AEROALLERGENS AND THE RESPIRATORY TRACT

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Summary. Episodes of rhinitis and asthma are often due to allergy to inhaled particles. The site of disease is determined by the particle size of allergens, by the nature of the immunological response of the subject, and, in the case of asthma, by the presence of bronchial hyperreactivity. Particles of greater than 10 μm diameter are deposited in the nose, of approximately 5 μm at a bronchial level, and of approximately 2 μm at an alveolar level. Allergic rhinitis is due mainly to the action on the nasal mucosa of active mediators released from mast cells by an allergen - immunoglobulin E reaction. A similar mechanism is responsible for some asthmatic reactions but hyperreactivity to these released mediators must also exist. This susceptibility may be assessed by bronchial inhalation challenge with aerosols of such agents as histamine and methacholine.

Epidemiological studies of allergic rhinitis and asthma in Australia indicate marked regional differences suggesting that regional aeroallergens are important determinants of both the prevalence and incidence of these diseases.

INTRODUCTION

In this paper certain aspects of the allergic diseases asthma and allergic rhinitis (hayfever) which occur as a result of inhalation of airborne allergens will be discussed. Some of the theory of inhaled particle deposition and the disturbed immunological reactions which characterize these diseases will be outlined as will the known environmental factors which might initiate and precipitate episodes of these diseases. The epidemiology of these diseases in Australia will be reviewed.

INHALED PARTICLE DEPOSITION

The average human inhales approximately 10 000 L of air each day. This may contain a great deal of suspended particulate matter both organic and inorganic. An extremely efficient defence mechanism against this environmental burden exists, principally in the nose. As a result of turbulent airflow virtually all particles over 10 μm are deposited on the nasal mucosa and then cleared posteriorly. Particles of less than 10 μm and particularly those around 5 μm in diameter are deposited on the mucus lining of the bronchial tree. They are transported upwards by the action of bronchial mucosal cilia and thence swallowed. Particles of less than 5 μm in diameter enter the air sacs or alveolar spaces and those of around 2 μm may deposit on the alveolar wall. Here the alveolar macrophage, the scavenger cell, is the most important clearance mechanism. It functions by ingesting these particles, then transporting and depositing them on the lowest part of the mucociliary escalator or clearing them through the lung lymphatic system.

A review of respiratory diseases associated with some of the more common fungal spores and pollens exemplifies the importance of particle size. The thermophilic Actinomycetes have relatively small spores (approximate diameter

2 μm) which are unlikely to be deposited on the bronchial wall but are likely to be deposited on the alveolar walls. These spores are responsible for an inflammatory reaction in the alveoli known as farmers' lung. The spores of Aspergillus, Cryptostroma and Cladosporium are all of a size (approximate diameter 5 μm) which would lead to bronchial wall deposition. They are commonly associated with episodes of asthma. Grass pollen has an average diameter of 30 μm and ragweed pollen approximately 20 μm. Thus these particles are likely to be deposited in the nose and are more likely to cause rhinitis than asthma. Clearly the nose will not act as an effective filter if it is affected by disease or if the subject is mouth breathing as he might during physical work. Here the chance of particles reaching the bronchi and the subsequent risk of asthma are increased. These agents may also cause an attack of asthma if they are broken down into smaller fragments which can then be deposited below the nose.

THE ALLERGIC REACTION

The existence of allergy to an inhaled agent in an individual implies that sensitization has occurred. Such sensitization has several phases: the deposition of the material on a mucosal surface, its transfer across the mucosa to where it would be ingested by a macrophage, the processing of the particular allergenic chemical by the immune system and in particular the B lymphocytes. This then results in the production of a specific immunoglobulin E (IgE) which circulates in the blood and becomes attached to mast cells. It is thought that the propensity to develop allergic diseases is more likely due to a breakdown in normal mucosal mechanisms rather than to an abnormality of the immune system itself. Compared to the other circulating immunoglobulins in plasma, IgE is present in nanogram rather than gram quantities.

