability of the allergen structure and may contribute to sensitization at lower levels of exposure than other allergens.

Previously, we have reported the cloning and expression of Bla g 4, which belongs to a super family of ligand-binding protein (calycins or lipocalins) [27]. This family includes other important allergens, such as mouse and rat urinary proteins, dog allergens Can f 1 and Can f 2, β -lactoglobulin from cow's milk, and bovine and equine allergens. The lipocalins are extracellular proteins that bind hydrophobic molecules with high affinity and selectivity. Three-dimensional models of the tertiary structure of Bla g 4 were obtained, and predicted a similar structure to other members of the calycin family [27]. Recombinant Bla g 4 expressed in bacteria and yeast has excellent allergenic activity [28]. A recent study revealed that Bla g 4 is expressed only in the adult male reproductive system and that the allergen production is stimulated by the juvenile hormone [29••].

Other *B. germanica* allergens include Bla g 5, which shows sequence homology to glutathione-S-transferase (GST) enzymes, and Bla g 6, a troponin [30]. GSTs are enzymes involved in the detoxification of endogenous and xenobiotic toxic compounds, and in insects, GST production is associated with resistance to insecticides. Allergens from *P. americana* that are reactive with sera from patients living in Taiwan have been reported, including Per a 3, an insect storage protein related to arylphorin [4].

Using sera from cockroach-allergic asthmatic children to screen a *P. americana* cyclic DNA library, we have identified a major cockroach allergen, which showed a high degree of sequence identity to tropomyosins from invertebrates, particularly from mites (80% identity) and shrimp (82% identity), and has been designated as Per a 7 [15]. More recently, tropomyosins from *B. germanica* and *P. fuliginosa* (the dusky-brown cockroach) have been identified, and sequence analysis revealed that these proteins presented 97% to 98.9% identity to *P. americana*

tropomyosin [31,32]. Tropomyosins had been previously identified as important allergens in mites (*D. pteronyssinus* and *D. farinae*, Der p 10 and Der f 10, respectively) and shrimp. Interestingly, a monoclonal antibody raised against *D. pteronyssinus*, shown previously to bind to shrimp tropomyosin, also recognized cockroach tropomyosin on immunofluorescence. Our results raised the possibility that tropomyosin may be the basis for cross-reactivity among mites, cockroach, shrimp, and other invertebrates and that the high degree of sequence identity has clinical significance.

In a recent study, the use of recombinant cockroach allergens to investigate IgE and IgG antibody responses in patients with cockroach allergy and to establish IgE reactivity profiles has been reported. Using a streptavidin CAP assay and a multiplex flow cytometric assay, the prevalence of IgE antibodies to recombinant allergens rBla g 1, rBla g 2, rBla g 4, rBla g 5, and rPer a 7 was 26.1%, 54.4%, 17.4%, 37.4%, and 12.7%, respectively, among cockroach-allergic patients [33••]. Sixty-four percent of sera presented IgE antibodies to at least one allergen, and specific IgE antibodies were associated with increased IgG-antibody levels. These results indicate that the potential use of recombinant allergens for diagnostic purposes may increase our ability to define distinct patterns of IgE and IgG reactivity among cockroach-allergic patients.

Cross-reactivity Among Insect, Mite, Food, and Parasite Antigens: The Role of Tropomyosin

Tropomyosins are proteins that have a functional role in contraction of muscle cells and participate in regulation of cell morphology and motility in nonmuscle cells [34]. In muscle, two parallel alpha-helical tropomyosin molecules are wound around each other to form a coiled structure. In invertebrates, tropomyosins have been recognized as an important cause of IgE antibody responses. Interestingly, the reported frequency of IgE reactivity to mite or cockroach tropomyosins has been much lower among allergic patients living in Europe or the United States (10% to 13%), compared with those living in Africa or Brazil (50%–55%) [15,33••,35•]. These observations may reflect sensitization by other invertebrates containing tropomyosin as a cross-reactive allergen, such as parasites.

