

ARTHROPOD ALLERGENS AND HUMAN HEALTH

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■ **Abstract** Many species of arthropods are the sources of potent allergens that sensitize and induce IgE-mediated allergic reactions in humans. Most of these arthropod allergens are proteins, and the allergic response mechanism to these allergens is the same as it is for allergens from other sources such as plant pollens, molds, and foods. Aside from ingestion of crustaceans (shrimp, lobster), among arthropods, humans have the greatest contact with insects and mites, and as a result allergies to these two groups of arthropods have been the most frequently reported. Because of the large number of people affected by allergic reactions to stinging insects, cockroaches, and dust mites, many allergens of these organisms have been extensively studied, purified, and immunobiochemically characterized and for some recombinant allergens, produced. Cocktails of these recombinant allergens have the potential for use in diagnosis and immunotherapy. In this chapter, we review the insects and mites that induce allergic reactions. Where the information exists, the immunobiochemical characterization of the allergens and the frequency of sensitivity or clinical reactivity in the human population are also reviewed. As background, the beginning of this review includes sections that define allergens, explain the allergic reaction mechanism, and describe the methods for naming allergens.

CONTENTS

INTRODUCTION	396
THE ALLERGIC REACTION	397
ALLERGEN NOMENCLATURE	398
CAT FLEAS	399
MOSQUITOES	400
HOUSE FLIES	402
NONBITING MIDGES	403
CONFUSED FLOUR BEETLES	404
RICE WEEVILS	405
STINGING INSECTS	405
Apids	406
Vespids	407
Fire Ants	408
SILKWORMS	408

COCKROACHES 409

MISCELLANEOUS INSECTS 411

 Kissing Bugs 411

 Silverfish 412

 Caddisflies 412

 Moths 412

 Deer Flies and Bedbugs 412

 Caterpillars 412

DUST AND STORAGE MITES 412

CHARACTERISTICS OF MITE ALLERGENS 416

PHYTOPHAGOUS, PREDACEOUS, AND PARASITIC MITES 417

CONCLUSION 418

INTRODUCTION

Allergic disease is a common disorder affecting 40% of the world population (122). More than 20% of the U.S. population are sensitized to various allergens, and on exposure, experience ≥ 7 days of clinical symptoms annually (188, 211). The allergens that trigger allergic reactions may be inhaled, injected, ingested, and absorbed through the skin or mucus membranes. Allergic reactions to aeroallergens and contact allergens usually manifest as rhinitis and conjunctivitis (hay fever), asthma, or atopic dermatitis. Clinical symptoms of these may be swelling, itchy and watery eyes and nose, erythema, difficulty breathing, headaches, skin rash, and itching. Drug and food allergies may manifest as abdominal pain, diarrhea, hives, and constipation. Exposure to allergens may also cause systemic reactions or anaphylaxis (a life-threatening, systemic allergic reaction).

An immunogen is a molecule that is capable of eliciting an immune response. Immunogens that induce IgE-antibody responses are termed allergens. Allergens are immunogens capable of sensitizing and inducing allergic reactions. In most cases, allergens are proteins or molecules with large protein components (e.g., glycoproteins). However, carbohydrates or the polysaccharide component of a glycoprotein can also elicit an immune response. The portion of the allergen recognized by antibodies and membrane receptors on immune effector cells is known as the epitope or antigenic determinant. The epitope region of an allergen is small. The variable region of an antibody combines with 5–7 amino acid residues of the allergen. The epitopes are 8–15 amino acid residues for T-cells because both the T-cell receptor (TCR) and the major histocompatibility complex (MHC) protein of the antigen-presenting cell binds to the allergen. The epitope may be sequential or nonsequential (conformational) (1). IgE antibodies on mast cells have their greatest binding affinities to conformational epitopes (1). Immune effector cells such as B- and T-cells (lymphocytes) are epitope specific and recognize only one epitope even though an immunogen/allergen may have many epitopes. In mammals, $\sim 10^9$ different epitope-specific B- and T-cell clones develop, so there is a large repertoire of epitopes that can be recognized.

The person who reacts to allergens is said to be allergic or hypersensitive. The reaction of a sensitized individual that occurs within minutes of exposure is referred to as immediate or Type I hypersensitivity. Substances (e.g., cytokines) released during the immediate reaction may induce a localized late-phase inflammatory reaction (4–48 h) involving infiltration and accumulation of neutrophils, eosinophils, basophils, macrophages, and lymphocytes. These cells and their products may exacerbate the immediate reaction. This cellular infiltrate results from the upregulated expression of adhesion molecules on vascular endothelial cells and the infiltrating cells in response to chemokines (cytokines that cause chemotaxis).

The hallmark of an allergic reaction is that it is mediated by IgE type immunoglobulin (antibody). Non-IgE-mediated allergic reactions exist, but the mechanism is poorly understood as yet. Immunogens that are not allergens induce secretions by plasma cells of other types of antibodies such as IgG, IgA, and IgM. Allergens may induce production of these antibody isotypes as well as IgE. Therefore, specific immune/inflammatory responses to an immunogen can occur, but they do not have to be allergic reactions with allergic symptoms. Products from arthropods can induce immune/inflammatory reactions that do not involve IgE. In this review, I discuss only IgE-mediated reactions to allergens from arthropods and allergic disease.

THE ALLERGIC REACTION

Most evidence suggests a genetic predisposition in allergic individuals that involves multiple genes. The first time a genetically predisposed person encounters an allergen, the allergen binds to B-cell surface receptors that recognize a specific epitope (antigenic determinant) on the molecule. The antigen is internalized by endocytosis into endosomes. Within the lysosome/endosome compartment, proteins are degraded by proteases into immunogenic peptides. These endosome/lysosome vesicles fuse with vesicles from the Golgi bodies bearing class II MHC molecules (MHC-II) on the inner membrane and form a peptide-loading vesicle. Within the peptide-loading vesicle, the immunodominant peptide is bound to the α chain of the MHC-II molecule, and the endosome moves to the cell surface and fuses with the plasma membrane in exocytotic fashion. Thus, the B-cell acts as an antigen-presenting cell and now displays on its surface the immunogenic peptide–MHC-II complex to type 2 CD4+ helper T-cells (Th2). A similar process occurs in other antigen-presenting cells such as macrophages, Langerhans cells, and dendritic cells. Presentation of immunogenic peptides and cytokines by these antigen-presenting cells to T-helper (Th0) cells serves to prime these cells to become Th1 and/or Th2 types (218). Primed Th2 type helper T-cells with a TCR complex recognize and bind to the B-cell displaying the allergenic peptide-bound MHC-II molecule. Other accessory molecules associated with the TCR such as the CD4, CD3, and CD45 molecules act to enhance the binding between the allergen-bearing B-cell and the CD4+ helper T-cell. Binding of the allergen to the TCR and to the

accessory molecules activates both the T- and B-cells. Activated Th2 cells produce a cadre of cytokines such as IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13. IL-4 and IL-13 enhance B-cell growth, proliferation, and differentiation into plasma cells that produce IgE and memory B-cells. These cytokines also attract mast cells, basophils, eosinophils, neutrophils, and lymphocytes to the sites of the allergic reaction. The IgE antibodies bind by means of the Fc region to the high-affinity IgE receptor on the mast cell and basophil surface. Mast cells in tissues (e.g., mucosal membranes of nose, eyes, and gut) are the main effector cells in allergic reactions, but basophils present in the circulation also can take part in allergic reactions.

The second and subsequent times a person encounters the same allergen, these allergens bind to the IgE molecules on the surface of mast cells in tissues and basophils in blood. Mast cells and basophils are activated by cross-linkage of IgE by multivalent allergens (137). Multiple valent allergens have multiple identical epitopes. Virtually all epitopes recognized by IgE on the surface of mast cells are conformational and not from a consecutive sequence of amino acids (1). Furthermore, an allergen the size of Group 1 dust mite allergens may bind up to 5–6 Fab fragments (1). Cross-linking of three IgEs is a stronger stimulant than cross-linking pairs (79, 232). The amount of allergen exposure is important because the amount of aggregation and degranulation that occurs is dose dependent when 1–15% of the receptors are involved (170). When two or more of these IgE receptors are cross-linked, primed mast cells in tissue and basophils in blood are activated within minutes, and they release powerful soluble chemical mediators. Depending on the cell type, these include histamine, chondroitin sulfate, heparin, protease enzymes (tryptase, chymase, carboxypeptidase, cathepsins), lipid mediators (leukotrienes, prostaglandins, thromboxanes), and a variety of cytokines (TNF- α , IL-4, IL-5, IL-6, and IL-13).

Among the cellular effects these mediators cause are vasodilation, airway reactivity, venular permeability, mucus secretion, and intestinal and bronchial smooth muscle contraction. These cellular effects may manifest as wheezing, sneezing, runny nose, watery eyes, edema, erythema, itching and dermatitis, and pain. The mechanism of the allergic reaction at the cellular level is the same regardless of the allergen's source. Therefore, allergens of dust mite, tick, ragweed and grass pollen, bee sting, mold, pet dander and saliva, foods, and medications all induce similar immune responses at the cellular level. The clinical signs vary depending on whether the allergens enter the body through the respiratory tract, the digestive system, mucus membranes, or the skin.

