

Inhalant Allergy to Arthropods

Clinical Significance of Arthropod Allergy

Howard J. Schwartz

*Department of Medicine, Allergic Diseases Center,
Case Western Reserve University School of Medicine
and University Hospitals of Cleveland, Cleveland, OH 44106*

INTRODUCTION

Rhinitis, conjunctivitis, and asthma have been attributed to inhalant sensitivity to the scales, hair, and other emanations of insects for many years. Ramazzini (1) first suggested this clinical relationship, and in the 20th century Parlato (2), Feinberg (3), and Perlman (4), were among the early workers in this field. Despite this recognition that inhalation of insect-derived material can cause allergic reactions, greater medical attention by far has been paid to those reactions caused by insect stings. This is undoubtedly a result of the dramatic nature of sting reactions, but the relative lack of attention to inhalant insect allergy is in part attributable to the scientific difficulties involved in studying inhalant reactions to insects.

Taxonomic problems abound, for while common usage employs the term "insect" for the whole arthropod world, the word "insect" is properly used to refer to a class in the phylum of arthropods (which consists of both insects and arachnids). Thus, there is a complex variety of insect-derived allergens in the environment. Some of these occur in appropriate size and sufficient numbers for entry into the respiratory tract, where they may induce sensitization in the same manner as pollens or other plant- and animal-derived allergens.

The diurnal and seasonal behavior patterns and atmospheric dispersion of insect emanations is unclear. Perlman has reviewed some aspects of the numbers and distribution of these allergens and it appears that there is a sufficiently frequent and intense appearance of ambient insect-derived materials in the atmosphere to significantly expose atopics by the inhalant route (4,5). Their dispersion is so widespread that geographic regionalization is less important than is true with pollens. Furthermore, insects may be found indoors, outdoors, at home, and in the workplace. Both living and dead insects may be a source of sensitization. This latter source, i.e., debris from dead insect carcasses, could, over many years, become a significant accumulation (warehouses, and so on).

Insects, in general, can be considered to be sources of injectant or inhalant allergies and sensitization can be produced by

1. Injection of venom via a sting;
2. Injection of saliva by mouth parts (after a bite); and
3. Inhalation of insect emanations (scales, body parts, such as wings, feces, etc.).

The insects to which humans are most frequently exposed include moths, flies, ants, cockroaches, lice, bugs, and the *hymenoptera*. The signs and symptoms in patients reacting to insect-derived antigens are typical of inhalant allergic reactions owing to inhalants such as pollens, animal danders, and dust. It is unclear how many insects cause inhalant allergy, nor is it understood how insect allergens become airborne. It has been suggested that protein debris from insects are part of environmental dust (6). Dust mite feces has clearly been shown to be allergenic in humans (7). The earliest reports of allergic respiratory disease from inhaling insect allergens involved may fly and caddisfly, with additional later reports of many other types (8-10). Feinberg et al. suggested that sensitivity to insect antigens constituted a major cause of respiratory allergy (3). Perlman reported that 50% of a series of 252 unselected patients with rhinitis and asthma gave positive prick skin test reactions to insect allergens; on additional intradermal testing there were 66% positive. Reactivity was seen as often with insect allergens as with other allergens, including dust, epidermals, and pollens (4), but was not limited to, or correlated with, reactivity to one particular class of other allergens (6). Wiseman et al. (11) found a much greater degree of reactivity to insect allergens in allergic

than nonallergic individuals, especially in patients with seasonal as well as perennial rhinitis. MacLaren et al. (12) found a greater number of positive skin test reactions with insect allergens in allergic patients as compared with nonallergic subjects. Thus, skin test surveys with insect allergens suggest a high frequency of sensitization in otherwise atopic individuals. Some authors have taken this to mean that inhalant insect allergy rivals dust allergy in prevalence and significance. However, the number of "well-documented" cases of respiratory allergy caused by inhaled insect materials is relatively small. The problem of inhalant insect allergy is complicated by the fact that there is a vast number of insect species. Perlman (5) has attempted to simplify this by classifying insects of potential importance in causing human respiratory allergy.

Allergens

Arthropoda is the largest phylum in the animal kingdom and is made up of a number of classes and orders, with *Insecta* and *Arachnida* being most important in this discussion. The aerobiology of their emanations is uncertain so that the level of inhaled exposure of atopic individuals in different areas of the world and at different times of the day and year is unknown. However, immunologic studies with passive hemagglutination and gel diffusion assays demonstrate that different orders of insects share common antigens (5). These may be unrelated to those capable of inducing IgE antibody synthesis (6-14).