Extensive studies on IgE-binding epitopes have provided strong molecular evidence for cross-reactivity among invertebrate tropomyosins [36]; however, currently, it is not clear whether allergenic cross-reactivity among mites, cockroaches, and food is clinically relevant. Symptoms of food allergy after ingestion of shrimp and snails have been reported in European patients allergic to mites, and many of these patients received mite immunotherapy [37]. IgE antibody reactivity to shrimp among Orthodox Jews, who are prohibited from eating shellfish, has been

reported. Evidence indicates that this reactivity appears to be due to cross-reacting tropomyosin [38].

Previous inhibition studies have identified IgE cross-reactivity of insects and parasites, and it has been suggested that this cross-reactivity may also be due to tropomyosin. Sequence of tropomyosin from *A. simplex*, a fish parasite associated with induction of urticaria and other allergic symptoms in subjects who have ingested contaminated food, revealed that tropomyosins in nematodes are highly conserved [34]. We have recently determined the complete sequence of the *A. lumbricoides* tropomyosin, and have demonstrated that *A. lumbricoides* tropomyosin is an IgE-binding protein. Sequencing revealed a high degree of identity of *Ascaris tropomyosin* to tropomyosins from mites, cockroach, shrimp, and other parasites such as *A. simplex* and *Onchocerca volvulus* (69% to 98%).

The relationship of asthma and allergy with helminthic infections remains controversial [39,40••,41••]. Several issues, including age of initial parasitic infection, parasite load, type of parasite, socio-economic conditions, lifestyle, and environmental allergen exposure, may play roles in the complex relationship of parasite infections and development of allergic diseases. Our results prompted us to speculate that cross-reactive allergens, such as tropomyosin, at the time of the initial *Ascaris* infections, could facilitate subsequent development of cross-reactive IgE antibody responses upon exposure to mite or cockroach, which could lead to airway inflammation and asthma. Therefore, infection with *Ascaris* could have an adjuvant effect on the development of asthma, in the subset of *Ascaris*-infected individuals who develop IgE responses to tropomyosin [39,42].

Environmental Control

Although cockroach allergens are found throughout the house, including beds, furniture, and carpets, cockroach allergen levels are highest in the kitchen [21]. Cockroach aeroallergen particles have similar properties to mite allergens, in that they are relatively large (> 10 µm diameter), are detectable mainly after disturbance, and are thought to fall rapidly. In keeping with this, patients are usually not aware of being allergic to cockroach and do not report symptoms of asthma on entering a house that is infested with roaches. Intranasal and air samplers, in conjunction with a sensitive immunostaining system, have been used to investigate the behavior of cockroach allergen-carrying particles. Bla g 1-carrying particles could be detected during quiet domestic activity or even under no disturbance, both in the air and in nasal filters, in houses containing low levels (geometric mean 1.5 U of Bla g 1/g of dust) of allergen in Australia. In agreement with previous studies, airborne particles containing cockroach allergen are associated with particles larger than 10 µm. These particles, described as flakes or fibers, may contain

sufficient allergen to induce sensitization and chronic inflammation upon inhalation [4].

Control of cockroach exposure has been considered difficult, and, as mentioned, this issue has been investigated in inner city houses. Although aggressive treatment of cockroach-infested houses with insecticides promptly reduces the number of roaches, allergen levels may remain elevated in the environment for up to 6 months [43–45]. It is suggested that cockroach extermination needs to be coupled with thorough cleaning measures to achieve effective control of allergen exposure. Indeed, more recent studies indicate that a combined intervention strategy, comprising occupant education, insecticide application, and professional cleaning, resulted in substantial reductions in cockroach-allergen concentrations in inner-city homes [46,47]. A home-based, individualized, intervention study carried out among inner-city children with atopic asthma, which included education and remediation for exposure to both allergens and environmental tobacco smoke, resulted in reduction of asthma-associated morbidity [48••].

