

IgE-Mediated Asthma and Rhinitis I: A Role of Allergen Exposure?

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Abstract: Exposures to airborne protein antigens, aeroallergens, may cause sensitization with production of Th2-dependent antibodies, including IgE. The IgE antibodies and associated cellular responses are responsible for the allergic airway diseases, allergic rhinitis and allergic asthma, which are increasing in societies with Western life style. Aeroallergens may have different potential to sensitize exposed subjects. Thus, there are only a limited number of important groups of aeroallergens, which are those from house dust mites, cockroaches, pets, pollens, and moulds. Allergy follows to a certain extent the pharmacological/toxicological paradigm of dose-response relationship. Unlike effects of pharmacologically and toxicologically active substances, allergens elicit their adverse effects in a two-stage process. In the first stage the immunologically naïve individual is sensitized to the allergen. In the second stage renewed exposure to the allergen elicits the disease response. Also, high concentrations of aeroallergens may induce immunological tolerance. The scientific literature suggests that many environmental factors contribute to the increase in sensitization and development of airway allergies. Nevertheless, the dose-response relationships apply (within certain limits) both to the sensitization itself and to the exacerbation of the diseases. This suggest that exposure reduction may be one of the methods for reduction of risk, in relation to control of the allergic airway diseases.

The prevalence of asthma (characterized by intermittent shortness of breath) is reported to increase in countries with Western life style (Schäfer & Ring 1997; Beasley *et al.* 2000), especially in children and young adults (Woolcock & Peat 1997; Weiss *et al.* 1993). Similarly, rhinitis (characterized by sneezing, rhinorrhoea and/or nasal congestion) has increased significantly over the recent decades (Schäfer & Ring 1997; Woolcock & Peat 1997). Many of the reported asthma prevalences are from repeated cross-sectional studies using questionnaires and thus the increase in prevalence may be influenced by differences in reporting, diagnosis and public awareness (Magnus & Jaakkola 1997). However, the trend is reported consistently in a large number of independent studies, suggesting that the increase is real. Furthermore, after a lag time the increased disease prevalence in children is also expected to appear in the adult population. This has been confirmed recently for allergic rhinitis in a population of Danes, aged 15 to 41 years (Linneberg *et al.* 2000). This study also determined serum specific IgE antibodies, which is an objective measure of sensitization to common respiratory allergens. The prevalence of being sensitized increased from year 1990 to 1998 (Linne-

berg *et al.* 2000). In the 1998 study, about 1/3 of the population was sensitized to at least one common respiratory allergen (Linneberg *et al.* 2000). In this report, we use the term allergen (aeroallergen) for airborne protein antigens, which induce allergen specific IgE productions, i. e. the subjects are sensitized to the allergens. If not otherwise stated, the considered allergies are caused by immune reactions to aeroallergens, and we use the term airway/respiratory allergy either for allergic rhinitis (hay fever), allergic asthma, their combination or for their symptoms.

Both asthma and rhinitis may be caused by allergic as well as non-allergic mechanisms. The two forms of the respective diseases, perennial allergic and perennial non-allergic rhinitis (Amin *et al.* 2001) and allergic and non-allergic asthma (Holt 1998), have infiltrations in the airways with the same types of inflammatory cells. Non-allergic asthma is often caused, for example, by occupational exposures to low molecular weight substances (Nielsen *et al.* 1995; Frew 1996). There is a close relationship in elderly subjects between the prevalence of asthma and total IgE level (Burrows *et al.* 1991), but more than half of the patients had the onset of their asthma in the setting of an upper respiratory tract infection (Bauer *et al.* 1997). However, the strong correlation between serum titers of total IgE antibodies and the manifestation of asthma in all age groups points to allergy as a major determinant of the dis-

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ease (Holt 1998). Non-allergic rhinitis may, for example, be due to vasomotor rhinitis or chronic sinusitis as well as induced by drugs or airway irritants (Settipane & Lieberman 2001). Allergic rhinitis has been estimated to affect about 20–40 million Americans, non-allergic rhinitis about 17 millions and their combination about 22 millions (Settipane & Lieberman 2001). As allergy seems to be a major determinant of asthma and rhinitis, we devote this review to the allergic reactions.

The importance of an increase in the length of the exposure period, which is expected to correlate with received dose of allergen, can only be determined from longitudinal studies as early events in infancy are important for predisposition to allergy (Holt 1998). Sensitization to common aeroallergens increases with age and thus with the length of the exposure period. Thus, in a recent Danish study (Ulrik & Backer 2000), male and female patients, aged 7 to 17 years, were followed for 6 years and skin prick tests were performed to the aeroallergens from birch, grass, mugwort, horse, dog, cat, house dust mites and the moulds *Alternaria iridis* and *Cladosporium herbarum*. Sensitization to at least one of the aeroallergens increased from 26 to 44% over the period. Also, allergic airway diseases increase with age (Ulrik & Backer 2000) and thus with the length of the exposure period. Similar results were found in other studies. A seven-year follow-up of American college students showed that new cases of hay fever occurred in 12.6%, non-seasonal allergic rhinitis in 4.8%, and new asthma in 2.5% (Hagy & Settipane 1976). A 23-year follow-up of the same students, now reaching a mean age of 40 years, showed a gradual increase of the cumulative incidence of hay fever during the entire exposure period. The final prevalence (31%) did not seem to level off (Greisner *et al.* 1998).