In his review of insect antigens, Shulman (15) pointed out that little is known concerning the immunochemistry of insects. How many distinct allergens exist for each insect species is not known. Skin test surveys with whole body extracts that indicate multiple sensitivities suggest the presence of common allergens in several different insect species. Several more recent studies have begun to address this difficulty.

Pruzansky et al. (14), in attempting to study the antigenic relationships between several different species, found in examining fly, may fly, cockroach, cricket, and silkworm, that there are antigens of major specificity for each species, as well as common antigens that are shared by several species. Extensive studies have also been carried out on *hymenoptera* and caddisfly antigens (15).

The lack of detailed data on the major arthropod antigens makes meaningful skin test surveys difficult to conduct and to interpret. The great number of potential allergens and the current inability to skin test by antigenically significant groupings remains a significant stumbling block in assessing the true clinical importance of this class of sensitizing agents.

It is difficult to develop a list of arthropods more or less likely to cause inhalant sensitivity. It has been suggested that silkworm, caterpillar, and locusts, as well as the various house dust mites, cause allergic inhalant reactions. Interesting reports detailing the role of cockroach allergy in syndromes of chronically ill, urban allergy patients further expand these possibilities (16–18). Thus, it may be that sensitization to perennially encountered arthropod antigens can explain some of the unexplained symptoms in patients with chronic rhinitis and/or chronic asthma.

Clinical State

The symptoms in patients with respiratory allergies caused by arthropods are similar to those inhalant allergies caused by other factors (e.g., pollens, dust, and so on). The pattern may be of either seasonal or perennial difficulty. Caddisfly sensitivity occurs in patients living in the Great Lakes region—especially in the Niagara River region. Caddisfly allergy as a cause of seasonal allergic rhinitis and asthma has been reported since 1929 (10). Clinical symptoms can be as intense as those owing to the more common seasonal pollen allergens. Diagnosis was made by skin and ophthalmic testing with whole body extracts of these insects. Experience since these initial reports indicates that both clinical symptomatology and skin test reactivity can be intense, and immunotherapy can be effective in controlling this clinical condition.

House dust allergy has been widely regarded as the major cause of perennial allergic respiratory disease for years, but it was not until the mid 1960s that a mite from the genus *Dermatophagoides* was reported to be the single most important allergenic component of house dust (19). Whether or not it is *the* single house dust allergen is a moot point; but skin testing, bronchial and nasal provocation tests, RAST analysis, histamine release, and immunodiffusion studies have corroborated the finding that mite antigen is a major allergenic component. Immunotherapy with mite extract

is now in use to treat such sensitive patients. However, it does appear from some studies that mite is only one of many allergens in dust, rather than the only important allergen.

The potential role of cockroach allergy in human disease has been a subject of increased attention in the last several years. Bernton and Brown (16) indicate that there are many species that are found in homes, restaurants, and food handling establishments. Exposure can be via the inhalation or injectant route (via biting), but oral exposure can also occur from contamination of food by insect body parts and/or exerta. They have been implicated in cases of rhinitis and asthma, especially in urban areas. Positive direct skin tests (16,17), passive transfer (16), RAST (18), and bronchoprovocation tests (18) have been carried out. Cockroach allergy thus appears to be well documented, with significant IgE antickroach antibodies (18), and can occur independent of house dust reactivity (16). However, there is a variable but high rate of skin test reactivity in the nonatopic population (16,17). The interpretation of this finding is unclear; these may represent false-positive reactions, or single sensitivities in hitherto undiagnosed patients with allergic disease. Further studies, with better antigen preparations, are awaited with interest.

Aphids, moths, butterflies, bees, and other flies have also been indicted as the cause of allergic disease, but the list of potential causative insects is far greater. It is certainly true that the insects to which people are exposed depend on geographic location and the local habitat (20). There are aquatic-derived insects and terrestrial-derived insects. Aquatic insects include may fly, caddisfly, water flea, mosquitos, and midges. Terrestrial insects include dust mites, storage mites, cockroaches, carpet beetles, moths, locusts, housefly, and the *hymenoptera* insects. It may be more simple to detect the role of inhalant insect allergy in seasonal disease than in perennial disease, since the exposure pattern to large numbers of swarming insect populations may be brought to the attention of the physician by the concerned patient. Perennial symptoms owing to chronic exposure of the allergy patient to insects is harder for both patient and physician to appreciate.

