ABC of allergies
Asthma and allergy

A J Newman Taylor

Definitions and distinctions

Asthma

Asthma is commonly defined as a narrowing of the airways that is reversible over short periods of time, either spontaneously or as a result of treatment. This clinical definition (which characterises asthma as reversible airway narrowing) distinguishes it from other predominantly irreversible causes of airway narrowing, such as chronic obstructive bronchiolitis and emphysema. Another cardinal characteristic of asthma is airway hyper-responsiveness, an exaggerated narrowing of the airways provoked by a variety of non-specific stimuli, such as exercise and cold air. The two defining characteristics of asthma—reversible airway narrowing and airway hyper-responsiveness—are manifestations of a characteristic pattern of airway inflammation (a Th2 lymphocyte dependent desquamative eosinophilic bronchitis).

Atopy

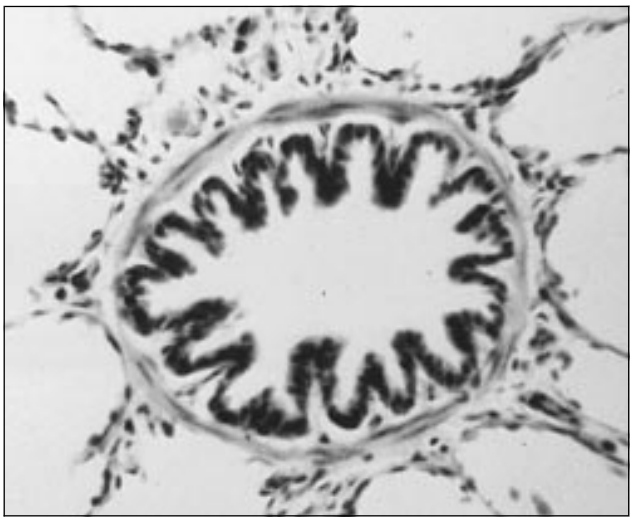
Atopy is the propensity to produce IgE antibody to allergens (antigens that stimulate the production of IgE antibodies) that are commonly encountered in the general environment—for example, pollens, mites, and moulds. Atopy is usually identified by the provocation of one or more immediate "weal and flare" responses in the skin to extracts of common inhalant allergens. Specific IgE antibody to common inhalant allergens can also be found in the serum samples of atopic individuals, who may also have a raised serum concentration of total IgE.

The development of atopy is influenced by both genetic and environmental factors:

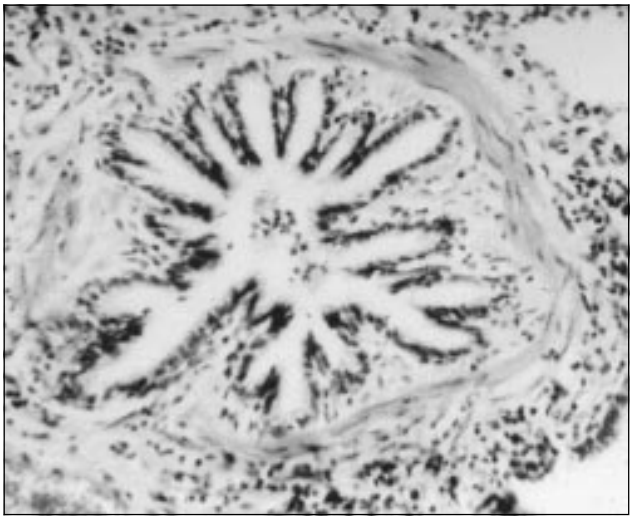
- The genetic basis of atopy is debated. Twin studies have consistently shown that atopy occurs more frequently in identical than non-identical twins. The findings in different family studies, however, have not identified a consistent pattern of inheritance. Recent molecular studies have suggested an association between atopy and polymorphisms of the high affinity IgE receptor on chromosome 11q (FCΣR1-β) and linkage with the interleukin 4 gene cluster on chromosome 5. It seems likely that atopy will eventually be associated with polymorphisms of many different genes.
- The twofold to threefold increase in the prevalence of asthma during the past 30 years has been accompanied by an increase in the prevalence of hay fever and eczema and of skin prick test responses to common inhalant allergens. The difference in the prevalence of asthma in children between cities in former East Germany (Leipzig and Halle) and West Germany (Munich) after reunification was wholly accounted for by the 2.5-fold greater prevalence of atopy in Munich. Changes in prevalence of this magnitude, which have occurred over decades, are too rapid to reflect differences in the genetic pool and are probably due to changes in important environmental determinants of atopy, possibly a decrease in respiratory infection in early life.