Not all sensitized subjects develop allergic airway diseases. Thus, the prevalence of asthma was 4.7% in male Danish conscripts born between 1973 and 1975 (Steffensen *et al.* 2000). A similar result (5.6%) was found in a random population of Swedish subjects, aged 20 to 46 years (Plaschke *et al.* 1999). However, the prevalence of allergic airway diseases is increasing in children and juveniles. In the recent Danish study that followed 7 to 17 years old subjects for 6 years, asthma rose from about 5 to 15% and rhinitis from about 14 to about 22% (Ulrik & Backer 2000). Higher values can be found in children in other Westernized countries. In an Australian birth cohort, established in 1989–92, 31% of the children had asthma diagnosed by a physician at the age of six years (Oddy *et al.* 1999). However, in 50% or more of infants with recurrent wheeze do the asthma symptom resolve before adolescence (Warner *et al.* 2000). Wheeze is a symptom that is used extensively in questionnaire studies to identify asthmatics. This symptom shows a close agreement with asthma diagnosed by respiratory physicians, although it tends to over-estimate the asthma prevalence in children (Jenkins *et al.* 1996) as viral infections may also trigger wheezing (Taussig 1997). This may offer an explanation why it also has been reported that asthma persisted in the majority (84%) in adulthood al-

though relief occurred in symptoms (Kjellman & Gustafsson 2000). Presence of eczema, hay fever, skin test reactivity, and any atopy in childhood was associated with increased asthma severity in later life (Wolfe *et al.* 2000).

Asthma is also a significant problem in elderly populations. Thus, in a population of Americans with a mean age of 73 years, 7.5% had asthma. Additionally, the age of the first attack was 40 years or more in 52% of the asthmatics (Burrows *et al.* 1991). In another American study, the incidence of asthma in adults, 65 years and older, was comparable to the incidence in young and middle aged adults (Bauer *et al.* 1997). In a cross-sectional study in asthmatics with a mean age of 74 years, 75% were sensitized to at least one common aeroallergen (Huss *et al.* 2001b).

There is a major hereditary contribution to the aetiology of allergic airway diseases (Sandford *et al.* 1996; Schäfer & Ring 1997). However, genetic homogeneous groups can vary enormously in frequency of allergic airway diseases (Schäfer & Ring 1997), suggesting that environmental factors play a main role in the increased occurrence of these diseases. Proposed explanations for the increase in allergic airway diseases include effects from diet, housing design, population density, allergen load, air pollution, environmental tobacco smoke and respiratory infections (Weiss *et al.* 1993; Woolcock & Peat 1997; Holt 1998). Clearly, allergen exposures are not the only explanation of the increase in allergic airway diseases. The epidemiological evidence available suggests that the population-based proportion of asthma cases that are attributable to atopy, defined as skin prick test positivity to one or more common aeroallergens, is usually less than one half (Pearce *et al.* 1999).

In the United Kingdom, allergic asthma and rhinitis account for the majority of reported cases of allergic disease (asthma, rhinitis, food allergies and dermatitis) in subjects aged 16 years or more. The prevalence was 12% for both diseases. Pollen, house dust mite excreta and pet allergens were the three most common allergic triggers, 42, 27 and 17%, respectively (Brown & Hawkins 1999). In a comprehensive study in California, patients with allergic rhinitis and asthma were prick-tested with 103 different allergens. About 57 aeroallergens accounted for about 90% of all positive responses. The rank order of positive responses was pollen (grasses > weeds ≈ trees) and house dust mites > pets (cat > dog) > cockroach and moulds (Galant *et al.* 1998). In the Danish study that followed 7 to 17 years old subjects for 6 years, the increase in the prevalence of sensitization to aeroallergens was associated to allergens from house dust mites, dog, cat, grass and birch (Ulrik & Backer 2000).

Occupational asthma cannot explain the increase in asthma prevalence. First, children in the Westernized countries are generally not exposed to occupational environments. Also, in adults with asthma, only 2–25% of cases are accounted for by occupational exposures (Mannino 2000), depending on the definition of occupational asthma as work-aggravated asthma or new-onset asthma (Mannino 2000). In a recent comprehensive study, occupational ex-

posures was shown to cause between 5–10% of cases of asthma among young men and women in European and other industrialized countries (Kogevinas *et al.* 1999). In this case, the definition of occupational asthma included both new cases of asthma and asthma that was exacerbated by work. Hence, the increase in respiratory allergy seems to be caused mostly by classical allergens as pollen, mites, pets and moulds. Afterwards, the sensitized subjects may develop asthma. Then the asthmatics may experience work-related aggravation of their preexisting asthma caused by workplace exposures to respiratory irritants such as dusts, fumes and sprays (Tarlo *et al.* 2000).

The health economic burden due to the increase in allergic airway diseases is considerable. Thus, in the United Kingdom in 1993, 11% of the total net ingredient costs of prescriptions were spent on asthma drugs (Warner *et al.* 2000).

This review addresses the role of exposures to common aeroallergens in Westernized societies, as these exposures may be one of several causes responsible for the increase in the allergic airway diseases. As will be highlighted in this report, sensitization and development of the diseases largely follow dose-response relationships. As an important consequence, reduction of exposures to the common aeroallergens may constitute one simple primary prevention measure in relation to risk-reduction of allergic airway diseases. However, it has to be taken into account that unlike effects of pharmacologically and toxicologically active substances, allergens elicit their adverse effects in a two-stage process. In the first stage, the immunologically naïve individual is sensitized to the allergen. In the second stage, repeated exposure to the allergen elicits the disease response (Corry & Kheradmand 1999; Poley & Slater 2000).

Properties of allergens

Sensitization to environmental allergens, which cause activation of type 2 helper (Th2) cells and formation of allergen-specific IgE antibodies, is the underlying mechanism in the development of allergic asthma and allergic rhinitis (Frew 1996; Corry & Kheradmand 1999). The immunogenicity (potency) of proteins to induce production of antibodies varies enormously. Thus, the sensitization against rat urinary proteins occurs in the pg/m³ range, with fungal α -amylase it is in the low ng/m³ range, while wheat flour proteins and proteins from pigs and cows cause sensitization in the μ g/m³ range (Heederik *et al.* 1999). Mouse and guinea pig studies analyzing the specific IgG1 antibody production, which is another Th2 dependent antibody, also showed that proteins have different potencies. From a preventive point of view, it is important to note that the two species ranked the potencies in the same manner. Not less important, the potencies were in alignment with clinical data on the prevalence of occupational sensitization (Robinson *et al.* 1998). However, individuals who make IgG, including IgG4, antibodies without IgE antibodies do not have an increased risk of developing asthma or rhinitis (Platts-Mills *et al.* 2000b).