Many groups of workers suffer allergies associated with their occupation. Entomologists and other workers with arthropods have been reported to experience this hazard. Several surveys

have indicated that allergy to insects is quite common among entomologists (21–23). Sensitivities to *lepidoptera* form two-thirds of the incidents in one reported series (23).

Various other aquatic and terrestrial insects have been identified as the sources of allergens associated with respiratory disease in both occupational and epidemiologic surveys. Significant skin test reactivity to several flies and flea whole body extracts have been reported. Skin test surveys have found that 50–60% of atopic individuals may react to nonstinging insect body extracts. Some investigators have found rhinitis, asthma, and conjunctivitis in occupational settings, but it has been more difficult to prove the relationship of specific insect allergens in nonoccupational environments.

There are several exceptions to this statement. The studies in house dust allergy have shown clearly that many such reactions are caused by the house dust mite and studies have included both skin tests, in vitro assays for antibody determination, and inhalant challenges.

Reports from Japan have indicated that many atopic individuals have insect specific IgE in their sera directed against worm, moth, and butterfly antigen (20,24,25). Significant numbers of patients have been found to have IgE antibodies against midge antigens in both Africa and in the US (26–28).

PATHOGENESIS

It has been considered that sensitization to arthropods can occur in a similar fashion to sensitization to other inhalant antigens. Thus, people, after sufficient exposure, develop IgE antibodies directed against one or several antigens in the inhalant, and, on reexposure, can develop a variety of syndromes. The sensitization to insects can thus express itself as a form of “hayfever” with symptoms primarily affecting the nose and eyes. There can also be rashes and urticaria in some individuals, especially those working with insects in industry. More serious symptoms can occur with cough, wheezing, and full-fledged asthma attacks. Typically, as is seen with other allergens, symptoms will remit when exposure to the antigen is interrupted but will reappear with repeat exposure.

It is not yet clear whether only otherwise atopic people develop inhalant sensitivity to insect antigens or whether anybody (atopic or not) will, with sufficient exposure, finally become sensitized.

DIAGNOSIS

The possible role of inhalant allergy in any individual patient can only be recognized by the physician on the basis of the carefully taken history. This will be greatly enhanced if the physician is knowledgeable about the types and behaviors of arthropods resident in the patient's community. Ultimately, the diagnosis of inhalant arthropod allergy depends on correlating exposure of a patient to insect allergens with subsequent clinical symptoms. This can be further documented by the demonstration of specific anti-insect allergen IgE. Currently, the most common methodology for this is direct skin testing, but as technology advances this will be assisted by the development of in vitro methods for demonstrating specific anti-insect IgE.

Skin testing is the most appropriate screening method to evaluate subjects presenting with inhalant disease, but the limited availability of proper panels of insect antigens is a serious difficulty the clinician cannot easily overcome. This difficulty is further compounded by our inability to easily identify high risk target populations for study. The clinical significance of a positive skin test is difficult. Seasonal patients may think their sensitivity is owing to pollen and not to seasonal insect emergences. Patients with perennial disease may not recognize the possible relationship of their symptoms to chronic insect exposure. Thus, skin testing must be done carefully, especially if the intradermal method is to be used. The additional possible production of anaphylactic reactions to skin tests in highly allergic unsuspecting patients is real. Concentrations for testing must be dilute and careful controls are critical, since false positive reactions will certainly complicate the clinical evaluation of the test result. Positive skin tests or in vitro tests in the absence of a significant clinical history cannot be taken as any sort of proof that the patient is truly sensitive to insect allergens. Test reagents may contain primary irritants or non-specific histamine releasers that can produce a false positive test. Differences

in methodology of antigen preparation, including techniques for determining their purity and stability, make it impossible to compare and evaluate studies from different research centers. Many of the already published studies on the role of inhalant insect allergy in human respiratory disease have utilized whole body extract preparations. MacLaren et al. (12) reported between 6 and 14% positive skin test reactivity in nonallergic controls, compared to 22–46% positive reactions in allergic patients tested intradermally with fly, moth, ant, aphid, and mosquito extracts. Wiseman et al. (11) reported that skin test reactivity in control subjects varied with the concentration of the test antigen, reporting 16/520 positive reactions when testing was carried out at a test concentration of 100 PNU/cc, and 103/520 positive skin test reactions when testing was done at 5000 PNU/cc. There was a much higher frequency of skin test reactivity in allergic subjects at both test concentrations, but there appears to be a significant overlap with controls, and the results must, therefore, be interpreted with caution. Perlman (6) and Bernton and Brown (16) have reported the successful passive transfer of skin test reactivity to insect antigens in humans, implying that this is owing to the presence of reagin. Specific IgE has not yet been demonstrated for most insects, but this appears to be simply a matter of time and technology, since isolation of major insect allergens and demonstration of specific IgE has been reported for several species (e.g., 18, 19, 24, 25, 29, 30).

