

Inhalant Allergy to Arthropods

Insects, Arachnids, and Crustaceans

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INTRODUCTION TO ARTHROPODS

Respirable materials from plants and animals are well known irritants of humankind, and may cause allergic rhinitis, allergic conjunctivitis, or asthma in susceptible individuals. Arthropods, or creatures with jointed legs, constitute 75% of the known animal species, and they may constitute the source of the most significant amount of organic matter available for airborne dispersal. It has been estimated that there are six million species in the Phylum Arthropoda, and of those identified, 90% have been characterized in the Class Insecta (Table 1).

The human immune response to arthropods depends in large part upon the way in which the antigen is delivered to the immune network. Therefore, antigens presented orally (crustaceans), inhaled (insect debris), or injected (Hymenoptera) will result in individually specific immune responses to offending antigens/allergens. What follows is a clinical review of inhalant allergy to insects, arachnids, and crustaceans with special attention to the problems of arthropod extraction, extract composition and standardization, and arthropod crossreactivity.

Table 1
Arthropod Classifications

Kingdom	ANIMAL	
Phylum	ARTHROPODA	
Subphylum	TRILOBITOMORPHA (extinct)	
Subphylum	MANDIBULATA	
Class	<i>Myriapods</i> (centipedes, millipedes)	
Class	<i>Collembola</i> (springtails)	
Class	<i>Crustacea</i> (crabs, lobsters, shrimps, crayfish)	
Class	<i>Insecta</i>	
Order	Coleoptera	(beetles, grain weevil)
Order	Ephemeroptera	(mayflies)
Order	Orthoptera	(cockroaches, crickets)
Order	Lepidoptera	(moths, butterflies)
Order	Trichoptera	(caddisflies)
Order	Diptera	(flies, midges, mosquitoes)
Order	Hemiptera	(bed, kissing, and assassin bugs)
Order	Siphonaptera	(fleas)
Order	Hymenoptera	
Family	Formicidae	(ants)
Family	Vespidae	(wasps, hornets, yellow jackets)
Family	Apidae	(bees)
Subphylum	CHELICERATA	
Class	<i>Merostomata</i>	
Class	<i>Pycnogonida</i>	(sea spiders)
Class	<i>Arachnida</i>	
Subclass	Araneida	(spiders)
Subclass	Opiliones	(daddy longlegs, harvestmen)
Subclass	Scorpionida	(scorpions)
Subclass	Acarina	(mites, ticks)
Order	Parasitiformes	(hard ticks)
Order	Trombidiformes	(demodex)
Order	Sarcoptiformes	
Suborder	Acaridiae	
Family	Pyroglyphidae	(house dust mite)
Family	Tyroglyphidae	(storage mites)
Family	Sarcoptidae	(itch mite)

CLINICAL FEATURES

The clinical diagnosis of inhalant allergy to arthropods is not distinguishable from pollen or mold allergy by history alone. Symptoms of asthma, allergic rhinitis, or allergic conjunctivitis may be seasonal (vast aquatic insect emergences; e.g., caddis-

flies) or perennial (predominant terrestrial infestations, e.g., cockroaches). Historical information from the patient is helpful when the source of the arthropod allergen is visible, such as the presence of cockroaches, ants, or mayflies. Most often, however, the arthropod allergens are invisible because they have become part of the respirable dust to which the patient is exposed. Occasionally, symptoms of arthropod-induced allergy will continue beyond the apparent seasonal appearance of a particular insect. This may be explained by the persistence of insect allergen as part of the dust of the local environment, depending on the stability of a given insect or arachnid allergen.

The local inflammatory response to arthropodan allergens and the disease one gets depend on both the intensity and anatomical location of exposure and the specific nature of that local immune response. Human immune defenses respond to arthropodan antigens when they are presented to the skin (contact), the sinopulmonary tract (airborne), the circulatory system (biting, stinging) and the gastrointestinal tract (oral). IgE mediated responses occurring in the skin, eye, or lung may result in symptoms of hives, conjunctivitis, and asthma, respectively (Table 2). More often than not, arthropod-human interaction does not cause disease. However, it may result in immunization, and this may explain the frequent finding of arthropod-specific IgG antibodies in both normal and atopic populations.

Skin testing with arthropodan extracts must be considered in all patients presenting with symptoms of inhalant allergy. The clinician must select the necessary allergens based on studies of the insect, arachnid, and crustacean fauna in the local environment.

As will be discussed, commercial arthropod products may contain extraneous material, inappropriate allergens, and may be less potent than the arthropod extract produced from local materials. When testing, care should be taken not to exceed 1:1000 weight-to-volume concentrations, since nonspecific skin irritants may be present. Also, arthropod allergens can be quite potent, and they may induce anaphylaxis in extremely sensitive subjects. As with other allergic conditions, the diagnosis of inhalant arthropod allergy cannot be made by serum RAST or ELISA studies alone.