Risk of sensitization shows exposure-response relationship and thus suggests the existence of a no-observed-effect level (Heederik *et al.* 1999). However, atopics, i. e. subjects that are inheritably predisposed to produce elevated amounts of IgE antibodies, are more easily sensitized than non-atopic subjects are (Heederik *et al.* 1999). As different subgroups exist, it is difficult to establish a population-based safe exposure level.

Overall, there is no recognized characteristic structural feature of allergens, and their ability to sensitize and induce antibody production (immunogenicity) cannot be predicted theoretically at present. In contrast, cross-reactive proteins share common features on the level of primary and tertiary structure. However, proteins with a similar tertiary structure, i. e. they have a similar folding, are not necessarily cross-reactive. Also, cross-reactive proteins need not themselves be immunogenic (Aalberse 2000). A number of important allergens are proteases. Thus, the allergen *Der p 1* and *Der f 1* from house dust mites are cysteine/thiol proteases (Breiteneder & Ebner 2000). They may cleave the low-affinity IgE receptor (CD23 or Fc ϵ R2) on the IgE producing B cells. As CD23 serves as a negative regulator of IgE production, protease activity may play a role in the allergic response (Corry & Kheradmand 1999). Additionally, occupational exposures suggest that enzymes at air concentrations of approximately 1 ng/m³ are important occupational allergens (Kampen *et al.* 2000).

The risk of developing an allergic airway disease and its type depends on the aeroallergen, which can be rationalized in crude rules of thumb. Indoor allergens from house dust mites, cats, dogs and spores from the indoor mould *Aspergillus fumigatus* are risk factors for the development of asthma in children and adults. This also applies to spores from the moulds *Alternaria* and *Cladosporium*, which predominantly occur in outdoor air. In contrast, sensitization to pollen, for example from grass and ragweed, constitutes a low risk for the development of asthma, but does constitute a high risk for the development of seasonal allergic rhinitis (Nelson 2000). This may be illustrated from cypress pollen rhinitis patients. In addition to rhinitis, about 80% had conjunctivitis, but asthma occurred only in 7–19% of the patients (Bousquet *et al.* 1993). However, half of the patients with seasonal rhinoconjunctivitis due to alder, hazel or hornbeam also had asthma (Troise *et al.* 1992). Seasonal allergic rhinitis is primarily caused by airborne pollen, hence the term pollinosis (Wu *et al.* 1999). The type of disease reflects partly the size of the allergen and thereby its deposition in the respiratory tract (Horner *et al.* 1995). Pollen grains have sizes from 15 to 40 μ m, but there are also airborne pollen-allergen-carrying particles of much smaller sizes than the intact pollens (D'Amato *et al.* 1998).

Sensitization to aeroallergens may also be responsible for the development of many food allergies due to IgE cross-reactivity. The phenomenon has caused special attention due to the steadily increase in prevalence of airway allergies (Breiteneder & Ebner 2000).

Clinically important aeroallergens

House dust mites.

In Britain, house dust mite and pet allergens are the predominant indoor allergens (Brown & Hawkins 1999). Exposure to dust mite allergens is suggested to be a worldwide problem as sensitization to the allergens may be an important cause of asthma (Platts-Mills & de Weck 1989). The highest number of mites is usually found in bedding (Dowse *et al.* 1985; Platts-Mills & de Weck 1989; Peat *et al.* 1996), but upholstered furniture and carpeting are other important sources (Platts-Mills & de Weck 1989). Additionally, clothing may be an important source of house dust mite allergen exposure (Lucca *et al.* 2000). House dust mites may also infest office environments, especially fabric-covered office chairs. In a recent publication (Janko *et al.* 1995), it was reported that one-half of the offices studied had dust mite infestation. About 30% of the offices showed levels of the dust mite allergen *Der p 1* from *Dermatophagoides pteronyssinus* greater than 1 µg/g dust. In approximately 15% of the offices, the dust mite allergens were the source of the health complaints.

The optimum temperature for mite growth is about 20° with an optimum humidity in the range of 55 to 75% relative humidity, depending on the temperature (Platts-Mills *et al.* 2000b).

In Australia, the levels of the house dust mite allergen *Der p 1* in dust from beds were low in the hot and dry inland area and high in the semi-tropical area. The *Der p 1* allergen level increased on a gradient corresponding with increased humidity. The percentage of children who were sensitized to the mites increased with increasing *Der p 1* level as did the risk of current asthma and the severity of airway hyperresponsiveness in sensitized children (Peat *et al.* 1996). In children, aged 5–12 years, with mild- to-moderate asthma, the prevalence of house dust mite sensitization was positively correlated with the increase in exposure-concentration and with the atopic status (Huss *et al.* 2001a). A population-based 2-year follow-up study in primary school children in Germany and Austria suggested that children not sensitized to *Der p 1*, but sensitized to other respiratory allergens (i.e. atopic subjects), had an increased risk of becoming sensitized to the mite allergen if exposed to mite allergen levels above 2 µg/g in dust from mattresses. Non-atopic children were less sensitive (Kuehr *et al.* 1994). Sensitization to house dust mite allergens followed the classical dose-response relationship, taking into account that subjects with and without atopy have different sensitivity.

House dust mite concentrations in dust from mattresses and beddings may play a major role in the maintenance of the allergic airway inflammation. Thus, in asthmatics with positive prick test to house dust mites, there was a dose-response relationship between the exposure level of the allergens and disease severity with increased bronchial hyperresponsiveness and variability of peak expiratory flow rate in addition to a decrease in forced expiratory volume in one second (Custovic *et al.* 1996). When patients with

mite-sensitive asthma were moved to a high altitude where mite allergen levels are low or to a mite-free environment of a hospital, their asthma improved clinically and physiologically. However, reexposure resulted in a rapid relapse (Custovic *et al.* 1998).