ALLERGEN NOMENCLATURE

The methods for designation (nomenclature) of the characterized allergens are standardized and described by King et al. (140) and Larsen et al. (155). In brief, an allergen is described by the first three letters of the genus, a space, the first letter of

the species, a space, and an Arabic number, all in normal type (not italics). In the case where the first letters of the genus and species of two species are the same, a modification must be made by adding a letter to either the genus or the species (140). Allergens that share similar biochemical properties, biological function, and have >67% identity of amino acid sequences are assigned to the same group. The use of the prefixes “r,” “s,” and “n” to designate recombinant, synthetic, and natural allergens is optional. Only allergens with greater than 5% IgE reactivity are included in the nomenclature. Allergens are designated as major if more than 50% of patients tested have serum IgE that reacts to the allergen.

CAT FLEAS

Homes with indoor cats and dogs may become infested with all life stages of cat fleas (*Ctenocephalides felis*) and contaminated with flea detritus. As fleas feed through the skin of humans, they inject salivary secretions containing immunogenic components. Flea detritus may contact the skin or become airborne. These injected or inhaled airborne materials can induce IgE responses. Trudeau et al. (258) reported that 18% of 100 consecutive patients with allergic complaints had positive skin tests to a commercial cat flea extract. Subsequent studies by Trudeau et al. (257) clearly showed that components of adult flea bodies and spent culture material are allergenic. Proteins in extracts made from whole bodies of adult fleas and flea culture material were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Immunoblots using sera from five cat flea skin test- and radioallergosorbent test (RAST)-positive patients identified proteins of 34, 35, 39, 54, and 60 kDa that bound IgE in these sera. Likewise, spent culture medium from flea cultures contained four IgE-binding proteins with molecular weights of 30, 45, 52, and 62 kDa. The IgE binding to proteins of different molecular weights in the two different extracts suggests that different life stages and/or detritus material contain different allergenic proteins. The allergenic components in spent culture could have included fecal matter, molting enzymes, larval and pupal bodies, and exoskeletons that contained allergenic molecules. A key conclusion from this study is that some allergens from fleas are not associated with their bite. Contact with flea allergens in substrates such as carpets and sofas or flea allergens that are aerosolized during disturbances can sensitize and induce allergic reactions.

Earlier studies had described two antigenic components of salivary secretions with molecular weights of 4–10 kDa (component A) and 1 kDa (component B) that caused papular urticaria (35, 278). None of the proteins identified by immunoblotting by Trudeau et al. (257) were the same molecular weights as these two antigenic components of the salivary secretions that caused papular urticaria. Therefore, it is not known if components A and B in flea saliva can induce IgE-mediated allergic reactions.

MOSQUITOES

Skin immune/inflammatory reactions to mosquito bites are common. Allergic reactions following mosquito bites have been reported, but anaphylactic reactions are rare. There are no reported cases in which mosquito body parts, such as hair, wings, particulate fragmented body parts, or feces, have become aerosolized, inhaled and induced an allergic reaction. However, it is possible that this could occur in an occupational setting where individuals work with large numbers of reared mosquitoes, as has been reported for other insects and mites. This has not been investigated.

Allergic reactions to mosquito bites follow the classical pattern for allergic disease. Predisposed individuals with no previous exposure give no reaction to an initial mosquito bite but they do to subsequent bites (195). The reactions are usually Type I immediate hypersensitivity responses and may involve delayed local cutaneous responses (90, 191, 199, 245) and even anaphylaxis (175, 217).

There are at least three recent reports of anaphylactic reactions to mosquito bites. One case involved a 22-year-old man on army field duty in New York who was bitten numerous times over a 14-h period. He developed the classical clinical reactions including shortness of breath, dyspnea, sneezing, dizziness and light-headedness, and lost consciousness (175). The mosquitoes in the area were *Aedes* sp. (44.4%), *Culex* sp. (33.9%), and *Anopheles* sp. (16.7%). The patient was skin test positive to *Aedes aegypti* and negative to *Culex pipiens*, whereas 10 other volunteers with similar exposure were prick and intradermal skin test negative. The patient was administered rush immunotherapy and was later found not to react (cutaneously or systemically) to numerous mosquito bites after he was relocated to Panama.

A second case involved a 23-year-old man living in the same New York area who developed "hives and giant welts" and other systemic symptoms after being bitten by mosquitoes. Some reaction occurred after only one bite. He was intradermal skin test positive to both *Ae. aegypti* and *Cx. pipiens*. Rush and slower immunotherapy were initiated, but both had side effects necessitating termination of the treatment.

A third case involved a 26-year-old man whose symptoms disappeared after administration of epinephrine and other drugs following anaphylactic reaction to mosquito bites (85). Western blot analysis showed this patient had serum IgE directed at two proteins of about 30 kDa and another of slightly smaller (~28kDa) in whole body extracts of *Cx. pipiens* and *Aedes communis*, respectively.

There are a number of reports of patients undergoing successful immunotherapy that resulted in complete or marked reductions in reactions to mosquito bites (34, 90, 200, 246, 275). However, immunotherapy is not widely used and the duration of its effectiveness has not been determined. A large number of mosquito species bite humans, and it is not known if immunization with each species is required or if there is enough cross-reactivity of relevant allergens that only a few species could be used. There is evidence that natural desensitization following repeated mosquito bites can occur (177).

Immediate and/or delayed reactions to mosquitoes are induced by components of the salivary secretions (111, 176). Hudson et al. (111) showed that bites by mosquitoes that had their salivary gland ducts cut did not induce cutaneous reactions in a sensitized individual, whereas mosquitoes with intact ducts did.

Extracts of the mosquito salivary gland contain more than 20 proteins, some of which are allergens (212). As many as 19 proteins in mosquito salivary gland extracts are allergenic and induce IgE responses (39).

Peng et al. (197) prepared salivary or salivary gland extracts from 10 mosquito species that had worldwide distribution. These included *Ae. aegypti*, *Aedes vexans*, *Aedes albopictus*, *Aedes togoi*, *Aedes triseriatus*, *Culex quinquefasciatus*, *Cx. pipiens*, *Culex tarsalis*, *Anopheles sinensis*, and *Culiseta inornata*. Proteins in the extracts were separated by SDS-PAGE, transferred to a nitrocellulose membrane, and immunoblotted using a serum pool from subjects allergic to mosquitoes. Three to 16 proteins in each of the 10 mosquito salivary extracts bound IgE. Their molecular weights ranged from 16 to 95 kDa. Several species had proteins of comparable molecular weights that bound IgE.

Salivary proteins of 68 and 37 kDa, designated Aed a 1 and Aed a 2, respectively, have been cloned (116, 216). Both recombinant proteins bind IgE and elicit skin reactions in mosquito-sensitive individuals, although rAed a 2 elicited fewer and smaller skin reactions than rAed a 1 (196, 274). To investigate if different species shared potential allergens, rabbit anti-rAed a 1 and anti-rAed a 2 were used to probe SDS-PAGE-separated proteins in salivary extracts of *Ae. vexans*, *Ae. albopictus*, *Cx. quinquefasciatus*, and the two recombinant proteins. Anti-rAed a 1 recognized comparable molecular weight bands in *Ae. aegypti*, *Ae. vexans*, and *Ae. albopictus*, but not in *Cx. quinquefasciatus*. Likewise, anti-rAed a 2 bound to comparable molecular weight proteins in the three *Aedes* species and *Cx. quinquefasciatus*. This indicates that these proteins from different species share allergenic epitopes. This was confirmed by obtaining positive immunoblots with serum from subjects who did not reside in regions where the mosquito was found. *Ae. vexans* had proteins of 75, 57.5, 54, 28, 23, and 17.5-kDa molecular weights that bound IgE in serum of subjects allergic to mosquitoes.

Peng et al. (198) performed immunoblot analyses of protein in extracts prepared from the heads and thoraxes of *Cx. tarsalis*, *Cs. inornata*, and *Ae. vexans* using pooled human serum from subjects allergic to mosquito bites. IgE and IgG antibodies bound to 12 proteins of *Ae. vexans*, 16 proteins of *Cx. tarsalis*, and 14 of *Cs. inornata*. Proteins of 24, 32.5, 40, 46, 50, 62, 65, 110, and 160 kDa in all three species bound human antibodies. Two species had six antigens with common molecular weights that bound human antibodies. Antigens of 18.5, 25, and 30 kDa were specific for *Ae. vexans*, *Cx. tarsalis*, and *Cs. inornata*, respectively. Side-by-side comparison of IgE and IgG binding to *Ae. vexans* showed most proteins bound both isotypes. This is consistent with earlier reports that many salivary antigens bind both IgG and IgE (215, 234).