Table 2
Human-Arthropod Interactions

Organ system	Route exposure	Immune response	symptoms	Immunologic disease
Epidermis	Contact	Cellular, IgE	Pruritus, raised scaling rash	Eczema
		IgE	Pruritus	Hives
		IgE, cellular	Linear, pruritic burrows	Scabies
	Biting	Cellular, IgE	Localized, delayed edema, and pruritus	Cutaneous Basophil hypersensitivity
Sino-pulmonary	Airborne	IgE	Rhinorrhea, sneezing	Allergic rhinitis
Circulatory	Biting, stinging		Wheezing, cough	Asthma
		IgE	Fever, arthralgia, erythema	Serum sickness
		IgE	Pruritus, shock	Systemic anaphylaxis
Gastro-intestinal	Oral	IgE	Diarrhea, distention, cramps, hives	Food allergy
Ocular	Airborne	IgE	Itching, burning	Allergic conjunctivitis

PREVALENCE OF ARTHROPOD HYPERSENSITIVITY

Inhalant allergy to arthropods was first recognized in 1913, when Wilson reported the case of a patient experiencing coryza and lacrimation in the months of May and June when exposed to swarms of mayflies, or "Canada soliders" as they were then known (1). Wilson used a single insect together with 2 cc of sterile saline to produce an extract for an ophthalmic challenge (1:2000 weight-to-volume). In his words, "The reaction in the patient's eye from the experiment was so great, and was attended with so much physical distress for from 24 to 26 hours, that no subsequent experiments have been attempted." This rather exciting beginning stimulated other physicians to investigate the relationship between inhalant allergy symptoms and arthropod exposures.

The rediscovery of inhalant arthropod allergy has a periodicity of nearly 20 years in the medical literature, because in 1929, Figley (2) reported four cases of mayfly-induced asthma and allergic rhinitis. One of Figley's patients was successfully desensitized using an aqueous extract of dried insects reaching a maintenance dose of 0.3 cc of a 1:30 weight-to-volume solution. Also, in 1929, Parlato (3) related the first of his studies on caddisfly-induced atopy. Osgood (4), in the 1950s, and Shulman and Arbesman (5) in the 1960s, extended Parlato's initial observations.

A number of studies have shown that the incidence of arthropod allergy in atopic populations ranges from 28 to 70%. Feinberg et al. (6) and Wiseman et al. (7) demonstrated that 50–60% of the North American atopic patients possessed skin test reactivity to inhalant arthropod allergens. In Wiseman's report, 195 of 328 atopic patients demonstrated at least a 1+ skin test to several of the 27 different species of arthropods evaluated. Prevalence studies in India by Shivpuri et al. (8) and in Central America by Benaim Pinto (9), established arthropods as clinically significant sources of inhalant allergens.

Occupational settings provide the more obvious illustrations of inhalant arthropod allergy. Ramazzini, in 1713, was the first to emphasize the ill effects of arthropodan-human interaction in grain handlers (10). Wirtz studied entomology personnel by questionnaire and found 115 individuals experiencing allergy symptoms due to arthropods (11). Forty-six of these entomology workers needed to change their studies to a different arthropod as a result of their atopic symptoms. Kagen et al. (12) found that nearly 40% of a work force exposed to caddisfly aeroallergens possessed both allergy symptoms and insect-specific IgE.

Taken together, these studies confirm the clinically significant contribution of arthropods toward the induction of inhalant allergy. Prior reviews of this subject also document this conclusion (13–18), as has been reviewed by Schwartz in this publication.

INHALANT ALLERGY TO INSECTS

As discussed above, the Class Insecta comprises 90% of the known arthropods; caddisflies, mayflies, midges, cockroaches,

moths, and beetles have all been proven to cause inhalant allergy. Since the review by Shulman (14), in 1967, newer techniques in immunology and aerobiology have been applied to the study of inhalant arthropod allergy. The following discussions will focus on the caddisfly because of its historical importance and its well established role in inhalant allergy.

TRICHOPTERA

Caddisflies

Caddisflies are small, inconspicuous insects that superficially resemble small moths. They are universally distributed, and several thousand species have been described. Most of their existence finds them submerged in streams as worm-like larvae, surviving by spinning silken nets to catch their food. The type of net that a given species spins determines its waterway location. A rigid, fine mesh catching net allows survival in rapid currents where smaller, pulverized organic matter occurs; whereas loose, voluminous net spinners are present in tail waters and moderate currents where larger particles exist (19,20).

Matings occur during emergences of caddisflies in May, June, and July, and are associated with both visible and invisible problems. The tremendous insect numbers in a hatch create visible problems of irritation, slippery streets, and contaminated or stained products within the industries located along the waterway. The amount of invisible, inhalable insect dust from these emergences has been estimated by Kagen and Yunginger et al. (12) to be in the range of several tons.

Incidence of Allergenic Activity

Parlato (3) first reported caddisfly allergy in 1929. In subsequent publications, he established that caddisfly wings caused positive ophthalmic challenges (23), that 5% (43 of 850) of his allergic patients were skin test positive to caddisfly extracts (21), that caddisfly alone could cause asthma without concurrent pollen and mold sensitivity (16 of 43 patients) (23), and that al-

lergic immunotherapy may be successful in reducing patient symptoms (23). Osgood (4) extended these findings and reported that 215 of 623 patients had moderate to marked skin test reactivity, and in 37 patients who were heavily exposed, he found 22 (60%) to have marked reactivity. Thus, skin test responses correlated with the intensity of insect exposure.

In Japan, Kino et al. (27) found that caddisfly wings were allergenic, and that in 56 asthmatics, insect RAST studies revealed 61% positive to silk, 48% positive to caddisfly, and 50% positive to midge allergens. In Wisconsin, Kagen et al. (12) reported a high incidence of RAST and skin test reactivity (40%) in workers exposed to "industrial doses" of caddisfly aeroallergens. These studies establish the caddisfly as a source of potent aeroallergens responsible for inhalant allergic disease.