Conclusions

Cockroach allergy is an important risk factor for asthma worldwide. In the United States, evidence consistently indicates that the combination of sensitization to cockroach and exposure to cockroach allergens in the home is associated with more severe asthma among children living in inner-city environments. Strategies to decrease environmental exposure to cockroach allergens require extensive cleaning, education, and insect extermination, which may be difficult to maintain. Further studies investigating novel therapeutic strategies for cockroach allergy may include the use of recombinant allergens or standardized extracts for allergen-specific immunotherapy.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. de Marco R, Pattaro C, Locatelli F, Svanes C: **Influence of early life exposures on incidence and remission of asthma throughout life.** ECRHS Study Group. *J Allergy Clin Immunol* 2004, 113:845–852.
 2. Kurukulaaratchy RJ, Matthews S, Arshad SH: **Does environment mediate earlier onset of the persistent childhood asthma phenotype?** *Pediatrics* 2004, 113:345–350.

3. Guilbert TW, Morgan WJ, Zeiger RS, *et al.*: Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004, 114:1282–1287.
 4. Arruda LK, Vailes LD, Ferriani VPL, *et al.*: Cockroach allergens and asthma. *J Allergy Clin Immunol* 2001, 107:419–428.
 5. Bernton H, Brown H: Insect allergy—Preliminary studies of the cockroach. *J Allergy* 1964, 35:506–513.
 6. Kang B, Vellody D, Homburger H, Yunginger JW: Cockroach as a cause of allergic asthma. Its specificity and immunologic profile. *J Allergy Clin Immunol* 1979, 63:80–86.
 7. Lluh M, Sastre J, Fernandez-Nieto M, *et al.*: Eosinophilic and neutrophilic sputum response to bronchial challenge with cockroach. *J Allergy Clin Immunol* 2003, 112:802–803.
 8. Patterson ML, Slater JE: Characterization and comparison of commercially available German and American cockroach allergen extracts. *Clin Exp Allergy* 2002, 32:721–727.
 9. Rosenstreich DL, Eggleston P, Kattan M, *et al.*: The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997, 336:1356–1363.
 - 10.●● Gruchalla RS, Pongracic J, Plaut M, *et al.*: Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. *J Allergy Clin Immunol* 2005, 115:478–485.
- The study focuses on the association of exposure and sensitization with asthma morbidity, and the results highlight the importance of cockroach allergy as a major factor associated with morbidity due to asthma in inner city US children.
11. Matsui EC, Wood RA, Rand C, *et al.*: Cockroach allergen exposure and sensitization in suburban middle-class children with asthma. *J Allergy Clin Immunol* 2003, 112:89–92.
 12. Gold DR, Burge HA, Carey V, *et al.*: Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med* 1999, 160:227–236.
 13. Klinnert MD, Price MR, Liu AH, Robinson JAL: Morbidity patterns among low-income wheezing infants. *Pediatrics* 2003, 112:49–57.
 14. Lin Y-C, Su H-J, Hsiue T-R, *et al.*: Levels of house dust mite-specific IgE and cockroach-specific IgE and their association with lower pulmonary function in Taiwanese children. *Chest* 2002, 121:121:347–1353.
 15. Santos AB, Chapman MD, Aalberse RC, *et al.*: Cockroach allergens and asthma in Brazil: identification of tropomyosin as a major allergen with potential cross-reactivity with mite and shrimp allergens. *J Allergy Clin Immunol* 1999, 104:329–337.
 - 16.●● Camara AA, Silva JM, Ferriani VPL, *et al.*: Risk factors for acute wheezing among children in a subtropical environment: role of respiratory viruses, IgE antibodies and allergen exposure. *J Allergy Clin Immunol* 2004, 113:551–557.
- Interesting paper that highlights differences in risk factors for acute wheezing in subtropical areas, as compared with temperate climates.
17. Silva JM, Camara AA, Tobias KRC, *et al.*: A prospective study of wheezing in young children: the independent effects of cockroach exposure, breast-feeding and allergic sensitization. *Pediatr Allergy Immunol* 2005, In press.
 - 18.● Tobias KR, Ferriani VP, Chapman MD, Arruda LK: Exposure to indoor allergens in homes of patients with asthma and/or rhinitis in southeast Brazil: effect of mattress and pillow covers on mite allergen levels. *Int Arch Allergy Immunol* 2004, 133:365–370.