Allergy

The concept of allergy was proposed by Clemens Freiherr von Pirquet in 1906 as a "specific acquired altered reactivity which follows initial exposure to foreign protein," a description that encompasses both immunity and allergy. Although allergy is



Normal bronchiole



Bronchiole from asthmatic patient narrowed by eosinophilic infiltration, oedema, and increased smooth muscle

Allergy in atopic patients

- As well as asthma, eczema and hay fever are also manifestations of allergy in atopic patients
- Not all allergy is atopic—for example, drug reactions
- Not all allergic asthma is atopic—for example, asthma induced by the low molecular weight chemical sensitisers (such as isocyanates in two part polyurethane paints)
- Asthma can also be provoked through non-immunological reactions—for example, non-steroidal anti-inflammatory drugs and β blockers

now distinguished from immunity by a disproportionate injury to host tissue, the immunological reactions underlying both immune and allergic responses are the same; they differ only in their clinical outcome. This article is predominantly concerned with reactions associated with Th2 lymphocyte dependent IgE response whose outcome is characterised by local recruitment and activation of circulating blood eosinophils. This would be considered to be an immune response when directed against parasites such as shistosoma and filaria but an allergic response when directed against pollens and mites.

In this context, allergy is the clinical outcome of IgE associated reactions to common environmental allergens in atopic individuals. The characteristic allergic reactions in atopic individuals are eczema, hay fever, and asthma, which can, but do not by any means always, coexist in the same individual. Asthma may therefore be one of the manifestations of allergy in atopic individuals.

Asthma in atopic patients

- Asthma is associated with atopy at all ages, although most strongly in children and young adults
- Atopic individuals may also have flexural eczema or hay fever concurrently, or have had them in the past
- The prevalence of asthma in different environments correlates with specific IgE antibody to the particular allergens present. For example, in cities in the United States asthma is associated in affluent areas with specific IgE to house dust mite and cat hair and in poor areas with specific IgE to house dust mite and cockroach
- Furthermore, the severity of asthma correlates with the concentration of specific allergens (such as house dust mite or cockroach) to which individuals are sensitised

Asthma and allergy

Allergens and asthma

Asthma can be initiated and provoked by allergens in everyday life—outdoors, indoors, and at work. In patients whose asthma is provoked by protein allergens encountered in everyday life (such as pollens, mites, and moulds), extracts of relevant allergens in solution will elicit immediate skin test responses, and specific IgE antibody can be detected in their serum. This is also true for protein allergens that cause occupational asthma and for some low molecular weight chemicals encountered at work—for example, platinum salts, acid anhydrides, and reactive dyes (but not, for example, isocyanates, resin, wood dust). In general, evidence of specific IgE antibody, either from an immediate skin test response or specific IgE in serum, is a very sensitive test (that is, there are few false negatives) but also a non-specific test (that is, many false positives). A negative result is therefore more valuable than a positive result as it can exclude a specific cause of asthma, whereas a positive result is less reliable for identifying a specific cause and must always be interpreted in the context of the clinical history.