Caddisfly Allergens

Caddisfly allergens have yet to be isolated and characterized completely. Shulman et al. (5) reported a major allergen to be 3000 dalton using techniques of starch block electrophoresis and ultracentrifugation. More recently, Kino et al. (28) found a molecule of greater than 230,000 dalton that seemed to possess reaginic activity.

Koshte, Kagen, and Aalberse investigated caddisfly allergens for possible cross-reactivity with carbohydrate determinants. Their results revealed significant antigenic cross-reactivity between caddisfly allergens and other invertebrates, including oyster, mussel, shrimp, crab, honeybee, and yellow jacket (110). The most significant allergen identified was a 13 kD protein that has oxygen-binding ability. R. Muthiah in our lab has identified this protein as a hemocyanin molecule that uses copper to bind oxygen. Most importantly, patients allergic to inhalent caddisfly allergens may experience systemic reactions following their first exposure to shellfish or after their first insect sting because of the presence of cross-reactive epitopes.

Caddisfly Allergen Extracts

Caddisfly extraction techniques vary between commercial companies, as does the species of caddisfly employed in allergenic

extract production. Shulman et al. (29) reported a "direct" technique using cold saline and a high-speed homogenizer, which was comparable to acetone precipitation after defatting with ether. Prolonged defatting resulted in loss of allergenic activity. The methods this author employs in caddisfly extract preparation include: adult insect acquisition with a light-trap, sorting and identification by an aquatic biologist, and subsequent extraction with buffered saline containing 0.4% phenol as preservative. Ether extraction is useful in removing both insect waxes and potential organic and environmental toxins. Although the phenol may interfere with protein determinations (e.g., Lowry and Bio-Rad protein assays), it can easily be removed by dialysis.

An electrophoretic comparison of two different commercial caddisfly extracts with a pure *Symphitopsyche bifida* allergenic extract prepared by the author is presented in Fig. 1. The companies were unaware of the species used in preparing their extracts, and used the acetone precipitation extraction procedure. Gel 1 (far left) contains molecular weight markers from 14,400–92,500 dalton. Gels 2, 3, 4, and 5 contain *S. bifida* adult mix, female larvae, adult mix, and male larvae, respectively. Gels 6 and 7 are commercially available caddisfly products. The commercial extracts contain few if any protein bands, and have a fair amount of material (waxes, precipitate) that could not work its way into the sodium dodecylsulfate polyacrylamide gels.

These same extracts were assayed for allergenic activity using sera from patients experiencing caddisfly induced allergic rhinitis and asthma symptoms. Table 3 demonstrates that when analyzed by ELISA, commercial extracts contain greater IgG reactive proteins than IgE specific proteins. In these studies, microtiter plates were coated with either Kagen-caddisfly adult extracts or commercial extracts, and patient sera were studied for caddisfly-specific IgE and IgG reactivity. Affected patients possessed less skin reactivity and lower IgE titers to commercial allergenic extracts than to Kagen-caddisfly allergens. Therefore, in these patients, Kagen-caddisfly extract appears to be preferable to commercial extracts for diagnostic and therapeutic purposes.

Cross-reactivity studies between caddisfly species, and between caddisflies and other insects, are complicated by the fact

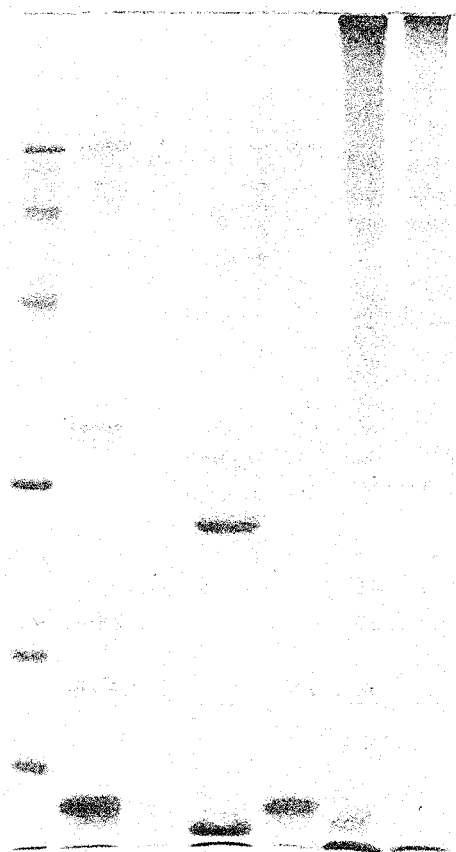


Fig. 1. SDS polyacrylamide gels of caddisfly extracts: (Far left (1) markers; (2) Kagen-caddisfly adult; (3) Kagen-caddisfly female-larvae; (4) Kagen-caddisfly adult; (5) Kagen-caddisfly male larvae; (6) Company 1 "caddisfly"; (7) Company 2 "caddisfly").

that commercial extracts are not well characterized or standardized with regard to insect content. Also, the extracts may have been prepared by different extraction techniques. Using caddisfly sensitive sera from local patients in plates coated with Kagen-caddisfly adult extract, ELISA inhibition studies revealed little crossreactivity with a commercial "caddisfly" extract (Fig. 2). This implies that either the two species of caddisfly do not share allergens, or that the commercial "caddisfly" extract is really something other than true caddisfly. *Dermatophagoides farinae*,