Encasing mattresses, pillows and duvet with a mite-impermeable membrane may cause a major reduction in exposure to the house dust mite allergens (Custovic *et al.* 1998; Jirapongsananuruk *et al.* 2000). Hot water wash of beddings is another of the measures for control of dust mite allergen exposures (Custovic *et al.* 1998). Reduction of humidity may also be used for mite control (Custovic *et al.* 1998). A novel treatment, which combined steam and heat treatment of home furnishings, dramatically reduced asthmatic patients' bronchial hyperreactivity. House dust mite antigen loads were reduced over a 12-month observation period (Htut *et al.* 2001). As carpets are an important microhabitat for mite colonization, they are a place from which beds can be reinfested (Custovic *et al.* 1998). A comprehensive reduction in mite allergen exposure requires integrated approaches as barrier methods, dust removal and removal of mite microhabitats (Custovic *et al.* 1998).

Many studies with allergen avoidance have shown disappointing results (Custovic *et al.* 1998; Gøtzsche *et al.* 1998). However, many of the studies were poorly controlled and used methods, which are now realized to be unable to reduce mite allergen exposure (Custovic *et al.* 1998). Also, patients with asthma who are sensitized to mites are usually sensitive to other allergens and, thus, elimination of one of the allergens may be of limited benefit (Gøtzsche *et al.* 1998). Nevertheless, beneficial outcomes are reported from studies, which achieved both a significant reduction in mite/allergen levels and where the follow-up times were sufficiently long (Custovic *et al.* 1998; Htut *et al.* 2001).

The importance of dust mite allergens as the cause of asthma can be illustrated from a classical study in the Papua New Guinea highlands (Dowse *et al.* 1985). The prevalence of asthma rose approximately by a factor 40 over about one decade where blankets and changes in sleeping habit occurred. This promoted growth and exposure to house dust mites. Additionally, dust mite allergens prevailed when compared with allergens from pollens, moulds, and animal dander (Dowse *et al.* 1985). A comparative study in Wagga Wagga in Australia showed that house dust mite counts increased from 1982–83 to 1992. Also in the first study period, 15% of the houses were infested with mites whereas this value increased to 90% in the latter period (Green *et al.* 1993).

High prices of energy have resulted in insulation and decreased ventilation of buildings in Westernized countries with a cold climate. This may cause optimal climatic conditions for growth of house dust mites, confirmed in a renovation project in the former East Germany where apartments were studied before and seven months after installation of insulated windows and central heating systems (Hirsch *et al.* 2000a). The renovation decreased the air-exchange rate and increased the building temperature. The

house dust allergen, *Der f 1*, from *Dermatophagoides farinae*, which was the most abundant house dust mite species in the area, nearly doubled in the dust from carpets and mattresses after the renovation. Also, carpet dust concentrations of *Aspergillus fumigatus* increased whereas the counts of other mesophilic fungi did not increase consistently.

Epidemiological studies suggest similar connections. In a comparative study between Erfurt in the former East Germany and Hamburg in the former West Germany, the allergens from house dust mites, *Der p 1* and *Der f 1*, were three and five times higher in Hamburg (Fahlbusch *et al.* 1999). In general, the prevalence of respiratory allergies and specific IgE levels were significantly higher in subjects from West German regions (Fahlbusch *et al.* 1999). In the former East Germany, the cost of heating was low. Thus, opening of windows was often used to control temperature in apartments. The West German buildings were better insulated and more airtight (Fahlbusch *et al.* 1999). Similarly in a Danish study (Harving *et al.* 1993), the number of house dust mites was higher in houses with low ventilation, resulting in higher air humidity. Furthermore, homes of mite-allergic subjects had higher concentrations of mites than did those of the non-mite allergic subjects. Also, the occurrence of mites increased over time, probably due to increased insulation.

Even in desert environments sensitization to house dust mites can be unexpectedly high. Thus, in Kuwait about 1/3 of the patients with allergic rhinitis had specific IgE antibodies to one of the three house dust mites, *D. pteronyssinus*, *D. farinae* and *D. microceras*, and these were among the prevalent indoor sensitizers. The use of air conditioners may have created indoor climate conditions that are conducive to mite growth (Dowaisan *et al.* 2000).

There are many indirect evidences, which support the hypothesis that dust mite exposures have increased in some parts of the world. However, only few studies have performed measurements over longer periods, which provide experimental support for the hypothesis. On the global level, the house dust mite allergen exposure may only be responsible for a minor part of the asthma prevalence. Thus, the weighted average of the population attributable risk in children was estimated to be no more than 4% for *Der p 1* (Pearce *et al.* 2000).

Overall, exposures to house dust mite allergens may have increased in some parts of the world and in these areas the exposures may account for a part of the increase in the allergic airway diseases. Thus, it has been suggested that reducing exposure to these allergens could have public health benefits in terms of asthma prevention (Peat *et al.* 1996). In general, allergen avoidance should be the first line of control of the inflammatory reactions of the allergic airway diseases. Low humidity in buildings is important for prevention of growth of house dust mites and moulds. Enclosure of mattresses and pillows together with hot water washing ($\geq 60^\circ$) of bed clothes and mattress pads are other methods of exposure-reduction. Carpets may represent an

important nest for mites and a reservoir for other allergens. Vacuum cleaners cannot remove live mites from carpets and therefore allow debris to accumulate. Removal of carpets and thorough cleaning may be other methods to decrease the allergen exposures (Platts-Mills *et al.* 2000b).

Cockroach.