The mosquito materials used for preparing extracts for immunologic investigations have consisted of whole bodies, heads, and thoraxes, or salivary glands.

All of these contain proteins not relevant to the antigenic molecules injected when mosquitoes bite. Regardless of the crudeness of these extracts and presence of irrelevant proteins, antigenic proteins in the mosquito saliva have been identified by specific antibodies in the serum of subjects with high reactivity to mosquito bites.

HOUSE FLIES

There are a few reports of the common house fly (*Musca domestica*) inducing allergic reactions in humans. Jamieson (117) provided the first evidence when he reported the house fly as a cause of nasal allergy. However, Lierl et al. (161) were the first to report house fly–allergen-specific IgE in allergic asthmatic children. These findings suggested that fly-derived particles (excreta, shed hairs, disintegrated bodies) and body secretions/saliva must become airborne in homes and schools and serve as aeroallergens.

Recently, Wahl & Fraedrich (271) reported a case of a 35-year-old female patient who suffered conjunctivitis and rhinitis associated with working in a barn infested by house flies (*Musca domestica*). The patient gave a strong conjunctival response after her eye was touched with the wing of a house fly. A similar test with three control patients was negative. An extract of house fly bodies was made and used for RAST and immunoblotting following IEF and SDS-PAGE. The patient's serum was RAST class III for IgE specific for *M. domestica* proteins. IEF of the extract coupled with immunoblotting using the patient's serum determined she had serum IgE specific for proteins in the pI ranges 4.6–5.8 and 6.8–7.5. Western blot analysis showed IgE antibodies to several proteins in the 43–60 kDa range with the most prominent allergen at 60 kDa.

In another recent study, SDS-PAGE immunoblotting assays were performed using sera from 29 patients allergic to household arthropods (172). More than 50% of the 29 sera had IgE directed at proteins of 36, 34, 31, 27, and 17 kDa in house fly extract.

Baldo & Panzani (30) assessed the spectrum of serum IgE antibodies to a wide range of insect species in 41 subjects diagnosed with inhalant allergies to insects. Western blot analysis of extracts of six species of flies showed IgE binding to a 37-kDa protein in all six extracts. These results suggested the possibility that *M. domestica* and five other species of flies may be the sources of some cross-reacting or common allergens. Thus, subjects may be sensitized to one or a few fly species but show serum IgE to other fly species or even other insects. The six species of flies they examined were *M. domestica*, *Calliphora stygia*, *Calliphora augar*, *Lucilia cuprina*, *Chrysomya bezziana*, and *Parasarcophaga* sp. However, each extract also contained proteins with unique molecular weights that also bound IgE, indicating that the five other species of flies are also the sources of some species-specific allergens.

NONBITING MIDGES

The body fluid of chironomid midges contains hemoglobin molecules, known as erythrocurorins, that have a high degree of polymorphism. In the case of *Chironomus thummi thummi* 11 forms occur with the primary structure of the various erythrocurorins differing by 16–48% of the amino acid residues (32). These hemoglobins of chironomids are potent allergens that can sensitize and induce allergic disease.

Exposure to nonbiting midges occurs among persons engaged in the production of fish food or the feeding of fish. Reactions result from exposure to dust of lyophilized larvae. Likewise, adult midges are a source of aeroallergens along waterways and lakes when swarms emerge and dead bodies accumulate on the ground around homes and lights (33, 96, 114, 115, 124). Dead bodies break up and can be inhaled. These chironomid particles are important sources of allergens.

Baur et al. (32) investigated the skin test reactivity and serum IgE of 43 individuals who had respiratory, conjunctival, or cutaneous reactions when they contacted dust containing larval chironomid components. Crude extracts were prepared from larvae and adults of *C. thummi thummi*, *Chironomus annularius*, *Chironomus tentans*, *Chironomus tepperi*, and from a commercially available fish food containing lyophilized larvae of different species. Hemoglobins were isolated from the crude extract of *C. thummi thummi* using Sephadex G-75 column, and then globins were prepared by removing the heme group. Twenty-nine of the 36 symptomatic subjects were skin test positive to crude extracts of mixed chironomid larvae, *C. thummi thummi* midges, and in most cases with *C. thummi thummi* hemoglobins III, IV, and VI. Thirty-three of the 43 symptomatic subjects had serum IgE that was detected by RAST using crude extracts of mixed larvae, *C. thummi thummi* midges, *C. thummi thummi* total hemoglobin, hemoglobin *C. thummi thummi* VI, and fragment 38–140 of *C. thummi thummi*. Sera of five sensitized persons had IgE antibody directed at proteins in extracts of *C. annularius*, *C. tentans*, *C. tepperi*, and *Cladotanytarus lewisi*. This suggests that there may be some cross-reactivity between species because the four species were from North America, Europe, Asia, and Africa, respectively.

Eriksson et al. (71) tested the skin of 2368 consecutive Swedish adult patients with asthma and/or rhinitis, with a chironomid extract prepared from fish food. Twenty-six percent of the atopics were skin test positive. Teranishi et al. (247) reported that a research worker developed allergic rhinitis to chironomid midges after 10 years of exposure to a number of species. The researcher was positive by both skin test and ophthalmic challenge, and RAST positive to *Polypedilum kyotoense*, *Chironomus plumosus*, *Tokunagayusurica akamusi*, and *Cricotopus sylvestris*. Immunoblot analysis of an adult midge extract showed that this researcher had IgE directed at a protein with the same mobility as hemoglobin in the larvae of *C. plumosus*.

Baur et al. (33) suggested that chironomids could be potent aeroallergens during the chironomid season after mass emergence of the midges in water-rich regions. Kay et al. (131) found that the midge *Chironomus lewisi* was a potent seasonal allergen and a major etiologic factor in asthma and rhinitis in Kalakla, Sudan. Other studies in Sudan, Egypt, and Italy reported a high incidence of IgE specific against *C. lewisi* (56, 84, 132). Baur et al. (33) reported allergic reactions to *Chironomus salinaris* among railway workers in Venice, Italy. Morsy et al. (186) skin tested 25 children who had respiratory allergy with no organic cause who lived close to the Nile. Twenty of 25 children tested gave a positive skin test to an extract of bodies of *Chironomus calipterus* with 17 having chironomid-specific IgE in their serum. In the United States, sensitization to *C. plumosus* was reported among atopic patients living around a reservoir in Wisconsin (124).

In Japan, Kimura et al. (136) reported that chironomid allergens were abundant in house dust and were also present in soil and air. Hirabayashi et al. (96) investigated the serum IgE levels among 123 adults with bronchial asthma who resided around hypereutrophic lakes with massive emergences of chironomids during several times of the year. IgE to the midges, *Chironomus yoshimatsui*, *C. plumosus*, and *T. akamusi*, mites, and silkworms were investigated. Incidences of serum IgE to *C. yoshimatsui*, *C. plumosus* and *T. akamusi* were 8.9, 6.5, and 2.4%, respectively. It is interesting that 22.8% had positive reactions to the silkworm, *Bombyx mori*. Ito et al. (114) reported that 32.3% of 105 selected asthmatic patients in Tokyo tested RAST positive for extracts of both larval and adult midges, and 38% of 303 asthmatics had positive skin prick tests.

Patients from other locations in Japan have shown positive reactions to *C. yoshimatsui* as high as 50.9% among nine populations investigated. In comparison, positive results to *B. mori* extract were exhibited in 23–62% in the same nine populations, with generally higher positive rates to *B. mori* than *C. yoshimatsui* (96). Fifty-nine percent of 51 patients sensitive to house dust mites in Japan showed IgE antibodies to the midge, *C. yoshimatsui* (149). The midge extract (whole body) contained 24 IgE-binding components with proteins of 73 and 55 kDa binding IgE in serum of 39% of the patients. Only two patients had IgE to proteins with molecular weights of 10–32 kDa that would correspond to hemoglobin.

Allergic reaction to chironomids may occur in some rather unsuspecting ways. For example, a 34-year-old woman experienced severe periorbital edema and conjunctivitis after she had fed her son's tropical frogs and fish (43). It was determined that she rubbed her eyes after handling and feeding the fish freeze-dried, gamma-radiated, deep-frozen larvae of *Chironomus plumosus*. She had not washed her hands before touching her eyes with her fingers.

CONFUSED FLOUR BEETLES

The confused flour beetle *Tribolium confusum* is a common pest of flour, cereals, boxed mixes (cake, pancake), nuts, peas, beans, dried fruits, spices, milk chocolate, fruits, snuff, cayenne pepper, and herbarium and insect museum specimens (237).

There are a few reports of allergic reactions to this beetle or to its products. IgE-mediated allergy to the confused flour beetle as a result of occupational exposure has been reported recently (5). While performing maintenance on a dough machine, a 35-year-old mechanic in a bread factory was exposed to old rye flour containing *T. confusum* that collected on the machine. Over a number of years, he developed rhinitis, conjunctivitis, contact urticaria, and asthmatic symptoms. Skin prick tests were positive to minced *T. confusum* but negative to clean flour, molds, storage mites, and enzymes.