Table 3
ELISA Studies of Caddisfly Extracts: IgE and IgG

Subject	IgE ^a			IgG ^b		
	Kagen	Co. #1	Co. #2	Kagen	Co. #1	Co. #2
1. Normal, unexposed	0.09	0.05	0.08	0.08	0.16	0.25
2. Nonatopic, exposed	0.17	0.19	0.21	0.24	0.52	0.79
3. Nonatopic, exposed	0.21	0.18	0.20	0.35	0.35	0.54
4. Atopic, exposed	0.51	0.19	0.20	0.43	0.56	0.79
5. Atopic, exposed	0.24	0.08	0.10	0.21	0.18	0.24
6. Atopic, exposed	0.26	0.15	0.18	0.43	0.37	0.50
7. Atopic, exposed	0.34	0.22	0.27	0.57	0.49	0.64
8. Atopic, exposed	0.62	0.20	0.24	0.43	0.37	0.50

^aIn these exposed patients, Kagen caddisfly extract possesses greater specific allergenic activity than commercial extracts.

^bCommercial caddisfly extracts possess more IgG than IgE binding materials.

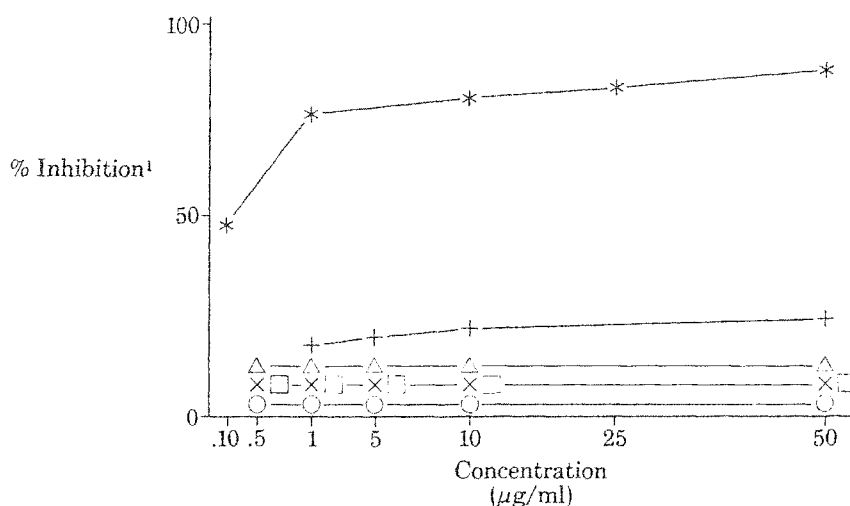
ragweed, and silk proteins (silk and fibroin) failed to inhibit the ELISA, confirming the absence of shared allergens between these unrelated inhalant allergenic materials.

Efficacy of Caddisfly Immunotherapy

There are no controlled studies of caddisfly immunotherapy. Several case reports and clinical studies from the 1930s (23) and 1950s (4), cited above suggest that desensitization therapy is associated with a reduction of symptoms, although it should be pointed out that the allergenic materials that were used successfully in those studies were produced locally by the authors of those reports. Commercial extracts may not be as effective as an allergenic extract produced from a source more proximate to affected patients. The clinical allergist must carefully compare available sources of caddisfly extract to determine the most appropriate material for use in desensitization.

Safety of Caddisfly Extracts

Caddisfly immunotherapy appears to be safe with regard to the risks of anaphylaxis when directed by someone skilled in allergy. Insects may, however, harbor viruses, carcinogens (30), and may concentrate organic and environmental toxins. The Kagen-caddisfly, and the commercial caddisfly extracts referred



¹ Using Caddisfly-sensitive sera in plates coated with Kagen-Caddisfly extract.

KEY

- △ Mite
- Sericin
- × Fibroin
- * Kagen-Caddisfly
- + Commercial Caddisfly
- Ragweed

Fig. 2. "ELISA Inhibitor Studies."

to above, were found to contain no toxins (PCBs, pesticides) when analyzed by gas-liquid chromatography and mass spectroscopy. Additional studies of caddisfly extracts for environmental toxins, infectious agents and carcinogens do not exist.

EPHEMEROPTERA

Mayflies

The life history of the mayflies mimics that of the caddisflies, for both are aquatic insects that emerge in vast numbers in the month of May. The incidence of mayfly allergy has not recently

been established, although in 1940, Figley (31) found that 7% of 1248 atopic patients gave positive skin test responses. Reports by Wilson (1), Figley (2,31), Parlato (32), and MacDermot (33) have established that the mayfly may induce allergic rhinitis and asthma. Forty patients were said to have received beneficial responses to immunotherapy (31).

The allergens and extracts of mayflies have not been characterized or standardized, and there have been no controlled trials of mayfly immunotherapy.

