

AN UNDERESTIMATED CAUSE OF RESPIRATORY ALLERGY: INHALANT ARTHROPODS AND INVERTEBRATES ALLERGY (WITH THE EXCLUSION OF MITES)

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INTRODUCTION

It is becoming increasingly evident that exposure to arthropods in man's and invertebrates' immediate environment (at home, outdoors and at work) result in sensitization to arthropods which can lead to inhalant allergies namely asthma and allergic rhinitis. As yet, little information is available on the worldwide incidence and distribution of arthropod allergies, the types of allergies encountered, the extent of cross-reactivities between arthropod allergens and the nature of these allergens. In addition, the relative importance of different species of arthropods as a source of inhalant allergy in different geographical locations is not well defined.

The world of arthropods which has surrounded man for millions of years and which includes mostly true insects and arachnids, is so important and so numerous that entomologists have not yet been able to identify all the species. Given the ubiquity of arthropods indoors and outdoors, it comes as a bit of a surprise that there are only a few reports in the medical literature of allergy to arthropods as inhalants compared to the many studies dedicated to pollens, molds and more recently to mites and stinging insects. Perlman was one of the first (1). Furthermore, most of the authors interested in this field have become interested by one arthropod, the cockroach, even though it has been demonstrated since the beginning of our studies that all arthropods could be involved in IgE mediated allergy in humans.

Respiratory allergy to some invertebrates will be included for we think as stated in our previous publications (2, 3, 4, 5) that there is an extensive cross reac-

tivity between insects, arthropods and most invertebrates leading to the concept of "Panallergy".

The commonest insects acting as aeroallergens

■ **Chironomid respiratory allergy:** Chironomid midges and larvae are known to contain potent allergens. In Sudan, it has been reported by Kay and Gad el Rab (6) that a small midge, *Cladotanytarsus lewisi* (green nemitti), occurred in enormous numbers in the Nile basin and that it caused asthma in people living close to the Nile. In Germany it has also been reported by Bauer *et al.* (7) that chironomid larvae which are widely used as fish bait either in the form of whole lyophilized insects or in mixed products cause IgE-mediated respiratory allergic reactions in a significant number of people exposed to these larvae through their occupation or their hobby.

Bauer *et al.* (8) have shown that the major larval allergens of *Chironomus thummi* and *Camptochironomus tentans* for humans are cell-free hemoglobins and that there is a cross reactivity between the different chironomid species. Hemoglobins of the larvae of *Chironomus thummi thummi* have been characterized and labelled Chi t 1; it comprises 9 homologous components. Furthermore they have demonstrated the persistence of hemoglobin allergenicity and antigenicity during metamorphosis of chironomidae.

In Japan, many species of chironomids are widely distributed in urban areas. Thus, it is probable that chironomid allergy occurs throughout the world.

■ **Cockroaches allergy:** Cockroaches are the most studied insects; three principal species of cockroaches are known to induce respiratory allergy in man: *Blattella germanica* (German cockroach), *Periplaneta americana* (American cockroach) and *Blatta orientalis*. Cockroach allergens are among the arthropods the only ones if we except mosquitoes (*Aedes aegyptii*: Aed a 1, apyrase, Aed a 2) which until now have been identified, sequenced, and cloned.

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➤ *Blattella germanica* (german cockroach):

- Bla g 1: protein of unknown function.
- Bla g 2: aspartic protease.
- Bla g 4: calycin, a calcium binding protein.
- Bla g 5: a glutathione transferase.
- Bla g 6: troponin.

➤ *Periplaneta americana* (american cockroach):

Per a 1: homology with Bla g 1

Per a 3 :homology to insect hemolymph protein.

The cockroach hemolymph proteins have a sequence identify to insect storage proteins, insect juvenile hormone-suppressible proteins and arthropod Hemocyanins:

- Per a 7: tropomyosin.

These allergens have been purified sequenced and cloned mostly thank to the works of: Chapman *et al.* (9), Arruda *et al.* (10), Wu *et al.* (11), Chou *et al.* (12), Helm *et al.* (13), Lehrer *et al.* (14).