Rudolph et al. (220) reported that of 1040 patients with perennial asthma and/or rhinitis, 16.5% had positive skin prick tests and 30.7% had positive intradermal skin tests to whole body extracts of *T. confusum*. Likewise, among 133 bakers tested by skin prick, 8.3% were positive to *T. confusum* (228). Schultze-Werninghaus and colleagues later reported that IgE in the sera of subjects exposed to rye and wheat flour bound to three *T. confusum*-specific proteins (229).

Humans ingest foods contaminated with flour beetles, their body parts, secretions, and fecal material. The importance of ingested flour beetle allergens has not been investigated. Allergic reactions to flour beetle allergens probably occurs from eating contaminated foods, but these reactions remain to be documented.

RICE WEEVILS

Allergic reactions to *Sitophilus granarius* are rarely reported even though this weevil is common in wheat. Circulating IgE and positive intracutaneous tests to *S. granarius* in bakery workers indicate that this pest is the source of allergenic molecules (133). Allergens from *S. granarius* undoubtedly are present in foods made from wheat contaminated with this pest. As with other stored-product insects, the importance of allergic reactions to rice weevil allergens in contaminated food is unknown.

STINGING INSECTS

Insects that sting humans include apids (honey bees and bumble bees), vespids (hornets, wasps, and yellow jackets), and formicids (fire and harvester ants). Venoms of apids, vespids, and formicids contain proteins that can cause IgE-mediated reactions. Both local and systemic IgE-mediated reactions may result from a sting. Local reactions are contiguous with the sting site, whereas systemic reactions are not (279). Sensitization to bee and wasp venoms requires only a single or few stings (73).

It is estimated that 0.3–3% of the U.S. population have allergic reactions, including anaphylaxis, to insect stings (139). However, prevalence of allergic reactions to insect stings is much higher in selected populations, such as beekeepers and people with a greater exposure to fire ants. Forty-two to 79% of beekeepers have honey bee venom-specific IgE (7, 162). However, sensitized beekeepers have higher serum

IgG and lower serum IgE than bee sting-sensitive nonbeekeepers (68). Systemic reactions to honey bee stings are 14–42% in beekeepers (7, 40, 41, 162). Annala et al. (7) reported from a survey of beekeepers that 26% had systemic reactions and 38% had large local reactions to honey bee stings, whereas similar reactions to wasp stings were only 2 and 13%, respectively. Likewise, stings from fire ants and allergic reactions are more prevalent in geographical areas where fire ants are endemic. Among the general population, the most common stings are from fire ants and yellow jackets.

Many patients are sensitive to multiple species of vespids (98, 109, 142, 214). Sensitivity to multiple species of stinging insects is not uncommon due to cross-reacting allergens or sensitivities to allergens of different species (243). In general, stinging insect allergens with >60% sequence homology are cross-reactive (145). In particular, various species of vespids (hornets, paper wasps, and yellow jackets) exhibit significant cross-reactivity because of the 60–92% amino acid sequence homology of some of the allergens (145). Overall, higher allergen sequence homology and cross-reactivity are associated with different species within a genus compared with species of different genera. Patients may not be sensitive to both bees (apids) and wasps (vespids) because most of the allergenic proteins from each group are unique. However, both honey bee and wasp venoms contain hyaluronidase with about 50% sequence homology, so cross-sensitizations and cross-reactions are possible.

Apids

Immunoblot studies of venom of the domestic honey bee, *Apis mellifera*, show it contains 10 proteins between 8 and 52 kDa that bind IgE in the sera of honey bee-venom-allergic patients (118). IgE binding profiles to these allergens vary between patients. In addition, honey bee venom contains other components such as apamin, mast cell-degranulating peptide, and histamine that may contribute to the allergic reaction. Four groups of allergens in honey bee venom (*A. mellifera*) have been characterized (73, 140, 145). The four allergens are Api m 1 (phospholipase A₂), Api m 2 (hyaluronidase), Api m 3 (acid phosphatase), and Api m 4 (melittin) (99, 140, 145, 279). Api m 1, Api m 2, and Api m 3 are 16-, 39-, and 43-kDa proteins, respectively. Api m 4 (melittin) is a small 3-kDa protein with only one epitope and is not a major allergen (141, 144).

Although bumble bee stings are not common, a few cases of allergic reactions to bumble bee stings have been reported (31, 61, 100, 148). Bumble bee (*Bombus pennsylvanicus*) venom contains Bom p 1 (phospholipase A₂) and Bom p 4 (protease). Api m 1 and Bom p 1 have high sequence homology but no homology with the allergen, phospholipase A₁, of the vespids. Allergen Api m 1 (phospholipase A₂) and Api m 2 (hyaluronidase) of honey bee venom show a high level of sequence identity with bumble bees (103, 104). Therefore, it is not surprising that bumble bee venom and honey bee venom contain some cross-reactive components (108). However, bumble bee venom contains some species-specific allergens absent from honey bee venom.

The relatively nonaggressive honey bees used for honey and beeswax production and pollination in the United States and Europe are the subspecies *A. mellifera ligustica* and *A. mellifera mellifera*. The aggressive Africanized bees or “killer bees” belong to the subspecies *A. mellifera scutellata*. These bees have migrated from Brazil northward through Central America and Mexico to the southern parts of California, Arizona, New Mexico, and Texas. These bees attack and sting a victim in large masses in comparison to the domestic bees. The venom content and volume of domestic and Africanized bees are similar. The allergens melittin, phospholipase A₂, and hyaluronidase in the venom of both the U.S. and Africanized bees are present in similar concentrations and quantity, and their comparable components are cross-reactive (189, 230, 231). These findings suggest that the number of stings and not the components of the venom of Africanized bees is responsible for the severe and sometimes fatal reactions (230).

Venom immunotherapy is effective for protection against honey bee stings. Venom-sensitive patients may need a modified schedule and dose for protection against the Africanized bees (230).

There are a few confirmed cases of allergic reactions to honey (167), but allergies to honey are rare (134). Honey contains pollens and glandular secretions from the bee. Reactions following ingestion of honey are thought to be due to proteins in the pollen and not to bee secretions. Royal jelly is a secretion of the hypopharyngeal and mandibular glands of honey bees. Humans consume royal jelly for its unproven medicinal benefits. Royal jelly is known to induce IgE-mediated asthmatic and anaphylactic reactions (44, 248, 249).

Vespid

White-faced hornet (*Dolichovespula maculata*) venom allergens include Dol m 1 (phospholipase A₁), Dol m 2 (hyaluronidase), and Dol m 5 (antigen 5) (143). European hornet (*Vespa crabro*) venom contains allergens Vesp c 1 (phospholipase A₁) and Vesp c 5 (antigen 5). Hornet antigen 5 has multiple epitopes (141). Paper wasp (*Polistes annularis*) venom contains the allergens Pol a 1 (phospholipase A₁), Pol a 2 (hyaluronidase), and Pol a 5 (antigen 5). Yellow jacket (*Vespula vulgaris*) venom contains Ves v 1 (phospholipase A₁), Ves v 2 (hyaluronidase), and Ves v 5 (antigen 5). These Group 1, 2, and 5 allergens of hornets, wasps, and yellow jackets are 34-, 38-, and 23-kDa proteins, respectively.

Yellow jacket (*V. vulgaris*) antigen 5 contains 204 amino acid residues and has 69% and 60% sequence homology with antigen 5 of the white-faced hornet, *D. maculata*, and the wasp, *Polistes annularis* (142). Likewise, yellow jacket hyaluronidase and phospholipase contain 331 and 300 amino acids, respectively, and they have 92% and 67% sequence homology with the comparable proteins of the white-faced hornet (142).

Yellow jacket and hornet allergens have more cross-reactivity than either of these species has with wasp allergens. Hyaluronidase allergens of the various species of yellow jackets show the greatest cross-reactivity in keeping with the greater sequence homology among species.

One to three Group 1 (phospholipase A₁), 2 (hyaluronidase), and 5 (antigen 5) allergens have been identified from venom of each of 14 or more different species of vespids (140). In addition to allergens of the species listed above, allergens have been characterized for yellow hornet (*Dolichovespula arenaria*), wasps (*Polistes dominulus*, *Polistes exclamans*, *Polistes fuscatus*, *Polistes metricus*), yellow jacket (*Vespula flavopilosa*, *Vespula germanica*, *Vespula maculifrons*, *Vespula pennsylvanica*, *Vespula squamosa*, *Vespula mandarinia*, *Vespula vidua*), and European hornet (*Vespa crabro*) (103–105, 110, 168).

Antigen 5 molecules of five vespid species have sequence homology with the fire ant allergen, Sol i 3 (102). Cross-reactivity of venom allergens with human protein may explain why sensitive people react to small amounts of venom allergens (139).