- This paper reports significant levels of exposure to mite and cockroach allergens and very low exposure to cat and dog allergens in homes of patients with asthma and/or rhinitis living in Brazil, which might be relevant for sensitization.
19. Sarinho E, Schor D, Veloso MA, Rizzo JA: There are more asthmatics in homes with high cockroach infestation. *Braz J Med Biol Res* 2004, 37:503–510.
 20. Rullo VE, Rizzo MC, Arruda LK, *et al.*: Daycare centers and schools as sources of exposure to mites, cockroach, and endotoxin in the city of Sao Paulo, Brazil. *J Allergy Clin Immunol* 2002, 110:582–588.
 21. Eggleston PA, Arruda LK: Ecology and elimination of cockroaches and allergens in the home. *J Allergy Clin Immunol* 2001, 107:S422–S429.
 22. Pomés A, Melén E, Vailes LD, *et al.*: Novel allergen structures with tandem amino acid repeats derived from the German and American cockroach. *J Biol Chem* 1998, 273:30801–30807.
 23. Helm R, Cockrell G, Stanley JS, *et al.*: Isolation and characterization of a clone encoding a major allergen (Bla g Bd90K) involved in IgE-mediated cockroach hypersensitivity. *J Allergy Clin Immunol* 1996, 98:172–180.
 24. Melén E, Vailes LD, Pomes A, *et al.*: Molecular cloning of Per a 1 and definition of the cross-reactive Group 1 cockroach allergens. *J Allergy Clin Immunol* 1999, 103:859–864.
 25. Arruda LK, Vailes LD, Mann BJ, *et al.*: Molecular cloning of a major cockroach (*Blattella germanica*) allergen, Bla g 2: sequence homology to the aspartic proteases. *J Biol Chem* 1995, 270:19563–19568.
 - 26.●● Gustchina A, Li M, Wunschmann S, *et al.*: Crystal structure of cockroach allergen Bla g 2, an unusual zinc binding aspartic protease with a novel mode of self inhibition. *J Mol Biol* 2005, 348:433–444.
- A very elegant paper describing the details of the three dimensional structure of Bla g 2 and the features that might be associated with lack of enzymatic activity and involved in allergenicity of the molecule.
27. Arruda LK, Vailes LD, Hayden ML, *et al.*: Cloning of cockroach allergen, Bla g 4, identifies ligand binding proteins (or calycons) as a cause of IgE antibody responses. *J Biol Chem* 1995, 270:31196–1201.
 28. Vailes LD, Kinter MT, Arruda LK, Chapman MD: High-level expression of cockroach allergen, Bla g 4, in *Pichia pastoris*. *J Allergy Clin Immunol* 1998, 101:274–280.
 - 29.●● Fan Y, Gore JC, Redding KO, *et al.*: Tissue localization and regulation by juvenile hormone of human allergen Bla g 4 from the German cockroach, *Blattella germanica* (L.). *Insect Mol Biol* 2005, 14:45–53.
- An interesting study describing in detail the biological aspects of production of the allergen Bla g 4 by the cockroach.
30. Arruda LK, Vailes LD, Platts-Mills TA, *et al.*: Induction of IgE antibody responses by glutathione S-transferase from the German cockroach (*Blattella germanica*). *J Biol Chem* 1997, 272:20907–20912.
 31. Jeong KY, Lee J, Lee I-Y, *et al.*: Expression of tropomyosin from *Blattella germanica* as a recombinant non-fusion protein in *Pichia pastoris* and comparison of its reactivity with its native counterpart. *Prot Expression Purification* 2004, 37:273–278.
 32. Jeong KY, Hwang H, Lee J, *et al.*: Allergenic characteristics of tropomyosin from the dusky brown cockroach, *Periplaneta fuliginosa*. *Clin Diag Lab Immunol* 2004, 11:680–685.
 - 33.●● Satinover SM, Reefer AJ, Pomes A, *et al.*: Specific IgE and IgG antibody-binding patterns to recombinant cockroach allergens. *J Allergy Clin Immunol* 2005, 115:803–809.
- Very elegant study, aimed at establishing IgE reactivity profiles of cockroach allergic patients using a panel of recombinant allergens.
34. Reese G, Ayuso R, Lehrer SB: Tropomyosin: an invertebrate pan-allergen. *Int Arch Allergy Immunol* 1999, 119:247–258.
 - 35.● Westritschnig K, Sibanda E, Thomas W, *et al.*: Analysis of the sensitization profile towards allergens in central Africa. *Clin Exp Allergy* 2003, 33:22–27.
- Excellent study using recombinant grass and mite allergens, instead of crude extracts, to compare the IgE reactivity profiles of patients living in Zimbabwe, Africa, and in central Europe.
36. Ayuso R, Reese G, Leong-Kee S, *et al.*: Molecular basis of arthropod cross-reactivity: IgE-binding cross-reactive epitopes of shrimp, house dust mite and cockroach tropomyosins. *Int Arch Allergy Immunol* 2002, 129:38–48.