Once a subject has been sensitized, re-exposure to the specific allergen and its reaction with specific IgE on the membrane of mast cells will result in degranulation of these cells with release of various chemical mediators such as histamine and slow-reacting substance of anaphylaxis. These mediators are potent bronchoconstrictor agents and also cause dilatation of blood vessels with resultant oedema and swelling. The presence of sensitization can be determined by using a simple skin test technique which, when positive, results in a wheal and flare reaction which is maximal some 15 minutes after challenge. Skin reactivity in the population at large is associated with hayfever, asthma or wheezy breathing. In Figure 1 the number of skin tests which, out of a total of six, were found to be positive in a community population is indicated. Positive skin tests were found in approximately 70% of subjects who admitted to hayfever but not to asthma or wheezy breathing; 55% of those who admitted to asthma; and, interestingly, 40% of those who denied asthma but admitted to wheezy breathing. Approximately 25% of subjects who denied hayfever, asthma and wheezy breathing were found to have at least one positive skin test. This analysis indicates that importance of the allergic reaction in these diseases in the community. Allergy is the most important determinant of allergic rhinitis or hayfever, whereas with asthma or wheezy breathing another factor must be present before clinical disease occurs. This other factor has been called bronchial hyperreactivity. It can be assessed by challenging subjects to increasing concentrations of aerosol histamine. Normal subjects will usually tolerate up to 16 mg m L^{-1} without a bronchoconstrictor response, while asthmatic subjects usually react with airway narrowing to concentrations of the order of 1 mg mL^{-1}.

An allergen is merely a substance producing an immune response and causing allergic symptoms. Contact is usually via a mucosal route, either the respiratory or gastrointestinal tract. Allergens are usually proteins of