■ **Moths and butterflies allergy: *Lepidoptera*.** Already known as aero-allergens since the works of Parlato (15) moths and butterflies have been implicated in Japan by Kino and Oshima (16) as a possible cause of respiratory allergy. They found that more than half of a randomly selected asthmatic population showed not only positive skin tests and positive RAST but also positive bronchial provocation reactions to these outdoor insects. Their results indicated that *Lepidoptera* sensitivity in Japan is as common as that mite sensitivity but there appear to be no cross-reactivity between the two groups of arthropods. Recently in Spain, Vega and Armentia (17) have described cases of allergy (urticaria, asthma, shock) to another lepidoptera, the pine processionary caterpillar (*Thaumetopoea pityocampa*) which generally gives only toxic local reactions.

Among the lepidoptera, we must mention two important insects: *Ephestia cautella*, common in baker's asthma, and *Tineola Biselliella*, the common cloth moth.

■ **Silk allergy:** Silk culture started in China and spread to Japan, India and other asian countries. Silk allergy offers a transition between professional and non professional allergy, since allergy to silk products is well known as an occupational hazard in sericulture, and silk allergy often follows (especially in China) exposure to bed quilts or clothes filled with silk waste. In contrast textile products made of pure silk have not, to the best of our knowledge, been incriminated as a cause of allergic reaction.

■ **Silverfish: *Lepisma saccharina*.** The presence of this insect in houses is common in the Netherlands as shown by Witteman *et al.* (18). It is also common in Roma as recently reported by Barletta and ourselves (19): an extract of silverfish has been characterized

and the different allergenic components have been identified. In a general population 6.4% of subjects are positive to at least one silverfish fraction. Besides silverfish extracts can be recognized by sera from subjects allergic to household insects. Furthermore the results indicate that the classical aqueous extract procedure is not completely satisfactory since several components are not soluble at the pH normally used to produce extracts; the insoluble allergenic material appears to play an important role.

■ **House fly: *Musca domestica* and diptera.** We found only three reports describing cases of respiratory allergy to house fly, one by Tee *et al.* (20), the second one by Rosemary *et al.* (21) in the context of an occupational disease, and the last one by Hemmer *et al.* (22) who described a case of specific sensitization to *Musca domestica* not related to insect panallergy. Among the diptera, we have the culicidae (mosquitoes) and the horse fly (*Gasterophilus intestinalis*), which can act as aero allergens.

■ **Arthropods and fish pets: "the aquarium syndrome".** In Europe, America, and all over the world people keep fish in aquaria and feed them with fish foods which vary in their composition according to their trade mark, and which contain dried Daphnae and other crustaceans, some fresh water worms, dried black larvae of culex (mosquito) and mostly dried red chironomus larvae. All these arthropods are able to give a respiratory allergy.

■ **Respiratory allergy to the emanations of stinging insects:** Numerous observations have been made of beekeepers with inhalant allergy to bee body components. Since 1932 Ellis *et al.* (23), hypersensitiveness to airborne bee allergen has been reported and more recently by Reisman *et al.* (24) and by Ostrom *et al.* (25). In these last publications the patients demonstrated skin tests positive to honey-bee whole body extract and negative to honeybee venom. The possibility that the dead bodies of other stinging insects can become allergenic is discussed by Agarwal *et al.* (26) in India for the mosquito *Anopheles Stephensi* and by Trudeau *et al.* (27), in Florida for the cat flea *Ctenocephalides felis*. But in both studies on one hand no inhibition studies were undertaken to see whether there is a cross reactivity between the mosquito, the flea and other arthropods such as house fly, cockroach, spider and on the other hand no skin tests to different arthropods have been performed. It is worth noting here that the major allergen of *Aedes aegypti* have been cloned and sequenced: Aed a 1, Aed a 2. As for us, we demonstrated that 20 patients allergic to the 2 mosquitoes *Culex pipiens* and *Aedes albopictus* strong local reactions after being stung by

mosquito and developed at the same time an allergic rhinitis; both symptoms disappeared after specific immunotherapy.