37. van Ree R, Antonicelli L, Akkerdaas JH, *et al.*: **Possible induction of food allergy during mite immunotherapy.** *Allergy* 1996, **51**:108–113.
38. Fernandez J, Reshef A, Patton L, *et al.*: **Immunoglobulin E antibody reactivity to the major shrimp allergen, tropomyosin, in unexposed Orthodox Jews.** *Clin Exp Allergy* 2003, **33**:956–961.
39. Arruda LK: **Asthma and parasites: new insights.** *Curr Allergy Asthma Rep* 2003, **3**:273–274.
- 40.●● Yazdanbakhsh M, Matricardi PM: **Parasites and the hygiene hypothesis. Regulating the immune system?** *Clin Rev Allergy Immunol* 2004, **26**:15–23.
Excellent review containing detailed discussions of the association between parasites and allergy at the epidemiologic, cellular, and molecular level.
- 41.●● Cooper PJ: **Intestinal worms and human allergy.** *Parasite Immunol* 2005, **26**:455–467.
Excellent review on epidemiologic data and immune mechanisms involved into the relationship of geohelminth infections and development of allergy and asthma.
42. Sales VS, Rodrigues CE, Trombone APE, *et al.*: **Infection with *Ascaris lumbricoides* in pre-school children: role in wheezing and IgE responses to inhalant allergens (abstract).** *J Allergy Clin Immunol* 2002, **109**:S27.
43. Williams LW, Reinfried P, Brenner RJ: **Cockroach extermination does not rapidly reduce allergen in settled dust.** *J Allergy Clin Immunol* 1999, **104**:702–703.
44. Eggleston PA, Wood RA, Rand C, *et al.*: **Removal of cockroach allergen from inner city homes.** *J Allergy Clin Immunol* 1999, **104**:842–846.
45. Gergen PJ, Mortimer KM, Eggleston PA, *et al.*: **Results of the National Cooperative Inner-city Asthma Study (NCICAS) environmental intervention to reduce cockroach allergen exposure in inner-city homes.** *J Allergy Clin Immunol* 1999, **103**:501–506.
46. Arbes SJ Jr, Sever M, Archer J, *et al.*: **Abatement of cockroach allergen (Bla g 1) in low-income, urban housing: a randomized controlled trial.** *J Allergy Clin Immunol* 2003, **112**:339–345.
47. Arbes SJ Jr, Sever M, Mehta J, *et al.*: **Abatement of cockroach allergens (Bla g 1 and Bla g 2) in low-income, urban housing: Month 12 continuation results.** *J Allergy Clin Immunol* 2004, **113**:109–114.
- 48.●● Morgan WJ, Crain EF, Gruchalla RS, *et al.*: **Results of a home-based environmental intervention among urban children with asthma.** *N Engl J Med* 2004, **351**:1068–1080.
This paper outlines an innovative strategy of environmental control, based on comprehensive and individualized intervention, which resulted in a decrease of morbidity among inner-city children with atopic asthma.