The significance of understanding the environmental distribution of insect allergens has recently been emphasized by reports from Japan demonstrating allergy to silkworm moths, including both direct skin test and RAST data. Crossreactivity with moth and butterfly but not house dust mite was also shown (14, 24, 25).

Positive bronchoprovocation testing has been reported in some patients, with inhalant asthma attributed at least in part to inhalant insect allergy. This type of diagnostic evidence is important in research studies, but it cannot be widely recommended as a diagnostic tool for routine office use because of the danger of eliciting potentially severe asthmatic attacks.

In summary, it would appear that a convincing body of data is appearing that demonstrates reagenic antibody against several arthropod species. The potential clinical significance of this data has not previously been synthesized in an organized fashion.

It is encouraging that data demonstrating specific sensitization is appearing, but the practicing allergist is still faced with the dilemma of how to best make the diagnosis of inhalant insect allergy. At present, it appears that a careful history is the cornerstone on which the diagnosis must rest. Positive allergy skin tests will best be able to offer laboratory support of this clinical diagnosis if it is carried out by the prick technique. If intradermal tests are done, end point titration will be helpful. As noted above, positive test reactions with dilute antigen preparations occur less often in nonallergic controls than when tests are done with more concentrated preparations; i.e., the incidence of false-positive reactions falls as the test material is more dilute.

TREATMENT

As is typical of other allergic disorders, proper treatment of the respiratory diseases caused by inhalation of arthropod allergens includes avoidance of the cause when this is possible, and symptom relief, when necessary, by the appropriate use of decongestants, antihistamines, and bronchodilators. Avoidance methods are available and have been reported to be successful (23). These techniques include good ventilation systems and the use of masks. Several reports have indicated effective results using avoidance in house dust mite allergy. Platts-Mills et al. have pointed out that patients using such methods develop a decrease in their airways hyperreactivity to other, nonspecific triggers (31). The effectiveness of avoidance therapy can be improved by concurrent use of inhaled disodium cromoglycate (cromolyn). If avoidance is otherwise impossible or impractical, symptom relief, including antihistamines, decongestants, and bronchodilator therapy, may be used. Obviously, inhaled steroids are preferable to systemic steroids if the patient is not controlled on the above medication.

The use of immunotherapy at this point would be empiric at best, since there is little published data to support its use and to delineate the risk/benefit ratio for each insect group involved. Parlato (2) reported satisfactory clinical results in a "large" percentage of patients with seasonal asthma from caddisfly allergy treated with injection therapy. Attempts at such treatment with moth scale

extracts gave few satisfactory results. Feinberg et al. (3) reported "encouraging" clinical results in patients given immunotherapy with extracts of may fly, silkworm, or a mixture of several insect antigens. This is aside from the situation that exists with house dust mite allergy. Several studies have shown that immunotherapy has been of significant usefulness in mite allergic patients (32-34). These studies suggest that there ultimately may be a place for immunotherapy in inhalant insect allergy, but much basic work on the immunochemistry and immunobiology of these materials must be carried out. Well organized, controlled clinical trials need to be conducted on well documented cases in order to demonstrate the safety and efficacy of immunotherapy for inhalant arthropod allergies.

FUTURE CONSIDERATIONS

While inhalant sensitivity has been documented by a variety of studies, the true impact of this problem in the general population is certainly not well appreciated. Future studies of a variety of sorts must be undertaken to clarify this issue. This would include epidemiologic surveys of various exposed populations and carefully conducted in vitro studies. To further establish the specific role of inhalant insect sensitivity in these disease states, properly controlled challenge studies using the eye, nose, and tracheobronchial tree should be carried out as well. These will have to be done in a double-blind fashion and in a carefully controlled hospital setting to guarantee patient safety. Only in this fashion can we attempt to separate irritant vs specific immunologic reactions to the insect world, and begin to appreciate the true impact of inhaled insect sensitivity on the day-to-day life of allergic individuals.