Fire Ants

The fire ants, *Solenopsis invicta* or *Solenopsis richteri*, inhabit portions of South America and the southeastern and south central parts of the United States. Their venom is the source of potent allergens. According to crossed-radioimmuno-electrophoresis (CRIE), extracts of the imported fire ant, *S. invicta*, contain 14 allergenic proteins when the gels were probed with serum from 24 subjects RAST positive to imported fire ants (190). Immunoblotting revealed binding of IgE to several protein bands with molecular weights ranging from 13 to 42 kDa. Four allergens, Sol i 1, Sol i 2, Sol i 3, and Sol i 4, have been isolated and purified from venom of the imported fire ant, *S. invicta* (106). Sol i 1 is known as phospholipase A₁ and is a 37-kDa allergen that appears to be cross-reactive with honey bee and/or vespid venoms (107). Sol i 2, 3, and 4 are proteins with molecular weights of 13, 24, and 13 kDa, respectively. Sol i 3 and Sol i 4 share 35% sequence homology (102). Sol i 3 shares 44–50% homology with 5 vespid venom antigen 5 molecules but limited IgE binding and cross-reactivity (102). Whole body extracts also contain the allergens present in the venom (194, 244).

A review of the records of 703 patients evaluated at Wilford Hall Medical Center Venom Clinic, a military hospital in San Antonio, Texas, between 1985 and 1995 showed that fire ants were responsible for 42% of the visits (81). Many of these patients received immunotherapy for fire ants. Immunotherapy for fire ants is widely practiced in states where fire ants are endemic (181). In a survey, Moffitt et al. (181) reported that of 329 allergists who responded to a survey, 96.7% treated fire ant sensitivity with immunotherapy.

SILKWORMS

Allergic reactions to silkworms, *Bombyx mori*, are not frequently reported, but clearly this insect is the source of allergens that induce IgE responses (96, 147, 149). Occupational exposure is the main source of atopy and asthma to silkworms (49). A main allergen of *B. mori* is in the wings (147). Komase et al. (149) found that 49% of 51 patients with house dust mite-sensitive allergic asthma in Japan had

specific IgE antibody to wing extract of the moth, *B. mori*, when measured by the Pharmacia CAP system (149). Immunoblotting using serum from these patients showed that 15 proteins bound IgE. The most frequent binding was to a 79-kDa protein followed by 72- and 82-kDa proteins.

Kino et al. (146) found that 69.6% and 53.6% of 56 randomly selected patients with asthma, but without any occupational exposure to insects, had intracutaneous reactions to silkworm wing and caddisfly wing extracts, respectively. In addition, 57.1% had positive intracutaneous reactions to a chironomid whole body extract. By RAST, IgE to silkworm wings, caddisfly wings, and chironomid whole bodies were detected in 82% (32 of 39), 83% (25 of 30), and 81% (26 of 32) of patients, respectively, with positive skin tests to silkworm.

There is evidence that components of the cocoon of silkworms are also allergenic. Vovolis & Galatas (270) reported a case of a 28-year-old with chronic rhinitis and asthma who handled cocoons while cutting them into shapes of butterflies and flowers. She had a strongly positive skin test to the outer surface of the cocoon. Her husband used cocoons in his art business that was located in their home. Her symptoms subsided and medication was discontinued a few months after the business was moved out of the house.

COCKROACHES

Cockroaches are common in human dwellings worldwide and are the sources of potent allergens. Allergy to cockroaches was first reported in 1964 by Bernton & Brown in New York (36), who showed that 40% of their asthmatic patients were sensitive to cockroaches. Since that time, many studies have shown that among exposed populations in the United States, China, Costa Rica, Hong Kong, Malaysia, Taiwan, Japan, and Europe, the sensitivity to cockroaches ranges from 23–60% (45, 88, 126, 127, 159, 160, 179, 227, 238, 240, 280). Among patients with atopic rhinitis, atopic dermatitis, and asthma, the prevalence of sensitivity to cockroach allergens in Italy, France, and Brazil is reported to be 12.5, 24.5, and 55%, respectively (37, 201, 223). Studies of inner-city areas of the United States reported that 36.8% of the children were allergic to cockroach allergens (219). In contrast, a cross-sectional study of schoolchildren, ages 5–11, living in Dresden, Germany, reported that 4.2% had specific IgE against the German cockroach (97).

Cockroach species known to be the sources of allergens include the Asian cockroach, *Blattella asahinai*; German cockroach, *Blattella germanica*; American cockroach, *Periplaneta americana*; and Oriental cockroach, *Blatta orientalis* (94, 128–130). The brown-banded cockroach, *Supella longipalpis*, commonly inhabits homes and is a potential source of allergens that has not been investigated. The cockroaches, *B. germanica* and *P. americana*, commonly found in human dwellings and schools worldwide, are the sources of many potent characterized allergens (53, 65, 125, 179, 208, 227, 265). Cockroach allergens are associated with fecal material, saliva, secretions (body washes), exoskeletons, and dead bodies (23). Extracts prepared from wash of bodies, dead bodies, exoskeletons, and feces

TABLE 1 Structure and function of cockroach allergens (51, 52, 93, 223, 226)

Source	Allergen	M.W. (kDa)	Frequency of reactivity (%)	Biologic function
<i>Blattella germanica</i>	Bla g 1	20–25	30–50	Unknown
	Bla g 1 (Bd90K)	90	77	Unknown
	Bla g 2	36	60	Binding protein (inactive aspartic proteinase)
	Bla g 4	18	40–60	Lipocalin (calyeyn)
	Bla g 5	23	70	Glutathione-S-transferase
	Bla g 6	18	50	Troponin C
<i>Periplaneta americana</i>	Per a 1	20–25	50	Unknown secreted into gut lumen
	Per a 3	72–78	100	Arylphorin-like protein
	Per a 7	33	50	Tropomyosin

all contain allergens (157, 180). The allergens Bla g 1, Bla g 1 (Bd 90k), Bla g 2, Bla g 4, Bla g 5, Bla g 6, Per a 1, Per a 3, and Per a 7 have been partially characterized (Table 1; 25, 26, 28, 93, 207, 226).

Bla g 1 and Per a 1 are cross-reactive and both show 30% homology with a protein secreted from blood-fed female *Anopheles gambiae* mosquitoes (178). Several of the other Bla and Per allergens show moderate homology to allergenic proteins including tropomyosins of dust mites, shrimp, and snails and glutathione-S-transferase of dust mites and insects (213). Recombinant Bla g 2, Bla g 4, Bla g 5, Per a 1, Per a 3, and Per a 7 have been produced (23), and some of these show biologic reactivity similar to the natural proteins (25, 260). However, possible use of recombinant cockroach allergens for diagnostic and immunotherapy purposes remains to be investigated and determined.

Cockroach allergy is associated with socioeconomic factors (6, 53, 59, 67, 182, 219). Exposure to cockroach allergen is reported to be a major risk factor for children with asthma in inner-city schools (45, 225). A study of inner-city residences in seven major urban areas of the United States found that Bla g 1 was the predominant indoor allergen compared with mite and cat allergens (65, 67, 219).

Litonjua et al. (165) reported that cockroach allergen exposure early in life was a predictor for development of asthma. A study by Huss et al. (112) suggested that the elimination or reduction of cockroach allergens in homes reduced the likelihood of children becoming sensitized. A related study of a birth cohort of children born from asthmatic or allergic parents living in metropolitan Boston found wheezing in the first year of life and T-lymphocyte proliferation by age two were associated with exposure to Bla g 1 and Bla g 2 during the first three months of life (80, 91).

Cockroach allergen-bearing particles are heavy and settle quickly, so little is airborne unless there is a disturbance (59). In a study in Strasbourg, France, Bla g 1 and Bla g 2 were measured in nine apartments by air sampling in kitchens, on kitchen surfaces (cabinets and floors), and on mattresses (59). High levels of Bla g 1 and Bla g 2 (3, 919, and 497 U/g of dust, respectively) were found in kitchen surface dust. Cockroach allergens were detectable in air samples during vigorous artificial disturbances but were undetectable 30 min after the disturbance. This rapid settling suggested that most cockroach allergens are mainly carried on particles $>10\text{ }\mu\text{m}$ in diameter. Likewise, air samples taken during disturbances from five cockroach-infested apartments in Blacksburg, Virginia, contained detectable levels of Bla g 1 and Bla g 2 (182). In the same study, surface dust from kitchen and living room floors contained significant amounts of Bla g 2. These results have been confirmed by De Lucca et al. (60) in a study conducted in Sydney, Australia. However, the study in Australia using intranasal and air samples also detected Bla g 1 in air when there was no disturbance or only quiet activity. This suggested that some allergens are carried on buoyant particles greater than $10\text{ }\mu\text{m}$ in diameter.