DIPTERA

Midges

Midges are aquatic insects present worldwide, and over 6000 species have been identified. They survive in reservoirs, lakes, and sewage treatment plants or ditches by burrowing into the available muck. The midge larvae spend their entire lifetime underwater except during early May, when they swarm in reproductive rituals. Midges have only four chromosomes, and yet some chironomid species produce up to 12 single-stranded hemoglobin (erythrocrucorin) molecules that are able to bind oxygen at varying pHs and temperatures. The presence of oxygen bound to erythrocrucorins is responsible for their nickname—bloodworms. Adult chironomids have imperforate mouths, and live for 3–11 d, all the while excreting the denaturing, desaturated erythrocrucorins. Once deposited on land and in the air, these molecules are responsible for the insect's bile odor, green staining, and allergenic capabilities.

Incidence of Allergenic Activity

Early reports by Lewis (34) in Africa, and Grodhaus (35) in California, pointed out the ability of the midge to induce allergic symptoms in populations intensely exposed. This was substantiated by Kay et al. (36), Gad el Rab et al. (37), and Cranston et al. (38) in the Sudan, where the prevalence of rhinitis and asthma was found to be higher in "green nimitti" midge exposed villagers.

Kay et al. (36) compared by questionnaire the prevalence rates of allergic rhinitis and asthma in *Cladotanytarsus lewisi* exposed and unexposed Sudanese villagers, and found the rate to be four times greater in the exposed population.

In the US, Kagen et al. (39) documented that a similar midge species, *Chironomus plumosus*, was responsible for respiratory allergy in 45% of heavily exposed atopic patients. Both adult and larval organisms contained the major allergen (17), as was later confirmed by Prelicz et al. (40). In Japan, studies by Ito (41) and Igarashi (42) confirmed that 38% of 303 asthmatics in Tokyo, and 14 of 74 asthmatic children in Toyama, respectively, possess skin test and RAST reactivity to midge allergens. Apparently, the rice paddies support a number of midge species. These studies establish nonbiting midges as clinically significant aeroallergens. Studies based on skin testing alone, however, may be misleading, since midge extracts can nonspecifically degranulate human basophils (J. Pruzansky; unpublished observation).

Midge Allergen Extracts

There are no commercially available midge extracts to compare. However, in collaborative efforts with other midge researchers, Baur (43) has found that 14 erythrocyte containing midge species cross-react. Methods of midge extract preparation are critically important with regard to producing a potent allergen extract. Once dehydrated or lyophilized, the insect extract loses some of its allergenicity as assessed by skin testing sensitive subjects (S. Kagen, unpublished observation). Preliminary RAST studies using lyophilized *Chironomus plumosus* larvae support this clinical observation (J. Yunginger, personal communication). Also, midge larvae have been shown to be a better source of allergen than are the adult species, since larval extracts contain fewer extraneous materials (17).

Midge Allergens

The major allergens of *C. thummi thummi* have been isolated, characterized and partially sequenced by Baur et al. (44). By means of RAST, RAST inhibition, skin testing, and bronchial

challenge, the chironomid hemoglobins were identified as the clinically significant allergens. The different hemoglobin proteins varied from 136 to 151 amino acid residues, and the 16,000 dalton *C. thummi thummi* allergens crossreacted with other midge hemoglobins, as mentioned above, as later confirmed by Tee et al. (45). Successful allergens isolation, gene cloning, and expression of the major *C. plumosus* hemoglobin allergen has been accomplished by our group, enhancing the possibility of using recent advances in biotechnology towards the diagnosis and treatment of allergic conditions (submitted for publication).

Midge Immunotherapy

In an open trial, Kagen et al. (46) studied the midge-specific IgG and IgE immune responses of sensitized patients to *C. plumosus* immunotherapy. Serial midge-specific IgE levels demonstrated the expected post-seasonal rise (Fig. 3). Midge-specific IgG levels were monitored in 21 treated and 12 control patients. Specific IgG increased during immunotherapy in the treated group, but not in the control group (Fig. 4), and this rise in specific IgG was associated with symptomatic improvement.

There are no controlled, double-blind studies of midge immunotherapy for review. Current research efforts by Kagen and Baur are focused on extract standardization with monoclonal antibody to *C. thummi thummi* hemoglobin VI. The recently successful cloning of *C. plumosus* allergens by Kagen should result in improved diagnostic and therapeutic modalities (manuscript submitted for publication).

Fruit Fly

Spieksma et al. (47) reported that 7 of 22 workers experienced allergic symptoms when exposed to *Drosophila melanogaster*. Six of the symptomatic workers possessed skin test and RAST positivity to an extract of the fruit fly. Dust collected from the culture room was able to inhibit allergen binding by atopic sera, thus confirming the presence of the insect allergen in the environmental dust.

Isolation of fruit fly allergen(s), extract standardization, and clinical trials of immunotherapy have not been reported.