REFERENCES

1. Ramazzini, B. (1940), *De Morbus Artificum Diatriba*, University of Chicago Press, Chicago.
2. Parlato, S. J. (1932), *J. Allergy* 3, 459.
3. Feinberg, A., Feinberg, S., and Benaim-Pinto, C. (1956), *J. Allergy* 27, 437.
4. Perlman, F. (1958), *J. Allergy* 29, 302.
5. Perlman, D. (1961), *J. Allergy* 32, 93.

6. Perlman, F. (1965), *Acta Allergologica* **21**, 241-253.
7. Tovey, E. R., Chapman, M. D., Wells, C. W., Platts-Mills, T. A. E. (1981), *Am. Rev. Resp. Dis.* **124**, 630.
8. Wilson, H. (1913), *JAMA* **61**, 1648.
9. Figley, K. D. (1929), *Am. J. Med. Sci.* **178**, 338.
10. Parlato, S. J. (1929), *J. Allergy* **1**, 35.
11. Wiseman, R. D., Wooden, W. G., Miller, H. C., and Myers, M. A. (1959), *J. Allergy* **30**, 191.
12. MacLaren, W. R., Eisenberg, B. C., Frank, D. E., and Kessler, J. (1960), *Calif. Med.* **93**, 224.
13. Shulman, S. (1968), *Prog. Allergy* **12**, 246.
14. Pruzansky, J., Feinberg, A. R., Schick, G., Feinberg, S. M. (1958), *Proc. Soc. Exper. Biol. Med.* **97**, 312.
15. Langlois, C., Shulman, S., and Arbesman, C. E. (1963), *J. Allergy* **34**, 385.
16. Berntson, H. S. and Brown, H. (1964), *J. Allergy* **35**, 506.
17. Kang, B. and Sulit, N. (1978), *Ann. Allergy* **41**, 333.
18. Kang, B., Vellody, D., Homburger, H., and Yunginger, J. W. (1979), *J. Allergy Clin. Immunol.* **63**, 80.
19. Voorhorst, R., Spieksma, F. T. M., Varekamp, H., Leupen, M. J., and Lyklema, A. W. (1967), *J. Allergy* **39**, 325.
20. Kino, T. and Oshima, S. (1979), *J. Allergy Clin. Immunol.* **64**, 131.
21. Stevenson, D. D. and Mathews, K. P. (1967), *J. Allergy* **39**, 274.
22. Burge, P. S., Edge, G., O'Brien, I. M., Harries, M. G., Hawkins, R., and Pepys, J. (1980), *Clin. Allergy* **10**, 355.
23. Wirtz, R. A. (1980), *Bull. Entom. Soc. Amer.* **26**, 356.
24. Kino, T. and Oshima, S. (1978), *J. Allergy Clin. Immunol.* **61**, 10.
25. Kino, T. and Oshima, S. (1979), *J. Allergy Clin. Immunol.* **64**, 131.
26. Gad El Rab, M. O. and Kay, A. B. (1980), *J. Allergy Clin. Immunol.* **66**, 190.
27. Kay, A. B., MacLean, C. M., Wilkinson, A. H., and Gad El Rab, M. O. (1983), *J. Allergy Clin. Immunol.* **71**, 345.
28. Kagen, S. L., Yunginger, J. W., and Johnson, R. (1984), *J. Allergy Clin. Immunol.* **73**, 187.
29. Chapman, M. D. and Platts-Mills, T. A. E. (1980), *J. Immunol.* **125**, 587.
30. Twarog, F. J., Picone, F. J., Strunk, R. S., and Colten, H. R. (1977), *J. Allergy Clin. Immunol.* **59**, 154.
31. Platts-Mills, T. A. E., Tovey, E. R., Mitchell, E. B., Morozora, H., Nock, P., and Wilkins, S. R. (1982), *Lancet* **2**, 675.
32. Smith, A. P. (1971), *Br. Med. J.* **4**, 204.
33. Price, J. F., Warner, J. O., Hey, E. N., Turner, M. W., and Soothill, J. F. (1984), *Clin. Allergy* **14**, 209.
34. Bousquet, J., Calvayrac, P., Guerin, B., Hejjaovia, A., Dhivert, H., Hewitt, B., and Michael F. B. (1985), *J. Allergy Clin. Immunol.* **76**, 734.