Cockroach allergen, Bla g 1, can be an important allergen in schools. The settled dust concentrations of Bla g 1 in four schools in Baltimore were investigated (224). Dust samples were obtained from floors in the four corners of classrooms, kitchens, lounges, cafeterias, libraries, hallways, offices, and gymnasiums over a 3-week period. Significant levels of Bla g 1 were found in all schools with high sample concentrations of 591, 51, 170, and 176 U/g of dust for the four schools. Twenty-nine of 98 classrooms sampled had Bla g 1 concentrations above detectable levels. Bla g 1 levels greater than 1 U/g of settled dust are clinically significant (92, 224). Bla g 1 levels were greater than 1 U/g of dust in more than two thirds of the 147 dust samples collected from the four schools.

The threshold levels of exposure for sensitization and symptoms are 2 U and 8 U of allergen per gram of settled dust, respectively (23, 240). It seems logical that by extermination of cockroaches and rigorous cleaning, the cockroach allergen levels in infested homes, schools, and other buildings can be reduced to clinically insignificant levels. However, few intervention studies have been conducted. In the National Cooperative Inner City Asthma Study, cockroach allergen treatment did not result in reduced cockroach allergen concentrations (89). An outline of an intervention program for elimination of cockroaches and removal of allergens in homes is provided by Eggleston & Arruda and Liccardi (66, 160).

MISCELLANEOUS INSECTS

Kissing Bugs

The saliva of *Triatoma* sp. contains allergenic proteins and can induce local allergic and anaphylactic reactions when they feed on humans (101). The allergens of *Triatoma protracta* and *Triatoma rubra* are species specific (171, 202).

Silverfish

Silverfish in house dust may be the source of allergens. Witteman et al. (273) found that house dust mite-sensitive patients had serum IgE that bound to proteins of silverfish (*Lepisma saccharina*). RAST inhibition studies showed that silverfish protein binding was inhibited to a variable degree in different patients by proteins in mite extract. This suggested that IgE recognized cross-reacting epitopes between house dust mites and silverfish. However, the variable degree of inhibition also suggested some specific silverfish epitopes on these allergens. Immunoblotting has shown specific IgE to proteins of the silverfish, *Cyenolepism longicaudata* (30).

Caddisflies

Positive RAST to caddisfly wing extract is frequent in Japan (146).

Moths

Immunoblotting has shown specific IgE to proteins of 30 kDa from the clothes moth, *Tineola bisselliella*, and the warehouse moth, *Ephestia cautella*.

Deer Flies and Bedbugs

The bite of deer flies (*Tabanus* sp.) and bedbugs (*Cimex* sp.) can cause local and systemic allergic reactions (272, 279).

Caterpillars

The pine processionary caterpillars (*Thaumetopoea pityocampa*) and other caterpillars can cause contact dermatitis, conjunctivitis, and IgE-mediated anaphylactic reactions (62, 63, 154, 269). The allergenic IgE-binding proteins are thaumetopoein (28 kDa) (153) and a 45-kDa protein (269).

It is not unusual for children to put caterpillars into their mouths or even ingest these lepidopteran larvae and have adverse reactions (203). It is not known if any aspects of these reactions involve IgE-mediated allergic reactions.

DUST AND STORAGE MITES

Dust mites are common in homes worldwide, and many species are the sources of potent allergens. Many species of stored-product mites occur in both residential and occupational environments and in processed foods and can cause allergic disease. In addition, humans may contact or be exposed to predaceous mites and parasitic mites of plants and animals that are also the sources of allergens that induce allergic disease. Information concerning elimination and/or avoidance of dust mites and their allergens is not discussed in this review. For information on these topics the reader is directed to several reviews (16, 77, 206, 254).

The most common mites found in homes in temperate climates are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. In temperate climates, these mites show pronounced seasonal fluctuations with high densities occurring during the humid summer months and lower densities during the winter months when indoor relative humidity is typically below 50% owing to the use of forced air heating (10, 22, 55, 204). In subtropical climates, seasonal fluctuations of these mites are less pronounced. Surveys in the United States and Europe show that 20–35% of allergic individuals are sensitive to the dust mites, *D. farinae* and *D. pteronyssinus*.

Euroglyphus maynei and *Blomia tropicalis* occur in some homes in temperate climates and occasionally may be as prevalent as *Dermatophagoides* sp. However, *B. tropicalis* is most prevalent and often the predominant species in homes in tropical climates. In homes in tropical areas such as Barbados, Costa Rica, Malaysia, Brazil, Columbia, and Venezuela, the predominant mite species in homes are *B. tropicalis* and *D. pteronyssinus* (75).

Most homes inhabited by dust mites contain multiple species of mites. However, the predominant species varies between homes within a geographical area and between geographical areas. In the United States, Arlian et al. (9) found in a survey of 252 homes in 8 different temperate and subtropical geographical areas that 82% were coinhabited by both *D. farinae* and *D. pteronyssinus*; however, the predominant species within a home varied. *Dermatophagoides* sp. mites were the predominant species in 247 homes, whereas *E. maynei* was predominant in 5. *D. farinae*, *D. pteronyssinus*, and *E. maynei* were present in 36% of the homes sampled in New Orleans, Galveston, Memphis, Delray Beach, and San Diego. *B. tropicalis* also was present in 15% of the homes in the subtropical locations.

Large numbers of storage mites such as *Tyrophagus putrescentiae* and *Lepidoglyphus destructor* may occasionally occur in houses (75). Sensitization to storage mites in urban dwellers has been reported in Spain, Denmark, Germany, and the United States (64, 76, 86, 150, 169, 221). Generally, the role of storage mites in sensitizing and causing allergy in an urban setting is not known.

Many species of storage mites are found in processed foods (flour, boxed baking mixes such as cakes, pancakes, and beignets); in stored hay, grain and straw; in dust in grain and hay storage; and livestock feeding facilities. Exposure to storage mite allergens can be by ingestion or by inhalation. Several studies report anaphylactic reactions after patients consumed beignets, cakes, pancakes, pizza, pasta, cornmeal cakes, and bread made from ingredients contaminated with mites (38, 70, 174, 222, 239). The importance of storage mites as ingested or aeroallergens in the urban population has not been studied extensively.

The greatest exposure to storage mites usually occurs in an occupational setting where allergies to storage mites are of major importance (262). Van Hage-Hamsten et al. (262) reported that 12% of 440 farmers tested were sensitive to the storage mites *Acarus siro*, *L. destructor*, *T. putrescentiae*, and *Glycyphagus domesticus*. Marx et al. (173) reported that sensitization to storage mites was common in a population of dairy farmers in Wisconsin. Similar sensitivities to storage mites have

been reported for farmers in Scotland (57, 113). Important storage mite species in occupational settings are *L. destructor*, *G. domesticus*, *A. siro*, *T. putrescentiae*, *Tyrophagus longior*, *Aleuroglyphus ovatus*, *Suidasia medanensis*, *Chortoglyphus arcuatus*, and *Carpoglyphus* sp.

CRIE studies show that *D. farinae* and *D. pteronyssinus* are each the source of at least 15 allergens (11, 12). CRIE and immunoblotting studies clearly show that there is a high degree of variability both between and within individuals in terms of their sensitivity and reactivity to these allergens. For any given patient, some allergens are more potent than others. Different patients recognize different numbers of allergens, and the allergens have different potencies for different individuals (11, 12). However, some of the allergens are recognized by most (>80%) mite-sensitive patients (Table 2).

Most sera from dust mite-sensitive patients contain IgE that reacts with proteins in extracts of both *D. farinae* and *D. pteronyssinus*. This can indicate that the patients are sensitized to specific allergens (epitopes) of each species or that the patients were sensitized to one species but reacted to cross-reactive epitopes on allergens of the other species. Heterologous crossed-immunoelectrophoresis (CIE) and CRIE studies clearly show that *D. farinae* and *D. pteronyssinus* extracts contain at least nine cross-reacting allergens (13). Monoclonal antibodies have been produced that recognize a common epitope present on both Der p 2 and Der f 2. Conversely, monoclonals have also been produced that specifically recognize an epitope unique either to Der f 1 or Der p 1, Der f 2 or Der p 2, or to Der f 1 or Der f 2. These monoclonal antibodies are now used to determine the relative amounts of dust mite allergen in sampled house dust.

CRIE analysis using sera of patients RAST positive to *E. maynei* identified 15 allergens (17). Six and four of these cross-reacted with *D. pteronyssinus* and *D. farinae*, respectively, using heterologous CRIE. IEF coupled with SDS-PAGE and immunoblotting has shown that there were 47 allergenic peptides with pIs of 4.8–8.0 and molecular weights between 10 and 180 kDa (184). A 14-kDa peptide (designated Eur m 2) was recognized by the monoclonal antibody 1D8 that also recognizes an epitope on Der p 2 and Der f 2 (193). Thus, Der p 2, Der f 2, and Eur m 2 all share a common epitope. Two other monoclonals, 7A1 and DpX, that recognize epitopes on Der f 2 and Der p 2, respectively, did not recognize the 14-kDa peptide of Eur m 2 (184).