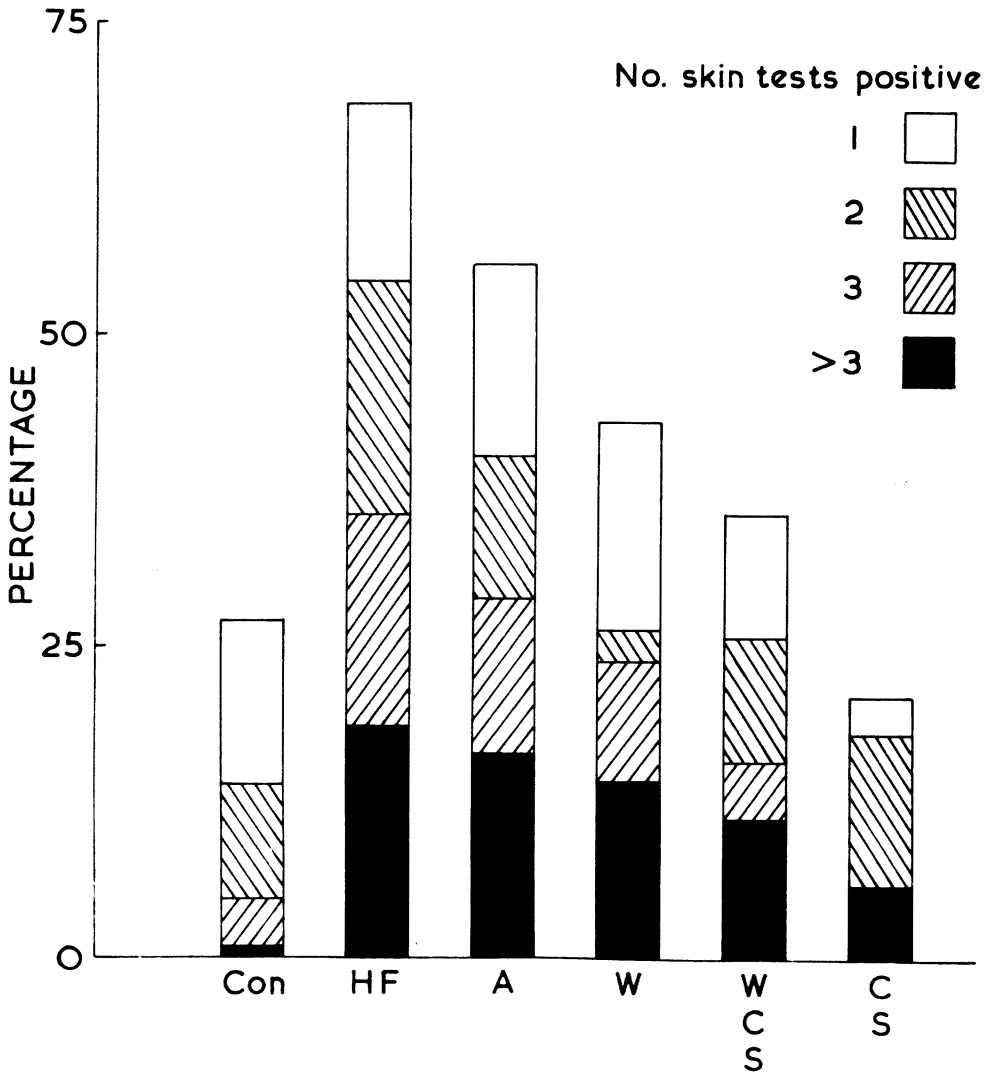

Figure 1. Immediate skin reactivity to six common allergens in subjects randomly selected from a community population. (A = admitting to asthma; W = admitting to wheeze, denying asthma; WCS = wheeze, cough and sputum, denying asthma; CS = cough and sputum, denying wheeze and asthma; HF = hayfever, denying asthma, wheeze, cough and sputum; Con = denying all symptoms).

molecular weights varying between 3000 and 40 000. The most important allergen originates from the house dust mite which is a *Dermatophagoides* species. These are invariabily present in human beds where the climatic conditions and adequate nourishment in the form of desquamated skin encourage their growth and reproduction. The average number of mites found in bed dust is 4000 g^{-1}. Between 80% and 90% of allergic asthmatics in Australia have positive skin test reactions to extracts made from these mites. The second most common allergen in the community is animal fur or dander. The next most frequent allergens are the grass pollens, particularly those of ryegrass, canary grass, wild oats and Rhodes grass.

The chemistry and immunology of allergy is extremely complex. For example, approximately 30 allergenic determinants have been identified to timothy grass pollen.

Another immune reaction which might be responsible, particularly for episodes of asthma and possibly rhinitis, is the Type III immune reaction. In this reaction immune complexes between allergen and IgG and possibly other immunoglobulins result in activation of complement and the subsequent attraction of neutrophil white cells into the area. There is subsequent release of various active enzymes from the neutrophils which results in an inflammatory reaction. This mechanism is probably important in allergic alveolitis as exemplified by farmers' lung and possibly in the late asthmatic reaction. In contrast to the Type I (IgE mediated) response which has a rapid onset at about 15 minutes, this Type III reaction occurs some 4 to 6 hours after antigen exposure.

CLINICAL FEATURES

Hayfever or allergic rhinitis is characterized by intermittent bouts of sneezing, rhinorrhoea (runny nose) and nasal obstruction. The onset usually occurs within minutes of exposure to the responsible allergen. It must be distinguished from nonallergic types such as vasomotor rhinitis. Here the nasal reaction appears to be due to an abnormal autonomic nervous system whereby exposure to cold results in nasal obstruction and sneezing. Viral infections, particularly if frequent, can be confused with allergic rhinitis. Probably many patients who suffer from recurrent "colds" have all allergic rhinitis.

Asthma is characterized by variable wheeze and breathlessness with or without chest tightness. Occasionally cough and viscid sputum production can be a significant feature. The onset of symptoms in response to a specific challenge may be immediate, late (that is, 4 to 6 hours after the challenge), or at night. This disease must be distinguished from recurrent bronchitis. In children particularly it is likely to have an allergic basis.

The immediate and late reactions are usually recognised as being caused by specific environmental exposures whereas with the nocturnal reactions a direct cause and effect relationship between exposure and reaction is not immediately obvious. Asthma is invariably worse at night. The clue to a specific environmental cause is that episodes tend to be worse on the night after exposure and best after a period away from exposure. With an occupational allergen the best night is often Sunday.

EPIDEMIOLOGY

Most of the data presented here has been extracted from the 1962-63 National Morbidity Survey. The seasonal patterns of the incidence of asthma by state is shown in Figure 2. There are clear-cut differences insofar as Queensland