Allergens (*Bla g 2*, *Bla g 4* and *Bla g 5*) from the German cockroach, *Blattella germanica*, cause sensitization in areas where infestation is common (Platts-Mills *et al.* 2000a). It can be an important sensitizer even in a desert country as Kuwait where about 50% of the patients with allergic rhinitis were sensitized to cockroach (Dowaisan *et al.* 2000). Sensitization to cockroach allergens is strongly associated with exposures. If food is available, they can survive at low humidity (relative humidity < 20%) as they can move around and find a water supply. However, as cockroaches are tropical in origin they cannot move from one house to another if the outdoor temperature is below 10° at night. Hence, they are generally not a problem in single-family homes (Platts-Mills *et al.* 2000b). Also, in communities where less than 5% of the houses have more than 10 units *Bla g 2/g* dust, sensitization to cockroach allergens will be rare and will not be associated with asthma (Platts-Mills *et al.* 2000a).

Pets.

A recent comprehensive review has dealt with the effect of pet allergen exposure (Ahlbom *et al.* 1998). Exposures to pet allergens in early infancy increase the risk of sensitization, development of symptoms and health effects as asthma and allergic rhinitis. Also, pet allergens occur ubiquitously, including locations where no pets are held. However, the exposure levels are highest where pets and people who have pets at home are present. In the mentioned comparative study from Erfurt and Hamburg, it was found that the concentration of the cat allergen, *Fel d 1*, was three times higher in Hamburg (Fahlbusch *et al.* 1999). This is consistent with the finding that cats and dogs were kept more frequently in West German homes (Hirsch 1999). Substantial differences in allergen concentration may be found in house dust samples from homes with and without pets. In a recent study, homes with cats or dogs had approximately 100 times higher levels of the respective allergens *Fel d 1* and *Can f 1* (Gereda *et al.* 2001).

Clothing is an important reservoir of cat allergen, especially woolen sweaters, jackets and cotton sweat shirts, which are less frequently washed, and worn T-shirts. Clothing of cat owners distributes the allergen into cat-free environments and it is an important source of exposure of non-cat owners, which therefore may inhale an increasing number of particles carrying cat allergens during the workday (Lucca *et al.* 2000). Also, the median levels of airborne cat allergen *Fel d 1* in school classes with many (>25%) cat owners were 5 times higher than the levels in classrooms with few (<10%) cat owners (Almqvist *et al.* 2001).

In Sweden in a random sample of the general population,

aged 20 to 44 years, about 15% were sensitized to cat and about 14% to dog allergens (data obtained from Plaschke *et al.* (1999)). Also, pet allergens were the most important in terms of development of asthma and bronchial hyperresponsiveness, whereas the relationships with sensitization to grass and house dust mites were less pronounced. In adult asthmatics, about 50% were sensitized to pets (cats and/or dogs), 40% to grass pollen and 20% to house dust mites. In Sweden the number of household pets has increased during the last decennia and 73% of the population were present or former pet owners. Additionally, 83% of pet owners allowed their pets in the bedroom and only 2.6% kept their pets outdoors. High exposures to pet allergens in Sweden have been proposed to explain a part of the increase in asthma prevalence (Plaschke *et al.* 1999).

In Sweden in the period 1990–1992, the prevalence of grass pollen positive subjects, aged 20 to 44 years, was about 15% (Plaschke *et al.* 1999). This can be compared with the 12% prevalence in the Copenhagen study in 15- to 41-year-old subjects in the year 1990 (Linneberg *et al.* 2000). A reasonable explanation is that the two geographically closely situated countries have approximately the same grass pollen exposure. In contrast, the prevalence of dog (4.2%) and cat (4.6%) allergy was much lower in the Copenhagen study. This may reflect that only 16% had a cat and 30% a dog in the Copenhagen study (Linneberg *et al.* 2000).

Nevertheless, the overall picture is complicated by the fact that tolerance may develop. Thus, a recent study showed that children exposed to cat during the first year of life were less often skin prick test positive to cat allergens at 12–13 years (Hesselmar *et al.* 1999). Similar results have been obtained in a number of studies (Platts-Mills *et al.* 2000b). They suggest that children living in environments with cat allergen levels of 4 to 20 µg *Fel d 1* per gram of dust are more likely to become allergic than those exposed to ≥ 20 µg per gram of dust. The high exposure level induces IgG and IgG4 antibodies to *Fel d 1* without skin sensitization and IgE production. This may be considered a modified Th2 response. Thus, removing the cat from the home of a family within a community where many families have cats may actually promote the development of allergy. If children first are sensitized to pets or pollen, they do not normally develop tolerance later in life (Kjellman & Gustafsson 2000).

Different mechanisms exist for development of tolerance. From studies in mice often with the model allergen ovalbumin, it is well known that high concentrations of specific IgE antibodies may be obtained by periodic injection of small doses (0.1 or 1 µg per animal), while the injection of a large dose (100 µg) of the allergen could only induce an early and transient IgE response (Tada 1975). Thus, a persistent IgE production may be absent at high exposure levels. However, a dose-response relationship for IgE production may exist at the low dose level (≤ 1 µg per animal) as shown in BALB/c mice that were injected with ovalbumin (unpublished results, S. T. Larsen from our group). Thus, it is tempting to speculate whether high pet allergen loads in

themselves may induce tolerance. Another recently discussed possibility is that the adjuvant effect of endotoxins (bacterial lipopolysaccharides, LPS) causes the development of tolerance (Martinez 1999; Gereda *et al.* 2001). LPS levels are much higher in house dust from homes with pets (Gereda *et al.* 2001). The high levels of LPS are possibly caused by gram-negative bacteria from the gastrointestinal tract of the animals as neither building type (house or apartment), home dampness, number of household inhabitants or young children, cleaning frequency, carpeting or presence of tobacco smokers influenced the dust LPS level (Gereda *et al.* 2001). LPS is a potent inducer of Th1-type cytokines (e.g. IL-12 and INF- γ) and therefore has the potential to inhibit Th2-driven development of IgE antibodies (Martinez 1999; Gereda *et al.* 2001).