From a clinical point of view we must add that patients having an inhalant allergy to arthropods do not generally have a notable reaction to Hymenoptera stings. It seems that the antigens of the venoms from Hymenoptera (bees, wasps and ants) and the antigens from the salivary secretions of Diptera (flies and mosquitos) and Siphonaptera (fleas) are different from the antigens of the whole body.

■ **The underground ecological niche:** In a recent study Berenger Leveque (28) found many arthropods in the Paris underground railway where the atmosphere is humid with a constant temperature between 28 to 35° centigrades all around the year realizing a kind of subterranean tropical entomologic jungle. The more important species were: the cricket, *Acheta domestica*, a spider, *Tenegeria domestica*, a fly, *Drosophila melanogaster*, two species of cockroaches, *Blattella germanica* and *Blatta orientalis*, a mosquito *Culex pipiens*, the silverfish *Lepisma saccharrina*, *Psychoda phalaenoides*, a dermestes, and a *Psocus* whose species was not precised.

We want to stress here the fact that, as far as we know, we found no report on the house spider *Tegenaria domestica* which, according to our observations, is one of the more important household insects.

■ **Recent findings:** It is interesting to note that all over the world people find new insects as a cause of respiratory allergy. Recently Niphadbar *et al.* (29) described *Psocoptera spp* (book loose) as a major house hold allergen in Mumbai (India). For Kagen (30) copepods: *Pseudocalanus elongates* is an important cause of respiratory allergy in the USA (Great Lakes area) and probably all over the word because this tiny aquatic animal crustaceans is distributed wherever water exists. In Spain, Feo Brito *et al.* (31) have described an occupational respiratory allergy among furrious and related to the inhalation of dermestidae which belong to the coloptera family. The above list is not of course exhaustive. We can mention here cases of respiratory allergy to:

- *Sitophilus granarius* among bakers and people working with cereals.
- The carpet beetles *Trogoderma versicolor*, *Anthrenus verbasci*.
- The cricket *Acheta domestica*.
- The role and allergenicity of predatory mites (*Cheyletus tenuipilis*, *Phytoseiulus similis*, *Hypoaspis miles* and *Amblyseius cucumeris*) which is a well known cause of respiratory allergy among greenhouse workers, must beexplored in a more systematic way.

Invertebrates acting as aeroallergens

Food allergy in relation to crustaceans, mollucs and gastropods is a well known phenomenon. We want to stress here the importance, in some precise cases, of invertebrates as aeroallergens. As far as we know this type of allergy is found in four cases.

■ **Allergy to fish baits:** The following cases occur mostly among hobbyists but also among people working in fish baits factories. Respiratory allergy to fish bait is not rare among fishermen. Flies are used by anglers in fresh waters: *Calliphora erythrocephala* (mosca carnaria), *Echinodorus plasmosus* larvae, *Tenibrio molitor* (beetle) larvae bee; *Eisenia foetida* which is a earthworm is also used. In sea fishing, marine worms are mostly used: *Marphysa sanguinea* in the Mediterranean area. In all these cases we have reports of allergy. In Provence the worms *Perenereis cultrifera*, *Nereis diversicolor*, *Sipunculus Nudus* and some crustaceans are also used.

■ **Sea squirt asthma:** It is also a professional disease. The inhalation of a marine sponge, as an occupational allergy, has been reported by Baldo *et al.* (32). Sea squirt asthma (Hoya asthma) (33) is an allergic asthma induced by inhalation of sea squirt (*Styela plicata*) substance first and mostly described by Mitsui *et al.* (34). *Styela plicata* is an ascidia (Tunicate) which firmly adheres to the outside of oyster shells and which is scattered by the hammer of the laborers during the seasonal period of shucking oysters. Three antigens have been isolated from sea squirt named Gi-rep, E1M and DIIIa of average molecular weight 106.000, 22.800 and 9.980 respectively.