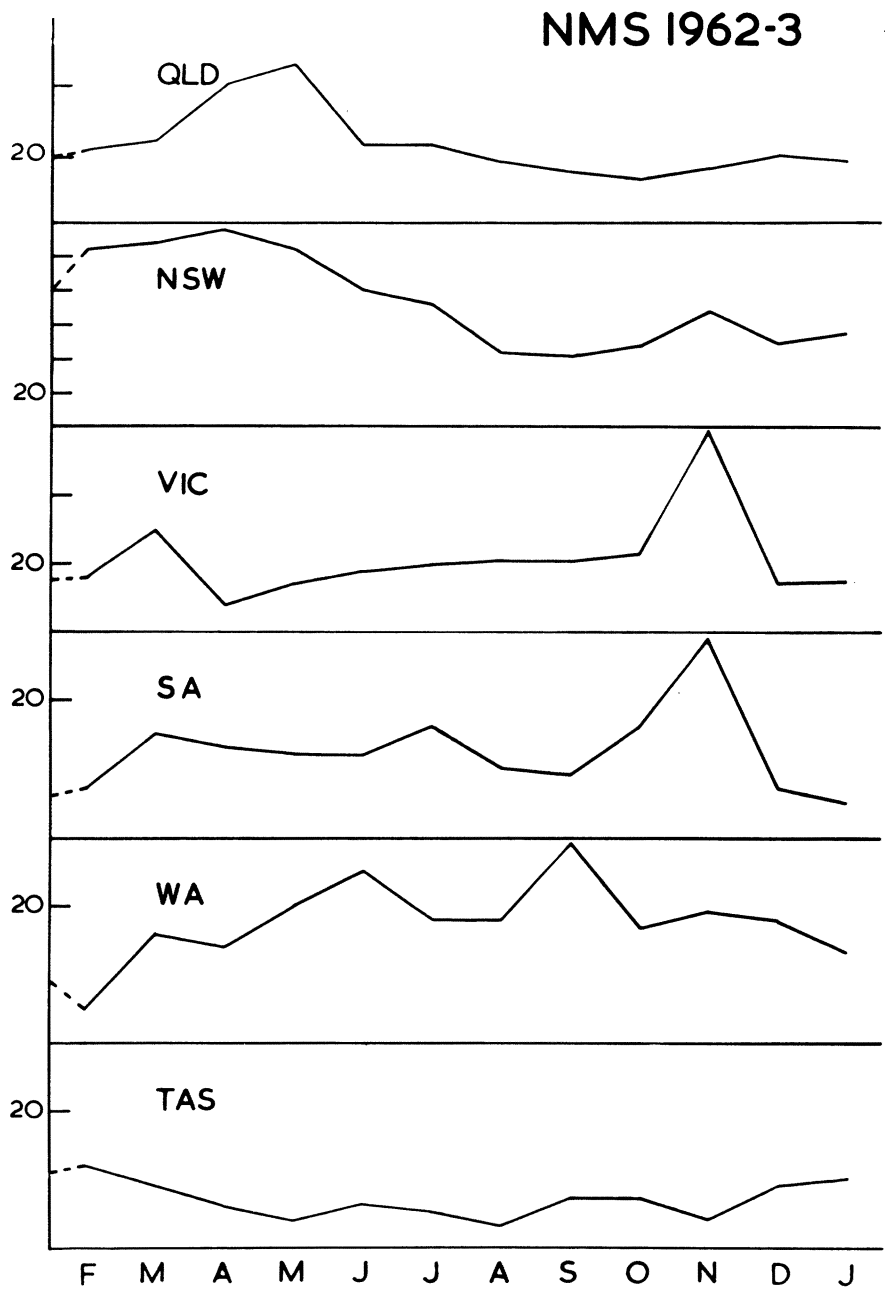

Figure 2. Episodes of asthma by month by state reported to general practitioners from the 1962-63 National Morbidity Survey.

and New South Wales have broad autumnal peaks whereas Victoria, South Australia, and Western Australia have more pronounced spring peaks. Presumably the latter are due to spring grass pollens which are more prevalent in the southern and western states.

There is no definite association between the incidence of asthma and hayfever. In Queensland (Figure 3) there appears to be an early spring peak in hayfever but no peak associated with that of asthma in autumn. In South Australia (Figure 4) however, the high incidence of hayfever in spring can be appreciated and there is a definite increased incidence of asthma at this time, although it is not impressive.

The cause of autumnal asthma in New South Wales and Queensland remains uncertain. The late Dr. E. Derrick attempted to determine the relationship between the incidence of asthma and various environmental factors. Despite recording data on most of the important environmental factors and analysing the results in some detail, no significant associations could be determined.

