GUEST EDITORIAL
INSECT ALLERGIES – FACTS, GAPS AND FUTURE DIRECTIONS

Evidence is steadily growing that environmental exposure to insects at home and in the workplace is a frequent cause of allergic sensitisation.[1] Subsequently clinical symptoms are mainly of a respiratory nature, manifested in allergic rhinitis and asthma, but can also include urticaria[2] and, in the case of stinging insects, systemic anaphylaxis.

Many species of insects are sources of potent allergens that induce IgE-mediated allergic reactions in sensitised humans. What makes this situation even more serious is the existence of numerous allergens as indicated by current research data, which differ greatly among the **diversity of insect species.** Now, we all know that there are a lot of different insects out there. But we are probably most surprised to hear that more than 50% of all known species on earth are insects. Furthermore, it is estimated that there could be a further 8 million insect species in the world which have not yet been described. The diversity of insects and a brief overview of some reported allergic reactions are outlined in this issue by Auerswald and Lopata. Consequently it is not surprising that detailed knowledge of the precise insect species (in particular geographical area), tissue source of allergen and the molecular structure of the allergen can assist a great deal in the development of more sensitive tests to evaluate individuals with species-specific allergy to insects. This information is also fundamental in the development of appropriate environmental monitoring techniques for the evaluation of bio-aerosols containing insect allergens. This is particularly true in the occupational setting. Insects (and indeed all arthropods) are characterised by an exoskeleton and segmentations which produce large amounts of allergens found in respirable dust particles or in aerosolised form.

Sources of allergens are the dried exudate, scales, hairs, fragmented dead remains and metabolic products such as faeces, silks and venom. An important source of allergens for many insect species appears to be the faeces. It is perhaps not surprising that some investigators have documented some cross-reactivity of insects with the house-dust mite, where faeces are also the main allergen source. Baldo and Panzani[3] suggested as early as the late 1980s that one-third of insect-sensitive subjects they investigated may have had 'pan-allergy' to insects. It has been shown for the order of Orthoptera that the faeces and particularly the peritrophic membrane (a midgut secretion that encloses ingested food and surrounds the faeces when excreted) contain potent allergens. Faeces particles are usually quite large (10-40 µm) but it has been demonstrated that allergens are carried on much smaller particles, which stay airborne for a much longer time and are more likely to be inhaled and deposited in the airways.[4] Our group recently demonstrated additional allergens in the wings of locusts.[5] These findings stimulate the old question raised by Baldo and Panzani of 'pan-allergens' between different insect species, which could perhaps also be found in the wings of different insects.

Several major allergens of insects have been characterised using protein and cDNA analysis. All these allergens have high molecular weights (14-80 kDa), with some having enzymatic functions (proteases) while others are regulatory proteins (transferase, tropomyosins). Tropomyosin particularly is a candidate pan-allergen. Tropomyosin belongs to a family of highly conserved proteins with multiple isoforms found in both muscle and non-muscle cells. Allergenic tropomyosins have been identified in invertebrates such as insects (cockroaches), arachnids (mites) and also crustaceans (shrimp, lobster) and molluscs (squid, abalone), whereas vertebrate tropomyosins are non-allergenic. Studies of cross-reactivities identified high degrees of sequence identity suggesting tropomyosin as an important cross-sensitising pan-allergen.[6] This seemingly frequently encountered cross-reactivity via tropomyosins may have significant clinical implications, as has been recently suggested for cross-sensitisation between certain food and aeroallergens.[7] This has been shown particularly for shellfish allergens and tropomyosins from mites, which are related to the insect group. A recent study[8] demonstrated sensitisation to shrimp tropomyosins in orthodox Jews, who are prohibited from eating shellfish, indicating sensitisation via the inhalation route. In a different study[9] immunotherapy to house-dust mites was found to lead to sensitisation to shellfish tropomyosin, which did not exist before therapy. Interestingly these immunological findings are supported by the suggestion of entomologists that crustaceans and insects be grouped as 'Pancrustacea', as described by Auerswald and Lopata in this issue.