■ Crustaceans respiratory allergy

Many of these crustacean have been sequenced and cloned:

- *Metapenaeus ensis* (greasy back shrimp) :
Met e 1 tropomyosin
- *Penaeus aztecus* (brown shrimp):
Pen a 1 tropomyosin
- *Penaeus indicus* (indian shrimp):
Pen e 1 tropomyosin
- *Parapenaeus fissurus* (Taiwan shrimp)
Par f 1 tropomyosin
- *Panulirus stimpsoni* (spiny lobster):
Pan s 1 tropomyosin
- *Homarus americanus* (american lobster):
Hom a 1 tropomyosin
- *Charybdis feriatus* (crab):
Cha f 1 tropomyosin

It is interesting to not that all these allergens are tropomyosins.

It has been mostly described among workers in crustaceans-processing factories. Several species have been involved:

- Prawns (*Nephrops norvegicus*) (Mc sharry *et al.* in Scotland) (35).
- Snow Crab (*Chionoecetes ophidis*) (Cartier *et al.* in Canada) (36).
- Shrimp (*Penaeus setiferus*) (Lehrer *et al.* in New Orleans) (37).
- *Limulus Amoebocyte* lysate (Ebner *et al.*) (38).

It has also been described the appearance of asthma or allergic rhinitis resulting from inhalation of cooking vapors of crustaceans or molluscs, on workers exposed to steam generated during the boiling of snow crab. At home in a kitchen, the same phenomenon may occur. It is a fact we must keep in mind for the smell of fishes may also trigger respiratory symptoms.

■ **Coelenterate professional allergy:** In a recent paper from Japan, Onizuca *et al.* (39). described a professional respiratory allergy among fishermen during the fishing season of spiny lobster due to a marine coelenterate, red soft coral (RSC), *Dendronephthya nipponica* which is caught together with the spiny lobsters. They have achieved the purification of the major allergen of RSC: Den n 1. Another red soft coral, *Alcyonium gracillimum*, has also been described and purified by Takeda *et al.* (40).

The concept of panallergy to invertebrates

Our clinical findings and our immunological works have established the concept of the existence of common epitopes between the extracts of various insects and arthropods (34, 35). As a further step we have shown that the concept of panallergy extends itself to all the invertebrates.

But what are the panallergens involved?

The following ones are good candidates: Tropomyosin, Paramyosin, carbohydrate cross reactive determinant (CCD) but probably others will show up in the future.

At a clinical point of view, this concept implies that when a patient is allergic to one insect or invertebrate, he is bound to be allergic to some others. This aspect of the question was fully expressed in a previous paper. As an example we found that patients having allergy to crustaceans, have positive skin test to a domestic spider, *Tegenaria domestica* (which belongs to the Arachnida class).

CONCLUSION AND PROSPECTS FOR THE FUTURE

Arthropod inhalant allergy seems to us an important and underestimated cause of respiratory IgE media-

ted allergy (mostly asthma and sometimes allergic rhinitis) all over the world. Spiders, cockroaches, house flies, and moths are the commonest indoor insects found. This allergy is much more common in subtropical and tropical areas. Very often the sensitization extends to all arthropods (insects, arachnids, crustaceans) and sometimes also to some invertebrates producing a "panallergy".

In order to clarify this topic the following points must be solved:

- 1° Firstly, identification around the world, as it has already been done with pollens, molds and mites, of the most important outdoor and indoor arthropods, the later probably being much more important than the former.
- 2° secondly, assessing the reality of this clinical entity by careful clinical history, skin test, RAST and nasal or bronchial provocation test.
- 3° Next, characterization and purification of the antigens of the commonest arthropods: Spider, House fly, silverfish, Ephestia, moth (in the case of cockroaches it has already been done) keeping in mind, however, the concept of pan-allergy which could probably simplify specific immunotherapy (SIT) if there is a primary common antigen such as tropomyosin, paramyosin or C.C.D keeping in mind that there is a possibility that other panallergens will be discovered.
- 4° Precise the relationship between these antigens and the antigens already purified of mites (house dust, storage and plant mites) by RAST inhibition studies.

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