Causes of occupational asthma

	Proteins	Low molecular weight chemicals
Animal	Excreta of rats, mice etc; locusts; grain mites	
Vegetable	Grain, flours; latex; green coffee bean; isphagula; latex	Plicatic acid (from western red cedar), pinewood resin
Microbial	Harvest moulds, Bacillus subtilis enzymes (in detergents)	Antibiotics—eg. penicillins, cephalosporins
Mineral		Acid anhydrides, isocyanates, complex platinium salts, polyamines, reactive dyes

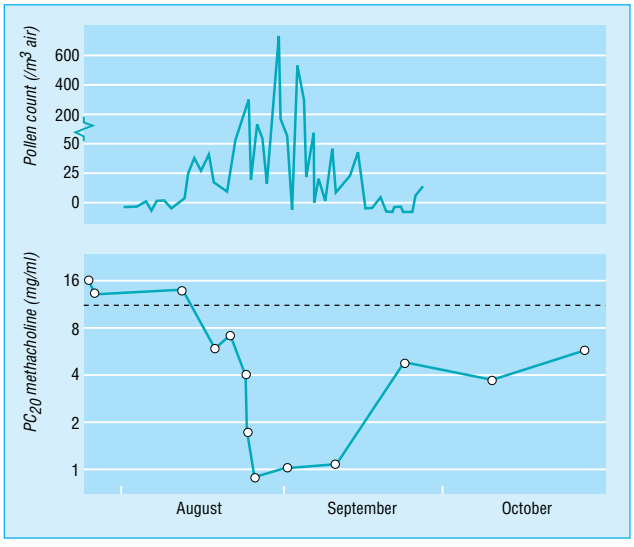
Allergens and asthma

Outdoors	Indoors
Pollens	*Mites*
Tree	Dermatophagoides pteronyssinus and farinae (house dust mites)
Grass	
Moulds	*Animals*
Alternaria alternata	Cats
Cladosporium herbatum	Dogs
Aspergillus fumigatus	Birds

Asthma and airway hyper-responsiveness

Exposure to allergens occurring naturally and in the laboratory can provoke airway narrowing and airway hyper-responsiveness. For example, patients allergic to ragweed pollen show a progressive increase in the severity of airway responsiveness during the ragweed season concurrently with the increase in the severity of their asthma.

Inhalation of soluble extracts of allergens provokes an immediate asthmatic response that peaks at about 20 minutes and resolves within about one hour. The provocation and severity of the immediate response is dependent on both the dose of inhaled allergen and the degree of airway hyper-responsiveness. In about 50% of patients a late asthmatic

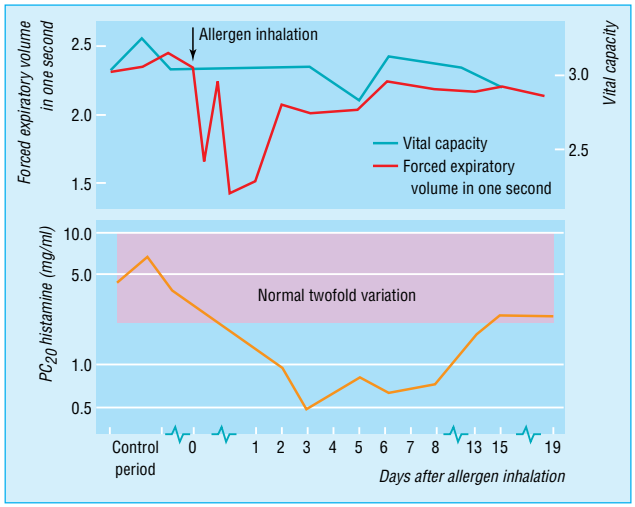


Increased airway responsiveness in patient allergic to ragweed pollen during ragweed season

response also develops after three hours; it peaks at 6-12 hours and may persist for 12-24 hours. Low molecular weight chemicals can provoke isolated late reactions.

The immediate asthmatic response is mediated by IgE dependent mast cell release of mediators such as histamine and leukotrienes. The late reaction is a manifestation of eosinophilic airway inflammation. Both are thought to be the outcome of a Th2 lymphocyte response to inhaled allergen.