We have recently completed a statewide survey of respiratory illness in Queensland schoolchildren and have found that some 25% of 8 year old boys and 18% of 8 year old girls had experienced attacks of asthma or wheezy breathing at some stage of their life. This prevalence is 50% greater than that noted in Tasmania using identical survey techniques. The reason for these regional differences is not known.

Finally, the incidence of hayfever and asthma in various occupational groups is shown in Table 1. The group comprising farmers, timber-getters, and related occupations shows on average a lower incidence of hayfever and asthma than most other occupational groups and certainly lower than the general population. It is important to realize that this may indicate true differences in the incidence of these diseases, or it may reflect either than such workers are less likely to consult their general practitioner than those in other occupations, or that susceptible workers have left these occupations and the incidence is that in a "survivor" or nonsusceptible group. Until a broad community-based survey is undertaken, these issues cannot be clarified.

Table 1. Episodes of morbidity per 1000 total episodes of morbidity reported by each occupational group for all patients aged 15 to 64 years.

Occupational group	Hayfever	Asthma	Bronchitis
Professional, technical, and related workers	7.8	7.8	11.6
Clerical workers	7.7	10.2	13.7
Farmers, timbergetters, and related workers	4.8	5.8	13.9
Labourers	2.1	7.7	16.5
Home duties	5.9	7.6	11.7
All occupations	5.3	7.5	13.5

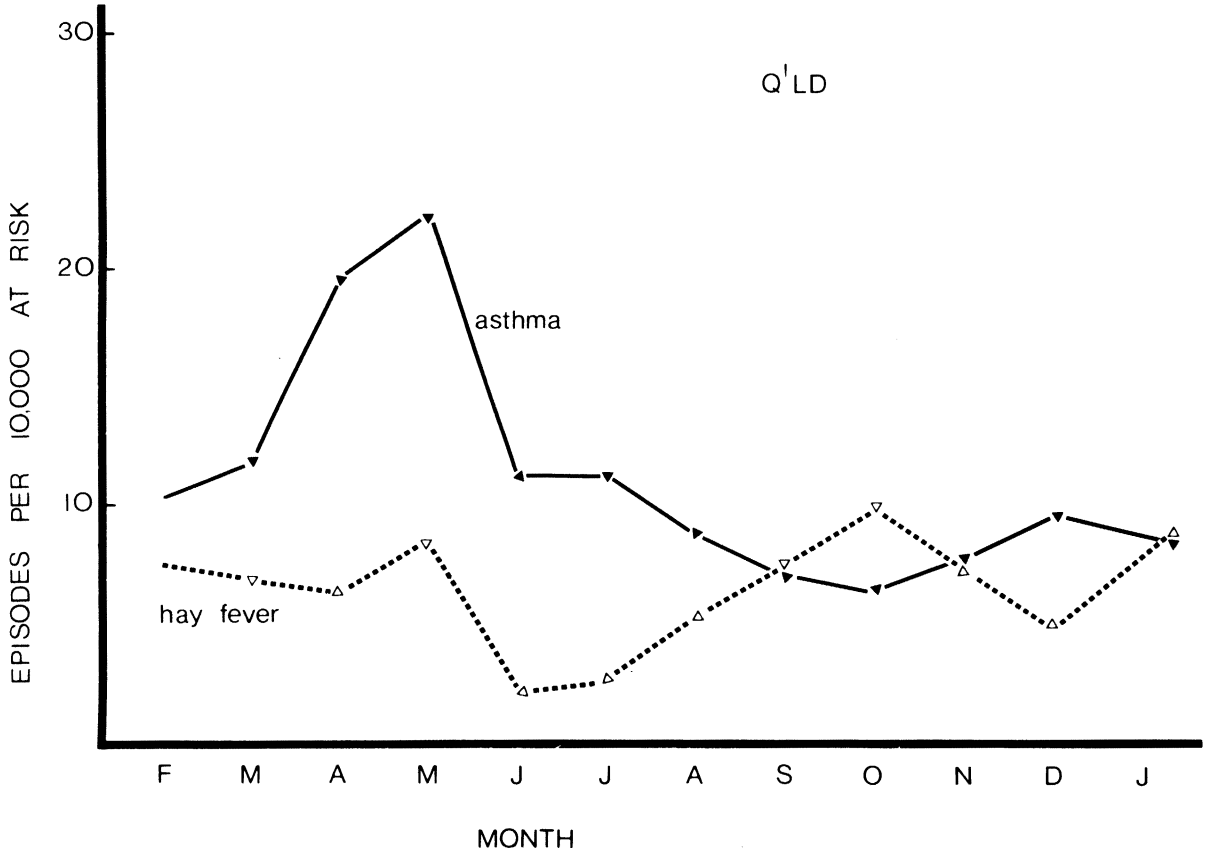

Figure 3. Episodes of asthma and hayfever by month reported to general practitioners in Queensland from the 1962-63 National Morbidity Survey.