B. tropicalis is the source of many allergens (19). The majority of patients in countries where *B. tropicalis* and *D. pteronyssinus* are prevalent are sensitized to both mites (27, 47). A number of studies have shown that sensitivity was due to cross-reactivity of the allergens from the two species as well as to species-specific allergens. Fluorescent allergosorbent inhibition test (FAST) and CRIE showed there is low to moderate cross-reactivity between *B. tropicalis* and *D. pteronyssinus* (54). Dot blot inhibition studies showed little cross-reactivity between proteins in a crude extract of *B. tropicalis* and *D. pteronyssinus* proteins (whole body extract), Der p 1, Der p 2, and Der p 5. Likewise, there is little cross-reactivity between Blo t 5 and Der p 5 despite sharing 43% sequence homology (27). Immunogenic

TABLE 2 Characterized house dust mite allergens and percent patient reactivity to them

Allergen group	Specific allergens characterized	M.W. (kDa)	Frequency of reactivity (%)*	Homology
Grp 1	Der f 1, Der p 1, Eur m 1, Der m 1	25	>90 (205, 241)	Cysteine protease, homology similar to enzymes papain, actinidin, cathepsin H & B, bromelain, frein
Grp 2	Der f 2, Der p 2, Eur m 2, Tyr p 2, Lep d 2	14	>90 (205, 241)	Homology with primate epididymal or insect molting protein
Grp 3	Der f 3, Der p 3, Eur m 3	28–30	57–>90 (241, 242)	Trypsin-like serine protease
Grp 4	Der f 4, Der p 4	56–63	25–46 (152)	Amylase
Grp 5	Der p 5, Blo t 5	14–15	45–60 (163, 256)	Unknown
Grp 6	Der f 6, Der p 6	25	40–60 (235)	Chymotrypsin-like serine protease
Grp 7	Der f 7, Der p 7	22–28	50 (236)	Unknown
Grp 8	Der p 8	25–26	40 (192)	Rat & mouse glutathione-S-transferase
Grp 9	Der f 9, Der p 9	24–28	80 (138)	Collagenolytic serine protease
Grp 10	Der p 10	33–37	>60 (3)	Melanogaster, rabbit & human alfa-tropomyosin
Grp 11	Der f 11	98	High (259)	Paramyosin
Grp 12	Blo t 12	14	50 (210)	Unknown
Grp 13	Blo t 13	15–17	10 (48)	Cytosolic fatty acid-binding proteins
Grp 14	Der f 15, Der p 15, Eur m 15	177–190	70 (69)	Apolipoprotein-like protein

Der f, *Dermatophagoides farinae*; Der p, *Dermatophagoides pteronyssinus*; Eur m, *Euroglyphus maynei*; Blo t, *Blomia tropicalis*; Lep d, *Lepidoglyphus destructor*.

*References given in parentheses.

comparison of crude *B. tropicalis*, *D. pteronyssinus*, recombinant Blo t 5 (rBlo t 5), and Der p 1 (rDer p 1) suggests *B. tropicalis* has unique epitopes and causes species-specific sensitization in areas where it is found (28). Other studies have shown low to moderate cross-reactivity between *B. tropicalis* and *Dermatophagoides* sp. (78, 166). In addition, Blo t 5 is cross-reactive with rLep d 2 (121).

There is little cross-reactivity between allergens of pyroglyphid mites and storage mites. CRIE analysis of *T. putrescentiae* extract utilizing sera from 24 occupationally exposed farmers identified 14 allergens (21). The number of individual

allergens recognized by each patient ranged from 5 to 11. Five allergens were recognized by all of the farmers' sera. The number of allergens recognized and the sensitivity to individual allergens varied between patients. Immunoblotting using sera of farmers identified a 16-kDa protein as a major IgE-binding component of *T. putrescentiae* extract (119). Heterologous CIE and CRIE showed that few allergens of *T. putrescentiae* cross-react with those of *D. farinae* and *D. pteronyssinus* (14). Tyr p 2 is a major allergen of *T. putrescentiae*. Tyr p 2 shows more than 50% sequence identity with Lep d 2 and about 40% with *Dermatophagoides* sp. (72).

L. destructor is a common allergy-causing mite found on farms (261). The major allergen of *L. destructor* (Lep d 2) shares at least one allergenic determinant with the 24-kDa allergen of *D. pteronyssinus* (119, 261). Lep d 2 shows more than 50% sequence identity with Group 2 allergens from *Dermatophagoides* sp. (120). However there is limited allergenic cross-reactivity between Lep d 2 and *D. pteronyssinus*. A recombinant Lep d 2 has been produced that gives skin test responses similar to those obtained with the whole extract. Immunostaining of frozen sections suggests the allergen could be associated with the digestive tract.

In addition to those discussed above, a limited number of recombinant mite allergens have been produced. Many of these recombinants show comparable IgE binding and skin test reactivity to their natural counterparts (51). Recombinant allergens have the potential to be used to make defined reagents with uniform allergen levels for allergy diagnosis (skin and RAST) and treatment (immunotherapy) (24, 50, 51, 123, 252).

CHARACTERISTICS OF MITE ALLERGENS

Fourteen groups of mite allergens have been isolated, biochemically characterized, and/or cloned, and for some the three-dimensional structure has been modeled. (Table 2; 1, 51, 187, 209, 253). Many of these allergens are major allergens and bind serum IgE from >50% of RAST-positive mite-sensitive patients.

Group 1 allergens are glycoproteins with cysteine protease that originate from cells lining the intestinal tract of the mite (241, 250, 255). Thus, mite fecal material is rich in Group 1 allergens. Der f 1 and Der p 1 exhibit 80% sequence homology and have both cross-reactive and species-specific epitopes. Most Group 2 allergens are nonglycosylated proteins associated with secretions from the male mite's reproductive tract or insect molting proteins (95, 164, 251, 277). Der f 2 and Der p 2 show 88% sequence homology and have some cross-reactive as well as species-specific epitopes. Lep d 2 is associated with the gut and other areas of the mite's anatomy (268). Group 3 allergens are trypsin-like enzymes with 25–30-kDa molecular weight (242). N-terminal sequences of Der f 3 and Der p 3 show about 85% homology (242). Group 4 allergens are 56–63-kDa proteins that show homology to amylase (152).

Group 5 allergens are 14–15 kDa (163, 256). Blo t 5 has 43% sequence homology with Der p 5 (27, 46). Their sequence is not homologous to other known

proteins. Group 6 allergens are 25-kDa serine proteases with activity similar to the serine protease chymotrypsin of both vertebrates and invertebrates (276). Der p 6 and Der f 6 have similar homology. In addition to sharing homology with Der f 6, Der p 6 also shows 37% homology with Der p 3 (276). The Group 7 allergens are Der p 7 and Der f 7 and have unknown homologies. Although their source is unknown, the two allergens are cross-reactive and have 86% sequence homology (235, 236). Group 8 allergens are proteins related to tropomyosin (3, 29). Der p 8 has strong homology with rat and mouse glutathione-S-transferase (192).

The Group 9 allergen, Der p 9, is a 24–29-kDa allergen with collagenolytic activity (138). Group 10 allergen, Der p 10, is mite tropomyosin but has sequence homology with alpha-tropomyosin of humans, rabbits, and fruit flies (29, 172). Tropomyosin is also a major allergen from shrimp, snails, and cockroaches (58, 158, 233). The protein Der f 10 is also a protein with homology to tropomyosin and is cross-reactive with tropomyosin of crustaceans (shrimp), mollusks (snails), chironomids, mosquitoes, and cockroaches (3). This cross-reactivity may explain the allergic reaction experienced by house dust mite-allergic patients or patients on mite immunotherapy after they ingest shrimp or snails (51, 264). Invertebrate tropomyosins have approximately 80% sequence homology with mammalian tropomyosins but show little cross-reactivity with them.

Group 11 allergen, Der f 11, is a paramyosin-like protein of muscle. Group 12 allergen, Blo t 12, is not homologous to other known proteins (210), whereas Group 13 allergen, Blo t 13, is similar to cytosolic fatty acid-binding proteins.

Most house dust mite allergens have molecular weights between 10–50 kDa (Table 2). Recently, two new larger molecular weight Group 14 allergens have been identified by cDNA clones and designated as Mag 1 and Mag 3 (4, 69, 82). These results confirm previous blot studies that identified some large molecular weight IgE-binding proteins in extracts made from the bodies and feces of *E. maynei*, *D. farinae*, and *D. pteronyssinus* (18, 20, 184). Both Mag 1 and Mag 2 are fragments of a high-molecular weight molecule of *D. farinae*, *D. pteronyssinus*, and *E. maynei*. Mag 3 (M177) has homology with the lipid transport apolipoproteins and shares some structural homology with the egg yolk protein vitellogenin. It is recognized by more than 70% of mite-allergic patients. Breakdown of the protein yields peptides with stronger IgE binding than does the complete protein (83). Two fragment peptides of Mag 3 have molecular weights of 80–83 kDa and 95–101 kDa, respectively (69).