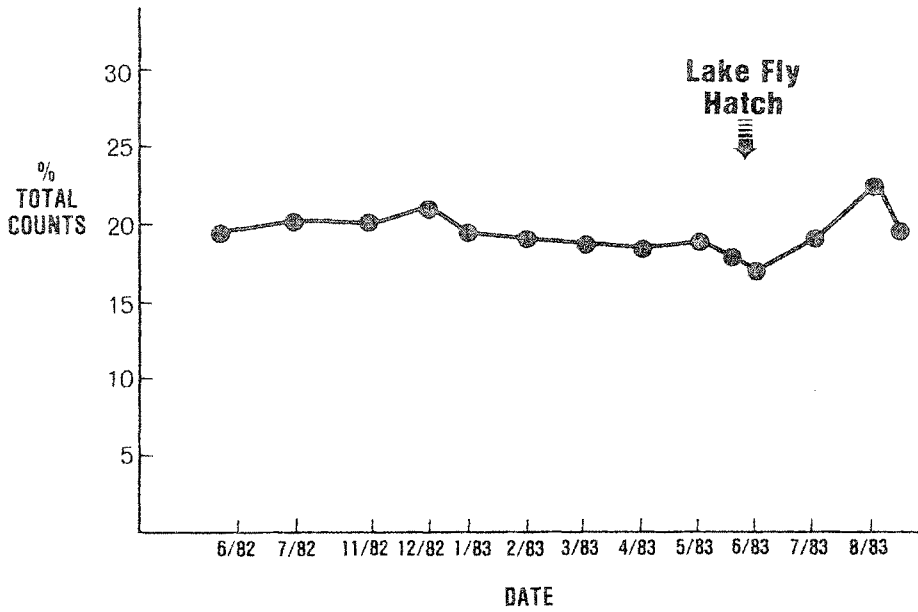


Fig. 3. Serial Midge-Specific IgE levels demonstrating a post-seasonal rise.

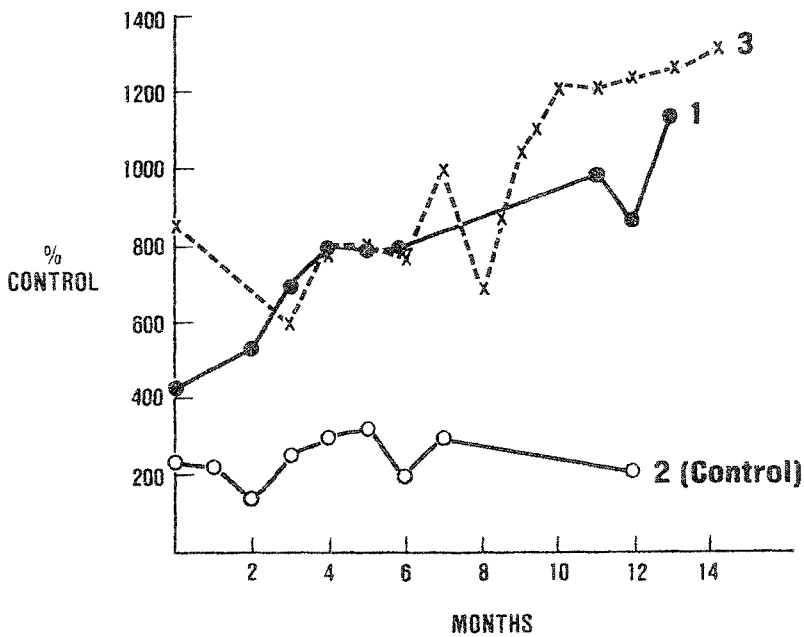


Fig. 4. Midge-Specific IgG titers during immunotherapy in treated (1, 3) and control (2) patients.

Screwworm Fly and Blowfly

The American fly, *Cochliomyia hominivorax*, has been shown to be a potent source of inhalant aeroallergens. Gibbons et al. (48) found that 70% of individuals involved in an eradication program developed symptoms of rhinitis and asthma when exposed to the insect during the dispersal of sterile males from airplanes. Subsequent investigations showed that 68% of workers involved in packaging the fly were affected (49).

Crossreactivity of the screwworm fly with an Australian sheep and human pest blowfly, *Lucilia cuprina*, was suggested by Kaufman et al. (50), although their data did not include RAST inhibition studies. Characterization, isolation, and standardization of screwworm and blowfly extracts do not exist, nor are there controlled studies of their efficacy in immunotherapy.

Mosquito

Evidence for participation of mosquitoes in inhalant IgE-mediated disorders is lacking. Several publications have appeared to demonstrate late, large local reactivity in some subjects when injected with mosquito extracts (51–53). Rockwell (54) reported large local skin test reactivity in six patients at 1:100,000 and 1:1,000,000 dilutions, whereas passive transfer studies were relatively unconvincing.

Modern studies of inhalant mosquito allergy do not exist. This author is unaware of any publications that demonstrate mosquito-specific IgE reactivity by RAST or ELISA.

House Fly

Jamieson (55) described the first case of rhinitis induced by the common house fly. Skin testing with fly wings, passive transfer, and nasal and ophthalmic challenges suggested that reaginic sensitivity existed in the patient. A subsequent investigation of this common pest reaffirmed its potential allergenicity (56).

Mushroom Fly

Mushroom flies appear in swarming clouds in spring and fall in areas of mushroom farms. In 1938, Kern (57) reported a case

of mushroom fly associated asthma that was documented by skin testing and passive transfer studies. Unaffected individuals were skin test negative, and Kern suggested that allergen immunotherapy was successful in reducing the patient's symptoms. Truitt (58), in 1951, studied 316 individuals and found 50 to be skin test positive. "Satisfactory responses" to immunotherapy using an aqueous extract were related in five abstracted cases.

Analysis of mushroom fly allergenic extract's composition and crossreactivity have not been published.

HOMOPTERA

Aphid

Gaillard (59) tested 121 atopic individuals in 1932, and found 75 to be skin test reactive to an aqueous extract prepared from aphids. Positive passive transfer studies in 15 of 17 allergic sera were noted. This report remains the sole evidence of inhalant allergy to aphids.