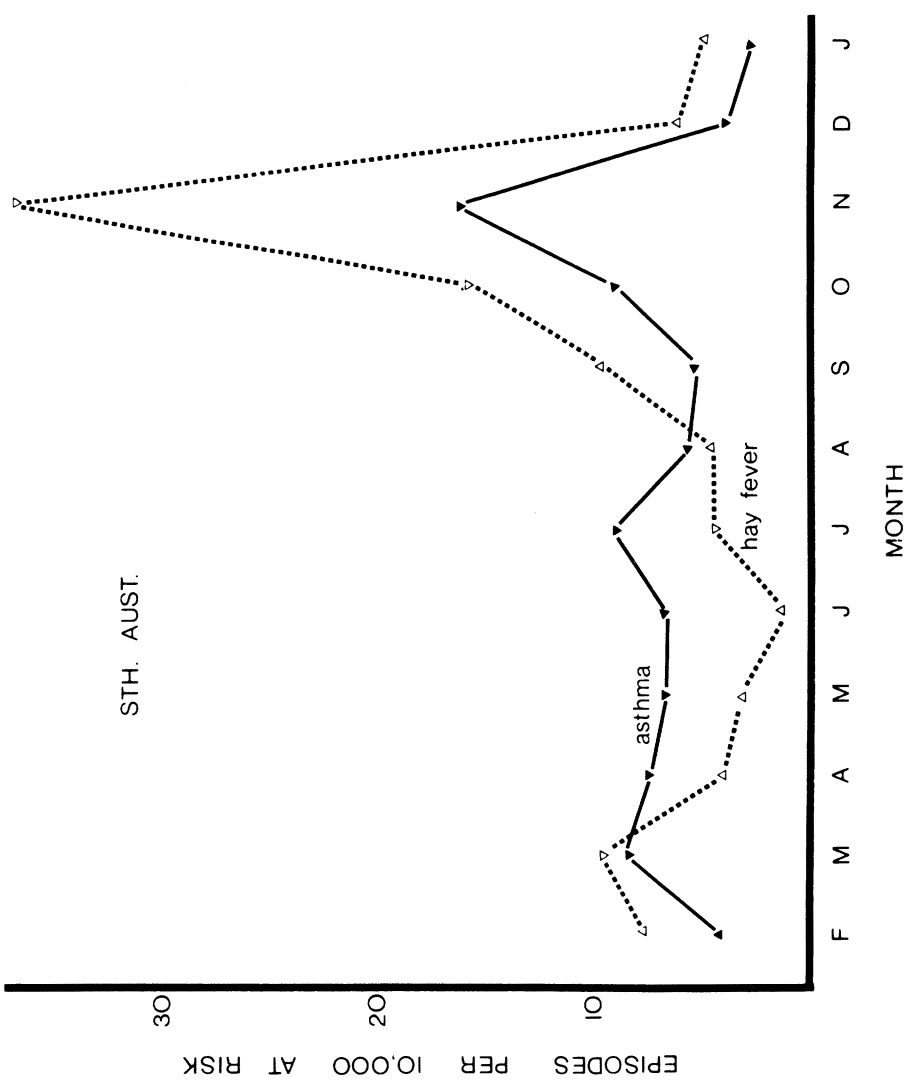

Figure 4. Episodes of asthma and hayfever by month reported to general practitioners in South Australia from the 1962-63 National Morbidity Survey.

CONCLUSION

Many of the mechanisms responsible for the diseases asthma and allergic rhinitis are now well understood. Considerable gaps exist in our understanding of those factors determining why some individuals are likely to become allergic and others not. Except for certain grass pollens and animal danders, those allergens responsible for episodes of asthma and rhinitis are not known. Avoidance of allergens will reduce the frequency of episodes of asthma and rhinitis and may reduce the number of subjects suffering from these diseases.