PHYTOPHAGOUS, PREDACEOUS, AND PARASITIC MITES

Mites are ubiquitous and thrive in many diverse environments. Thus, humans contact many species of mites and their products in their daily lives (8). The role of these less-known mites in causing allergic disease is not yet known.

Phytophagous mites of fruit trees; vegetable crops; and yard, greenhouse, and house plants can cause allergic disease in at-risk populations (135, 151, 156). A

study of 725 Korean farmers working in apple orchards found that 23.2% and 21.2% were sensitive based on skin tests to the two-spotted spider mite, *Tetranychus urticae*, and the European red mite, *Panonychus ulmi*, respectively (135). In this study population, the prevalence of sensitivity to these mites was greater than it was to the house dust mites, *D. farinae* and *D. pteronyssinus*. Another study by this group found that skin tests of 14.2% of 1055 children living around citrus orchards were positive to *P. ulmi* (156).

Predaceous mites, such as *Phytoseiulus persimilis* and *Amblyseius cucumeris*, that feed on spider mites and larvae of thrips, respectively, can sensitize greenhouse workers (263). This raises the possibility that predaceous mites, used for biological control of pest species in fields and orchards, may be important sources of allergens for gardeners, farmers, and people living around fields and orchards.

Hemisarcoptes cooremani that feeds on scale insects that parasitize trees and shrubs in orchards, yards, and gardens can induce allergic disease (15). Immunoblotting of extracts of this mite showed that they contain 16- and 19-kDa proteins that bound IgE in the serum of an exposed and symptomatic individual.

The saliva of ticks in the family Ixodidae contains immunogenic proteins that can induce IgE-mediated reactions while they feed (2, 42, 87, 266, 267). Cases of anaphylactic reactions from a tick bite have been reported. Proteins of 80, 37, 35, 25, and 20 kDa in an extract made from *Rhipicephalus* sp. bound IgE in the sera of a goat herder who suffered an anaphylactic reaction to a bite of this tick.

Molecules from *Sarcoptes scabiei*, which burrow in the stratum corneum of the skin, induce IgE production and an IgE-mediated reaction in some parasitized human hosts (74, 185). This mite is the source of 12 antigens, seven of which bind IgE in the sera of scabies-infested patients (183, 185). Many of these immunogens are cross-reactive with antigens of the dust mites, *D. farinae* and *D. pteronyssinus* (18, 20).

The capability of mites, such as follicle mites, chicken mites, and sheep scab mites, inducing IgE reactions in humans needs to be investigated.

CONCLUSION

The saliva of parasitic insects and mites/ticks and the venom of stinging insects contain an array of immunogenic, immune-modulating, and other pharmacologically active molecules. In addition, body secretions, saliva, excreta, exoskeletons and disintegrating bodies, and body parts of nonparasitic insects and mites contain molecules that induce immunogenic responses in humans. Many molecules from insects and mites that are injected, contacted, or inhaled can sensitize and induce IgE-mediated allergic reactions in humans. For some species of dust and storage mites, cockroaches, and Hymenoptera (bees, wasps, ants), many of the IgE-inducing molecules have been immunobiochemically characterized and even produced by recombinant methods. However, for most insect and mite species (e.g., biting flies, fleas, lice, chiggers, predaceous mites, parasitic mites of plants,

parasitic mites, and ticks of birds and mammals that bite humans), neither the allergic reactions to them nor the molecules that induce the allergic reaction have been characterized. This is an area of research with great opportunity for medical entomologists.

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CONTENTS

ROSS RIVER VIRUS: ECOLOGY AND DISTRIBUTION, <i>Richard C. Russell</i>	1
BIOLOGY AND MANAGEMENT OF THE SMOKYBROWN COCKROACH, <i>Arthur G. Appel and Lane M. Smith II</i>	33
SEQUESTRATION OF DEFENSIVE SUBSTANCES FROM PLANTS BY LEPIDOPTERA, <i>Ritsuo Nishida</i>	57
REGULATION OF DIAPAUSE, <i>David L. Denlinger</i>	93
BACTERIAL SYMBIONTS OF THE TRIATOMINAE AND THEIR POTENTIAL USE IN CONTROL OF CHAGAS DISEASE TRANSMISSION, <i>C. Ben Beard,</i> <i>Celia Cordon-Rosales, and Ravi V. Durvasula</i>	123
STRATEGIES AND STATISTICS OF SAMPLING FOR RARE INDIVIDUALS, <i>Robert C. Venette, Roger D. Moon, and William D. Hutchison</i>	143
BIOLOGY AND MANAGEMENT OF THE JAPANESE BEETLE, <i>Daniel A.</i> <i>Potter and David W. Held</i>	175
BIOLOGY AND ECOLOGY OF HIGHER DIPTERA FROM FRESHWATER WETLANDS, <i>Joe B. Keiper, William E. Walton, and Benjamin A. Foote</i>	207
INVASIONS BY INSECT VECTORS OF HUMAN DISEASE, <i>L. Philip Lounibos</i>	233
OMNIVORY IN TERRESTRIAL ARTHROPODS: MIXING PLANT AND PREY DIETS, <i>Moshe Coll and Moshe Guershon</i>	267
HOW TO BE A FIG WASP, <i>George D. Weiblen</i>	299
ALTERNATIVES TO METHYL BROMIDE TREATMENTS FOR STORED-PRODUCT AND QUARANTINE INSECTS, <i>Paul G. Fields</i> <i>and Noel D. G. White</i>	331
ECOLOGY AND BEHAVIOR OF FIRST INSTAR LARVAL LEPIDOPTERA, <i>Myron P. Zalucki, Anthony R. Clarke, and Stephen B. Malcolm</i>	361
ARTHROPOD ALLERGENS AND HUMAN HEALTH, <i>Larry G. Arlian</i>	395
COMPETITIVE DISPLACEMENT AMONG INSECTS AND ARACHNIDS, <i>Stuart R. Reitz and John T. Trumble</i>	435
ENDOCRINE INSIGHTS INTO THE EVOLUTION OF METAMORPHOSIS IN INSECTS, <i>James W. Truman and Lynn M. Riddiford</i>	467
BIOCHEMISTRY AND GENETICS OF INSECT RESISTANCE TO <i>BACILLUS THURINGIENSIS</i> , <i>Juan Ferré and Jeroen Van Rie</i>	501

IRON METABOLISM IN INSECTS, <i>Helen Nichol, John H. Law, and Joy J. Winzerling</i>	535
CAN GENERALIST PREDATORS BE EFFECTIVE BIOCONTROL AGENTS?, <i>W. O. C. Symondson, K. D. Sunderland, and M. H. Greenstone</i>	561
ARTHROPODS ON ISLANDS: COLONIZATION, SPECIATION, AND CONSERVATION, <i>Rosemary G. Gillespie and George K. Roderick</i>	595
THE POPULATION BIOLOGY OF OAK GALL WASPS (HYMENOPTERA: CYNIPIDAE), <i>Graham N. Stone, Karsten Schönrogge, Rachel J. Atkinson, David Bellido, and Juli Pujade-Villar</i>	633
SHORT, LONG, AND BEYOND: MOLECULAR AND EMBRYOLOGICAL APPROACHES TO INSECT SEGMENTATION, <i>Gregory K. Davis and Nipam H. Patel</i>	669
BIOLOGY AND MANAGEMENT OF ECONOMICALLY IMPORTANT LEPIDOPTERAN CEREAL STEM BORERS IN AFRICA, <i>Rami Kfir, W. A. Overholt, Z. R. Khan, and A. Polaszek</i>	701
THE ECOLOGY AND EVOLUTION OF ANT ASSOCIATION IN THE LYCAENIDAE (LEPIDOPTERA), <i>Naomi E. Pierce, Michael F. Braby, Alan Heath, David J. Lohman, John Mathew, Douglas B. Rand, and Mark A. Travassos</i>	733
SYMPATRIC SPECIATION IN PHYTOPHAGOUS INSECTS: MOVING BEYOND CONTROVERSY?, <i>Stewart H. Berlocher and Jeffrey L. Feder</i>	773
HOST PLANT QUALITY AND FECUNDITY IN HERBIVOROUS INSECTS, <i>Caroline S. Awmack and Simon R. Leather</i>	817
ECONOMIC, ECOLOGICAL, FOOD SAFETY, AND SOCIAL CONSEQUENCES OF THE DEPLOYMENT OF BT TRANSGENIC PLANTS, <i>A. M. Shelton, J.-Z. Zhao, and R. T. Roush</i>	845
CONTROL AND BIOCHEMICAL NATURE OF THE ECDYSTEROIDOGENIC PATHWAY, <i>Lawrence I. Gilbert, Robert Rybczynski, and James T. Warren</i>	883
THE BIOLOGY OF THE DANCE LANGUAGE, <i>Fred C. Dyer</i>	917
INDEXES	
Subject Index	951
Cumulative Index of Contributing Authors, Volumes 38–47	987
Cumulative Index of Chapter Titles, Volumes 38–47	991

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