HYMENOPTERA

Honeybee

Inhalant allergy to honeybee body dust was first described by Benson and Semenov (60) in 1930, and later characterized by Ellis and Ahrens (61). Honeybees may produce fine dusts that can induce rhinitis and severe asthma symptoms in susceptible patients (62). Yunginger et al. (63) and Reisman et al. (64) demonstrated that honeybee-specific IgE reactivity can be directed toward allergenically distinct epitopes of honeybee venom and/or whole bee body. The allergens of honeybee body as yet remain undefined.

Yellow Jacket

Sensitization to yellow jacket (YJ) body proteins may occur directly by exposure to inhalable YJ body dusts, or indirectly, by injection of YJ venoms that contain extraneous visceral compo-

nents. By whichever route sensitization is acquired, symptoms of inhalant allergy may result. Reisman et al. (65) reported the case of a 16-yr-old boy who likely acquired YJ-specific IgE as a result of the occurrence of YJ nests above his bedroom ceiling. In an extensive evaluation for YJ venom sensitivity, it was found that his sera contained IgE binding activity for YJ body allergens. Both the incidence of sensitization to and the characterization of YJ body allergens are unknown.

COLEOPTERA

Beetles

Allergy specialists have always felt as though they are "doctors of the bizarre," because many of their cases are unusual with regard to both the altered state of their patients' reactivity and the endless variety of environmental allergens. Sheldon and Johnston's case report (66) of beetle-induced rhinitis and asthma illustrates this point. They described a museum curator who developed inhalant allergy to dermestid larvae that he used to clean the institution's skeletons. A nasal challenge and passive transfer test confirmed the presence of reaginic activity. Menon and Das (67) later demonstrated that beetle skin test reactions may involve cellular mechanisms. They demonstrated a 48-h reaction to intradermal testing, and this same 48-h response occurred in a bronchopulmonary challenge of the same patient. Biochemical and immunological analyses of beetle allergenic extracts do not exist.

GRAIN WEEVIL

In the 1960s, several reports of inhalant allergy to the grain weevil, *Sitophilus granarius*, were published. Frankland and Lunn (68), described two laboratory workers who developed specific-IgE responses to two species of *S. granarius*, and they were also found to be sensitive to some brands of flour. The authors suggested that several of the flours were contaminated with grain weevil fecal dust. Lunn (69) and Lunn and Hughes (70) further

substantiated the role of the grain weevil in inhalant allergy when they reported immediate and late bronchial reactivity in flour mill workers.

Grain weevil allergens remain to be characterized. There are no studies evaluating the potential benefits of immunotherapy using allergenic extracts of grain weevil.

Mealworm

Sensitization to mealworms has been described by Rudolph et al. (71) in 1980. Of 48 exposed workers, 32 had positive skin tests, and 27 demonstrated a positive nasal challenge. Bernstein et al. (72) also confirmed that inhalant allergy could be induced by occupational exposures.

LEPIDOPTERA

Moth and Butterfly

Inhaled allergy to moths and butterflies occurs in both occupational and residential environments (73–78). Urbach and Gottlieb (79) and Stevenson and Mathews (80) reported several cases of moth-induced rhinitis and asthma in entomology workers. Of greater significance to the practicing allergist, however, is the work of Kino and Oshima (81,82) in Japan. Their studies demonstrated

1. That the incidence of moth and butterfly sensitivity is comparable in Japan to that of dust mite (56% of atopics);
2. That moth, butterfly, and silkworm moth wing allergen extracts share common allergens, but do not crossreact with mite (*D. farinae*); and
3. That moth immunotherapy was clinically effective in one patient.

Moth aeroallergen detection studies by Wynn et al. (83) have confirmed that respirable moth allergens exist in Minnesota, with seasonal peaks in June and August through September. Cross-reactivity between moth species was documented by Wynn and by Kobayashi et al. (84), but it is likely that both shared and unique moth allergens will be found.

There have been several reports describing the isolation of Lepidopteran allergens. Dewair et al. (85) reported the presence of five separate silk allergens by immunoblotting techniques. Storms et al. (86) identified two allergens in the miller moth, *Euxoa auxiliars*.

These studies establish moth and butterfly species as potent, clinically significant community and occupational aeroallergens. Their importance in any given patient can only be determined by the physician with the knowledge that such associations exist. It is this author's opinion that moth extracts should be reclassified into Category IIIA for skin test diagnosis and immunotherapy purposes. Future investigations concerning the safety and efficacy of immunotherapy should be focused on the use of standardized moth allergenic extracts, presumably high in moth wing allergen content.

ORTHOPTERA

Locust

Inhalant allergy to locusts is primarily an occupational disease as first illustrated by Frankland (87), and later studied by Burge and coworkers (88). Locusts emanate sufficient material to induce atopic symptoms in as many as 26% of exposed workers. Further studies of incidence, crossreactivity, allergenic extracts, and allergen identification are needed.

Crickets

Cricket hypersensitivity has been reported in occupational and recreational settings. Cazort and Johnston (89) described a case of inhalant sensitivity in a fisherman raising crickets as bait, and commented that desensitization was effective. Baganstose et al. (90) established crickets as a cause of inhalant allergy when they reported positive skin testing, passive transfer, RAST, and histamine release studies in two patients with definite work related symptoms.