Patients that are allergic to cats or dogs often develop symptoms within minutes of entering a home with one of these pets as they may inhale large amounts of the aeroallergens (Custovic *et al.* 1998). Also, indirect cat exposure at school is able to exacerbate symptoms in asthmatic children with cat allergy (Almqvist *et al.* 2001). This suggests the importance of exposure reduction in subjects with pet airway allergy.

Pet allergens may be important causes of asthma at the population level. Thus, the weighted average of the population attributable risks of asthma in children due to dog (*Can f 1*) and cat (*Fel d 1*) allergens has been estimated to 6 and 11%, respectively (Pearce *et al.* 2000).

All in all, asthma may be associated with sensitization to different allergens in different areas. Also, exposure to pet allergens, either due to an increased number of pets or allowing pets to stay inside the homes, may in certain areas be responsible for a part of the local increase in allergic airway diseases. However, as tolerance may develop, establishment of the dose-response relationship between pet allergen exposure and development of allergic airway diseases is complicated, especially as tolerance may be caused by a co-exposure to LPS from pets. If the exposure levels are below the high levels, which may induce tolerance, it still seems reasonable to assume that dose-response relationships exist for exposures to pet allergens in infancy. Therefore an increase in dose may increase the risk of sensitization, development of symptoms, and health effects.

Pollen

Grass pollen-induced allergic airway diseases is the most common pollen allergy in Europe with a prevalence of skin prick test positivity in pollinosis patients varying from 30–90% (D'Amato *et al.* 1998). The pollen counts reflect partly the areas of land under grass, the seed mix of sown pastures, and the replacement of haymaking by silage production, when grasses are cut before they flower (Burr 1999). Thus, exposures may strongly be influenced by anthropogenic behaviour and has, for example, been declining in certain areas and rising in other areas of United Kingdom (Burr 1999).

Birch is the major pollen-allergen-producing tree in

northern Europe whereas cypress and olive are the most important ones in Mediterranean regions (D'Amato *et al.* 1998).

In the northern Mediterranean area in Italy the exposure to pollen from alder, hazel and hornbeam increased in the period from 1981 to 1990 (Troise *et al.* 1992). This was due to an increase in their use as ornamental trees and/or due to climatic variations. In the same period, the incidence of skin prick positive reactions to these pollens increased from 6 to 24% in patients affected by seasonal rhinitis and/or asthma. All of the positive patients had seasonal rhinoconjunctivitis and half of them had asthma. Among the positive patients, 24% were hypersensitive to food, especially apples, peaches and nuts. The increase in the amount of local allergen could account, at least partly, for the local increase in atopic diseases.

The increasing pollinosis induced by Cypressaceae plants is probably related to the increasing use of these species for gardening, reforestation (D'Amato *et al.* 1998) or other uses as demonstrated in the study of Charpin *et al.* (1993), which investigated the relationship between pollen exposure and prevalence of allergic respiratory symptoms. Exposure effects were compared in two towns, Senas and Marseille, situated 50 km apart in southeastern France. Senas is located in a farming area where several hundred thousand of cypress trees have been planted to protect crops and orchards. Thus, the cypress and grass pollen counts were much higher in Senas than in Marseille. The questionnaire data showed that 31.5% of subjects from Senas and 14.1% from Marseille had hay fever. The percentage of subjects complaining of hay fever and having positive skin tests to grass or cypress pollen was 13.6% in Senas and 5.5% in Marseille (Charpin *et al.* 1993), demonstrating a clear exposure-effect relationship. The prevalence of asthma was similar in the two communities.

The cypress tree pollen counts (pollen/m³ of air) were much higher than the grass pollen counts both in Senas and Marseille (Charpin *et al.* 1993), a relationship also found from other Mediterranean areas (Bousquet *et al.* 1993). Nevertheless, skin sensitization to grass pollen was more common than sensitization to cypress pollen in hay fever patients (Charpin *et al.* 1993), suggesting that cypress pollen allergenicity is lower than that of grass pollen (Charpin *et al.* 1993). Thus, the type of pollen should be considered in relation to risk assessment of pollen-induced diseases.

Ragweed pollen is responsible for about half of all cases of pollinosis in the United States. Sensitization is increasing in Europe due to the gradual expansion of the weed in many areas (D'Amato *et al.* 1998).

Introduction of new plants may cause exposures to new aeroallergens as e.g. the wall pellitory (*Parietaria judaica*) in southern England (Rusznak & Davies 1998). Even with the scant vegetation of the desert environment in Kuwait, pollen was the major sensitizing allergen in patients with allergic rhinitis. Specific IgE antibodies to *Chenopodium* were present in 64% of the patients whereas 55% were sensitized to Bermuda grass and 50% to the *Prosopid* tree, all

imported and cultivated for the purpose of "greening" the desert. No more than 37% were sensitized to the date palm, the main plant native to the Arabian desert (Dowaisan *et al.* 2000).

All in all, sensitization and development of symptoms are related to pollen exposure levels. Also, different types of pollen may have varying allergenicity. Additionally, the anthropogenically induced pollen exposures may account for a part of the increasing prevalence of allergic airway diseases in some parts of the World.

Moulds.

Fungi have no chlorophyll (Robbins *et al.* 2000). They are ubiquitous saprophytes that rarely behave as pathogens in the airways of healthy individuals, but they are important airway allergens, especially in atopic individuals (Kauffman *et al.* 1995). Thus, fungi may cause IgE-mediated allergic asthma and rhinitis without causing infection (Kauffman *et al.* 1995; Fink 1998). Fungi may secrete proteases, which may promote sensitization as they may cause desquamation of epithelial cells, activation of the cytokine production in epithelial cells, and promotion of the Th2-driven sensitization (Kauffman *et al.* 2000). Horner *et al.* (1995) have published a comprehensive survey on fungal allergens.