Because of the large number of people affected by allergic reactions to cockroaches and stinging insects, the major allergens of these organisms have been extensively studied, purified and immunobiochemically characterised. Some recombinant allergens have consequently been produced and currently evaluated for diagnostics and immunotherapy.[10] Despite the plethora of insect species currently known to cause allergic reactions, commercial tests allow the exact quantification of specific IgE antibodies for only just over 20 insect species.

Worldwide, the prevalence of cockroach sensitivity varies between 30% and 70%. To show the significance of sensitisation to very closely related insect species Lopata *et. al.* highlight in this issue the frequency of **sensitisation to three different cockroach species** in southern Africa. Currently the standard diagnosis in southern Africa relies mainly on the detection of specific IgE to the German cockroach (*Blatella germanica)*, while many other species are widespread. The data presented clearly show that individuals living in areas at high altitude (Pretoria and Harare) develop specific IgE mainly to *B. germanica*, whereas specific IgE to *Blatta orientalis* and *Periplaneta americana* are frequently encountered in Cape Town and Durban. This IgE response is evidently a direct response to environmental exposure; the dry and colder winter months in areas of higher altitude seem not to favour the growth of the American and Oriental cockroach. Species-specific sensitisation to different cockroaches needs to be given diagnostic consideration in southern Africa.

In general, sensitisation to insects occurs in about 30% of individuals with high-risk exposure. Allergenic insects are not only found at home but frequently in various types of workplaces which engender exposure to a number of insect species concurrently. However, few studies have analysed the entire spectrum of possible storage pests. A recent study of sensitised grain-mill workers in Spain[11] demonstrated prevalence rates of up to 36% and 50% for the Oriental cockroach and mealworm respectively. In the current issue Jeebhay *et al*. present epidemiological data on **a cross-sectional study conducted among 111 workers employed in a grain-mill** in Cape Town. Prevalence rates of sensitisation to five different insect species ranged from 13% for mealworm to 22% for the German cockroach. Sensitisation to five different mite species was also very common with up to 41% sensitive to house-dust mite. When looking at predictors for respiratory symptoms and asthma among grain-mill workers, as expected, the different mite species play an important role. However, very surprisingly two insect species, the Oriental cockroach and mealworm are significant predictors of work-related wheezing, hay fever and doctor-diagnosed asthma. The findings of Jeebhay *et al*. support previous studies that storage pests are an important consideration in symptomatic grain-mill workers, particularly those who fail to demonstrate IgE reactivity to cereal grains and storage mites on initial testing.

If we think one step further from the contaminated grain in the mills to the final end-user product, we have to recognise that insect allergens are a reality as hidden allergens in food products. Data on anaphylactic reactions to storage-mite-contaminated flour have recently been published.[12] This results in blurring the distinction between the domestic and occupational settings when trying to attribute causation for symptoms observed in affected individuals.

Sensitisation to insects is commonly associated with **allergic reactions to the venom of stinging insects** such as bees, but also wasps and ants. Severe allergic reactions have been encountered by sensitised individuals since thousands of years ago, as reported of the Egyptian Pharaoh Menes (2640 BC). Again, hypersensitivity to bee venom is not only seen in the domestic environment but also frequently among bee-keepers. Not only venom but also body dust is a major source of allergens for those employed in the honey production industry or those using bees as a means of pollinating greenhouse crops. The role of the pollens originating from the plants used to feed the bees should also not be overlooked as a potential sensitising agent. In this issue Potter gives a comprehensive overview on local and systemic IgE-mediated reactions following bee stings. Subsequent to positive diagnosis, via skin-prick tests and ImmunoCAP, patients can undergo immunotherapy. Immunotherapy to bee-venom hypersensitivity is highly effective in over 80% of cases, but has to be continued for up to 5 years. Interestingly immunotherapy to fire ants is also available and widely administered in countries where these insects are endemic.

In conclusion, we have identified a great need for further detailed characterisation of insect allergens which will allow the specific detection of sensitised individuals. Subsequent productions of pure recombinant allergens have the potential for application in diagnosis and immunotherapy. These findings will ultimately refine immunotherapy to stinging insects and hopefully stimulate studies into other very common insect allergies.

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