Cockroach

A thorough review of cockroach allergy is presented by Kang elsewhere in this publication. Bernton and Brown (91,92) were

the first investigators to show that humans could develop atopic responses to intense cockroach exposure, and later presented evidence that cockroach excrement played a role in its allergenicity (93). Cockroach allergy is not rare. As high as 53% of asthmatics in a Chicago population were found to be sensitized when studied by Kang and Morgan (94). Other evidence reaffirms the worldwide importance of inhalant allergy to the cockroach, and its trailings (95–98). Swanson et al. (99) recently quantitated cockroach aeroallergens in domestic environments.

Cockroach allergens have been partially identified by Twarog et al. (100), and documentation of partial crossreactivity between American and German cockroaches has been presented (101). A comprehensive study of cockroach allergen composition, stability, and effectiveness in desensitization therapy would be of great clinical usefulness. As it is with other insect extracts, comparison of case reports using unstandardized cockroach materials is difficult. In spite of this, encouraging results have been published (102).

A summary known of inhalant arthropod allergens is presented in Table 4.

INHALANT ALLERGY TO ARACHNIDS

The Acari include a clinically significant order in the Arthropodan class Arachnida. The mites and ticks in this order possess eight legs in the adult form, compared with six legs in the class Insecta. The family Pyroglyphida consists of the ever present house dust mites *Dermatophagoides pteronyssinus*, *D. farinae*, and *Euroglyphus maynei*. The storage mites are classified as Tyroglyphidae and include *Glycyphagus destructor* (hay), *G. domesticus* (house, sugar), *Acarus siro* (grain, flour, oats), *Tyroglyphus siro* (cheese), and *T. putrescentia*. All mites can be found either in or out of doors, depending on the available food source, temperature, and humidity. The house dust mites, *D. pteronyssinus* and *D. farinae* are the most important mites clinically, and are, perhaps, the single most important worldwide aeroallergen. An elegant, extensive review of mites, and their association with house dust allergy, has been written by Voorhorst, Spieksma,

Table 4
Inhalant Arthropod Allergens

Organism	Allergen source	Molecular weight
Midge		
<i>C. plumosus</i>	larvae, adult	13,500
<i>C. thummi thummi</i>	insect erythrocytins	16,000
Silkworm moth	sericin proteins	70,000
		45,000
		40,000
		14,000
Cockroach	feces, whole body	
American	Cr-I	25,500
	Cr-II	65,000
German	Cr-III	10,000
Moth		
<i>Euxoa auxiliars</i>	whole body	44,000
		77,000
Caddisfly	hemocyanin	13,000
	wing	>230,000
	whole body	3,000
Dust mite	feces	
<i>D. pteronyssinus</i>	Der p I	24,000
	Der p II	15,000
<i>D. farinae</i>	Der f I	24,000
	Der f II	15,000
	Der f III	29,000
Locust	body, feces	Unknown
Honeybee	whole body	Unknown

and Varekamp (103). It is required reading for those wishing a complete understanding of mite biology and mite allergy.

Fowl Mite

The northern fowl mite, *Ornithonyssus sylviarum*, is an ectoparasite of chickens. Lutsky et al. (104) employed skin test, RAST, and bronchial challenge studies on 15 affected patients to establish this mite as an occupational allergen of poultry farmers. Allergen identification, extract composition, and prevalence data are unavailable.

INHALANT ALLERGY TO CRUSTACEANS

Snow Crab

Crustacean allergens from snow crab, shrimp, and lobsters may become airborne during their preparation. This author has

cared for a restaurant owner who suffered from inhalant asthma caused by lobster vapor inhalation, and symptoms of bronchospasm occurred within several minutes of entering his restaurant's kitchen. These symptoms were evident on Friday evenings only when lobster was being boiled. Bush et al. (105) recently isolated a 14,750 dalton snow crab allergen that did not cross-react with other crustacean extracts of lobster or shrimp. Interestingly, the boiling process enhanced its allergenic activity as determined by skin test and RAST reactivity. Cartier et al. (106, 107) have demonstrated that processors of fresh crab may also develop occupational asthma caused by inhalant crustacean materials.

Water Flea and Prawn

Way (108), in 1940, described the case of a pet fish enthusiast who developed *Daphnea pulex*-induced asthma. The water fleas were being used as fish food. Extracts of it elicited a strong immediate skin test and a positive passive transfer was possible.

There are no known studies of water flea allergen extracts, nor are there any other reports of clinical sensitivity. A study of prawn workers by Gaddie et al. (109) illustrates once again the potential allergenicity of arthropodans.

SUMMARY

Inhalant allergy to arthropods is of major social, economic, and medical importance. As seen in this review, immunologic techniques for evaluating the multitude of clinical problems that are known to exist are beginning to enable the clinical allergist to deal with these problems in more effective ways. Successful application of newer biotechnology methods in areas of protein isolation, characterization, and sequencing together with gene cloning technology should result in significant advances in our understanding and management of inhalant arthropod allergy.

ACKNOWLEDGMENTS

These efforts have been made possible because of the encouragement and cooperation of John W. Yunginger, S. Roger Hirsch,

Howard J. Schwartz, V. P. Kurup, and R. Muthiah. David Rades has been of valuable assistance in arthropod identification while functioning as Chief of Aquatic Biology at the Institute of Paper Chemistry, Appleton, Wisconsin.

The technical and organizational expertise of Mary Witte is hereby acknowledged as well.

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