Allergic fungal sinusitis and allergic bronchopulmonary mycoses are both infectious and allergic diseases, which are caused partly by IgE-IgG mediated reactions (Kauffman *et al.* 1995; Fink 1998). Important is the *Aspergillus fumigatus*-induced allergic bronchopulmonary aspergillosis. *A. fumigatus* produces spores of the size from 3 to 5 µm, which can penetrate into the lungs. Additionally, they have optimal growth at body temperature, and they produce proteolytic enzymes as well as mycotoxins (Kauffman *et al.* 1995).

High exposure levels, for example workplace exposures or exposures from mould contaminated ventilation systems, may cause another allergic disease, extrinsic allergic alveolitis/hypersensitivity pneumonitis. This is an IgG (precipitating antibody)-mediated reaction (Horner *et al.* 1995; Fink 1998) and partly a cell-mediated (delayed, type IV) hypersensitivity response (Horner *et al.* 1995).

Moulds also produce mycotoxins, which are secondary metabolites that are injurious to vertebrates upon ingestion, inhalation, or dermal contact. Typical examples are aflatoxins, which are teratogenic, carcinogenic and immunosuppressive, and ochratoxin, which can cause kidney damage. Ingestion or inhalation of high levels of trichothecenes from *Stachybotrys atra* may cause death due to hemorrhage (Robbins *et al.* 2000). Nevertheless, the current literature does not provide compelling evidence that exposures to mycotoxin levels expected in most mould-contaminated indoor environments are likely to result in measurable health effects (Robbins *et al.* 2000). However, whether the toxins at the low concentration levels may promote sensitization to the common aeroallergens seems not to have been studied.

The normal exposures to moulds are from outdoor and indoor air. The common outdoor moulds are *Cladosporium*, *Alternaria*, *Aspergillus*, *Penicillium*, *Candida*, *Helminthosporo-*

rium and *Botrytis*. The common indoor moulds are *Penicillium*, *Aspergillus* and *Cladosporium* (Fink 1998).

Skin test results suggest that at least 3 to 10% of adults and children worldwide are affected by fungal allergens (Horner *et al.* 1995).

In an Israeli rural community with a population aged 4 to 70 years, 11 to 17% of the population (depending on the cut point of the degree of sensitization) were skin prick test positive to moulds with the sensitization prevalence in the order *Aspergillus* > *Alternaria* > *Penicillium* > *Cladosporium*. *Alternaria* and *Cladosporium* are the most prevalent outdoor moulds in Israel, while *Aspergillus* is a typical indoor mould. About 29% of the population were sensitized to the house dust mites, *D. pteronyssinus* and *D. farinae*. Allergy to moulds themselves had a low predictive value to development of bronchial asthma and allergic rhinitis symptoms. Thus, only 15% of the subjects sensitized exclusively to moulds had allergic symptoms. In contrast, subjects sensitized to moulds together with pollens and/or house dust mites had symptom prevalence above 50%. This suggests that mould sensitivity alone is not as important as the other allergens in inducing allergic symptoms (Katz *et al.* 1999).

In Californian patients with respiratory allergy, 11 to 22% were sensitized to a common mould allergen, which is lower than the sensitization rate to grass pollen and house dust mites, both about 50% (Galant *et al.* 1998). Similarly in spring allergic rhinitis patients from central Indiana, the sensitization rate to fungi was about half of the sensitization rate to tree or grass pollens. Also, the symptom scores correlated with tree and grass pollen counts, but not with mould spore counts (Wu *et al.* 1999). Thus, fungal spores play a minor role in spring allergic rhinitis despite their presence at much higher concentrations than pollen grains (Wu *et al.* 1999).

As the diagnosis of mould allergy is difficult (Horner *et al.* 1995), this limitation tends to promote underestimation of the extent of fungal sensitization (Verhoeff & Burge 1997). This should be remembered when comparing the prevalences. Also, mould allergy may have severe consequences as, for example, being sensitized to *Alternaria alternata* has been associated with life-threatening asthma (Neukirch *et al.* 1999). Additionally, fungal spore exposure levels accounted for about 9% of asthma exacerbation in children that prompted an emergency department visit. The percentage increase in daily visits were additive for the moulds, deuteromycetes, basidiomycetes and ascomycetes, and they accounted for the mould-induced emergency visits. Pollens from weeds, grasses and trees were not associated with asthma exacerbations, which were in most cases due to viral infections (Dales *et al.* 2000).

Exposure reduction may be an efficient method for control of acute allergic airway symptoms caused by moulds as shown from the following examples. Indoor air exposure to *Alternaria*, which had colonized the air conditioner unit, caused outbreak of acute asthma and rhinitis in a female who was skin prick test positive to *Alternaria*. After re-

medial actions were taken, which successfully removed moulds from the air conditioner, her symptoms resolved within one week (Fung *et al.* 2000). The mould *Aspergillus versicolor* extensively colonized a new building with severe moisture content. This caused outbreak of asthma and hypersensitivity pneumonitis in the occupants of the building. A vigorous remediation was performed with removal of all visibly infested material and all fine dust on interior surfaces. The reoccupation of the building caused no cases of recrudescence or new-onset allergic chest disease (Jarvis & Morey 2001).

Overall, fungal allergy probably causes problems indoors for fewer people than do major allergens from cats, mites or cockroaches (Horner *et al.* 1995). However, several recent epidemiological studies showed positive association between home dampness and respiratory morbidity, including allergic asthma. Additionally, positive associations were apparent from fungal levels and health outcome in several of the reviewed studies (Verhoeff & Burge 1997). Indoor mould growth may be prevented. Fungal growth requires a relative humidity over 70%, except for the xerophilic fungi that are able to grow under lower water activity (Horner *et al.* 1995). Thus, dry and properly ventilated buildings prevent growth of most moulds and in addition may decrease exposure levels of house dust mites. Both conditions are expected to decrease airway allergy-induced morbidity.

Other allergens.

Other allergens may cause severe reactions in affected subjects, but at the population level they are less important.

Dust from soybean hull liberated into the air during unloading of ships has caused outbreak of epidemic asthma in several cities in the world. Surprisingly, about 6% of healthy individuals living in urbanized areas without a known source of exposure were sensitized to soybean (Codina *et al.* 2000). Both sensitization and elicitation of responses were dose-dependent. Thus, in Argentines with asthma or allergic rhinitis, the prevalence of sensitization to soybean was dose-dependent. Additionally, development of symptoms was dose-dependent in patients that were sensitized to soybean. As sensitization exclusively (i.e. monosensitization) to soybean was absent, this indicates that both an atopic background and exposure to soybean are necessary for the sensitization (Codina *et al.* 2000).

Natural rubber latex antigens from the rubber tree (*Hevea brasiliensis* (Frankland 1999)) are important sensitizers in health care workers, due to use of latex gloves, and in children with spina bifida, due to multiple surgeries that cause contact with rubber (Frankland 1999; Poley & Slater 2000). Thus, latex allergy can occur from direct contact with latex-containing products, but aerosol transmission of antigen has also been well documented (Poley & Slater 2000) and thus constitutes a special problem in operating theatres (Frankland 1999). The immediate hypersensitivity to rubber latex is an IgE-mediated reaction to the numerous allergens in latex. Commonly, health care workers are sensitized to the rubber allergens *Hev b 2*, *Hev b 4* and *Hev b 5*,

whereas spina bifida patients are sensitized mainly to *Hev b 1* (rubber elongation factor), *Hev b 3* and *Hev b 5*. The *Hev b 1* and *Hev b 3* allergens have a low solubility and they are bound mainly to particles (Poley & Slater 2000). Although latex allergens appear to be bioavailable across the skin and mucous membranes, including from aerosol exposures (Poley & Slater 2000), the exposure route partly determines what become the major allergens.

Latex contains potent allergens, which have a potency that lies between that of α -amylase and rat urinary proteins (Poley & Slater 2000). However, latex-reactive IgE antibodies without clinical relevance may appear and be due to cross-reactivity with allergens from fruits, e. g. banana, chestnut and avocado (Poley & Slater 2000).

Exposure appears to be the most significant risk factor of latex allergy, although atopy may also be a risk factor among health care workers. The reported prevalence of latex allergy varies from 5–15% in health care workers and from 24–60% in spina bifida patients (Poley & Slater 2000). The prevalence in the general population is less than 1% (Poley & Slater 2000). However, the prevalence depends strongly on the cut point of the latex-specific IgE level and, thus, could be between 1 and 7% in 9 to 10-year-old children (Hirsch *et al.* 2000b). Additionally, only about 3% of the children with latex-specific IgE were monosensitized against latex (Hirsch *et al.* 2000b). The comprehensive study included 2505 children, aged 5–11 years, and showed that latex allergens from road traffic was not associated with sensitization in children and that traffic exposure is not an important determinant for the development of latex allergy (Hirsch *et al.* 2000b).

Further information about allergens may be obtained from lists of occupational sensitizers, e. g. a recent comprehensive list (Kampen *et al.* 2000) that deals with a broad range of sensitizing chemicals and allergens with origin in animals, plants and microorganisms. Often, the occupational exposures are higher than exposures in the general population, suggesting a higher sensitization prevalence and thereby a better possibility of identifying possible allergens.

Conclusions

Exposures to airborne protein antigens, aeroallergens, may cause sensitization with production of Th2 type antibodies, including IgE. The IgE antibodies are responsible for the allergic airway diseases, allergic rhinitis and allergic asthma. In countries with Western life style, the prevalence of sensitization and development of the allergic airway diseases is increasing. It is generally accepted that this is due to several environmental factors. This review suggests that the exposure level of allergens is one of the possible factors. Thus, several local studies show an increase in allergen exposures over time, which may have accounted for a part of the local increase in the allergic airway diseases. However, the importance of global changes in allergen levels and the development of allergic airway diseases cannot be suggested due to lack of data.

From a population point of view, there are only a limited number of groups of common allergens. They are from mites, animals, pollen and moulds. Thus, the list of the most important allergens has not changed over time. However, it should be noted that different allergens have different geographical importance. Also, the available data do not allow evaluation of the relative importance of allergen exposures and other risk factors for the increase in the development of the allergic airway diseases.

Allergens have different abilities (immunogenicities/potencies) to induce IgE production, which is accessible not only from clinical and epidemiological studies, but also from animal bioassays. Combining bioassay results with clinical experiences from known allergens may allow risk assessment of allergenic effects of new proteins. However, the relevance of the risk assessment is mainly limited to occupational exposures, for example, in relation to production and the use of new enzymes and other new proteins.

Unlike effects of pharmacologically and toxicologically active substances, allergens elicit their adverse effects in a two-stage process. In the first stage, the immunologically naïve individual is sensitized to the allergen. In the second stage, renewed exposure to the allergen elicits the disease response. Furthermore, sensitization may deviate from the pharmacological/toxicological paradigm as high concentrations of aeroallergens may induce tolerance or tolerance may be due to co-exposure to bacterial products that promote a Th1 response and thereby suppresses a Th2 response with IgE production.

Sensitization to allergens and elicitation of allergic airway responses follow, at least partly, dose-response relationships. Thus, exposure-reduction is one of the important methods for controlling the allergic airway diseases, i. e. for prevention of an exacerbation of the diseases, as well as for an amelioration. Additionally, exposure-reduction may also, at the exposure levels where tolerance is not induced, be a method for reduction of sensitization, which prevents the emergence of the diseases.

Sophisticated measures may be used to reduce exposures to aeroallergens, but simple approaches should be used first. Buildings should be kept well ventilated with clean air and with an appropriate low humidity, which prevent survival of house dust mites and growth of moulds. Penetration of water through roof and leaking water pipe installations should immediately be repaired. A thorough clean up is necessary if flooding has occurred. Additional methods to reduce exposures to house dust mites include covering mattresses, hot washing of bedding, and removing carpets from bedrooms. Allowing pets to be kept in living areas of buildings may constitute a significant risk of developing respiratory allergy.

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