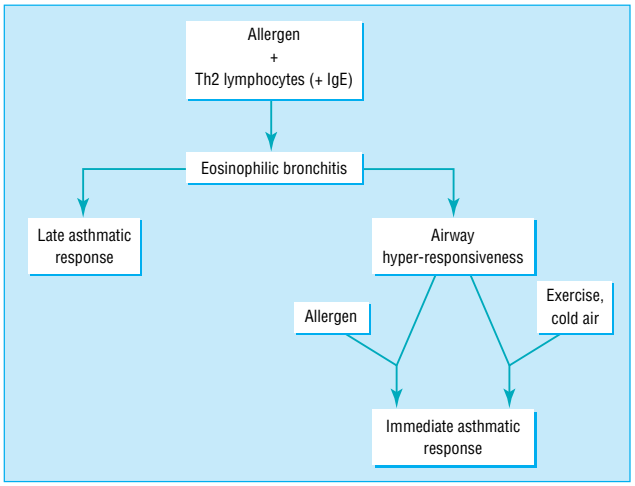
The late, but not immediate, reaction is associated with the development of airway hyper-responsiveness, probably as a manifestation of the induced airway inflammation. The induced airway hyper-responsiveness occurs independently of the reduction in forced expiratory volume in one second and in airway calibre during the late reaction and can be sustained for several days after the forced expiratory volume has returned to normal. During the period of increased airway responsiveness the normal diurnal variation in airway calibre may be exaggerated, causing recurrent nocturnal asthma, and non-specific stimuli (such as exercise, cold air and smoke), as well as specific allergens to which the individual has developed specific IgE antibody, can provoke immediate asthmatic responses.



Increased airway responsiveness associated with late asthmatic reaction provoked by ragweed pollen

Allergen exposure and chronic asthma

Exposure to allergens induces late asthmatic responses and associated airway hyper-responsiveness. Airway hyper-responsiveness is an important determinant of immediate airway responses both to non-specific stimuli (such as exercise and cold air) and to exposure to specific allergens. By increasing non-specific airway responsiveness, allergen exposure can increase the development and persistence of chronic asthma.



Allergen induction of airway inflammation and hyper-responsiveness permits provocation of immediate asthmatic responses by both allergens and non-specific factors, such as exercise and cold air

Implications for treatment

This model has important implications for the management of asthma. Reducing allergen exposure at home or in the workplace will reduce not only the frequency of immediate asthmatic responses but also the severity of airway responsiveness and the capacity for allergens to provoke asthmatic responses. This is particularly important when a single "dominant" allergen is primarily responsible for the induction of asthma. Examples are occupational asthma and some cases of asthma caused by allergens in the home, such as house dust mite, cat, or cockroach, where avoidance measures have been shown to be effective.

Identification of allergens in the home and of allergens or chemicals encountered at work is therefore important when avoidance is practicable. In the home, pets are particularly relevant, and, with improved avoidance measures, identification of allergy to house dust mite is becoming more relevant.

In the workplace, accurate and early identification of the specific cause of allergic asthma (either allergen or chemical) to enable avoidance of further exposure is the cornerstone of management of occupational asthma.

The first graph is adapted with permission from Boulet et al (*J Allergy Clin Immunol* 1983;71:399-406), and the second is adapted with permission from Cockcroft et al (*Clin Allergy* 1997;7:503-73).

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The ABC of allergies is edited by Stephen Durham, honorary consultant physician in respiratory medicine at the Royal Brompton Hospital, London. It will be published as a book later in the year.

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Criteria for diagnosing hypersensitivity induced occupational asthma

History

- Exposure to a sensitising agent
- Initial symptom free period of exposure (or employment)
- Improvement in severity of asthmatic symptoms during absences from work—eg, weekends or holidays—and progressive deterioration during periods at work

Objective evidence

- Serial peak flow measurements showing work related asthma
- Specific IgE (skin tests or in serum) to specific agent
- Reproducible late asthmatic response and increase in airway responsiveness provoked by inhalation test with specific agent in less than toxic concentrations*

*Inhalation tests should be undertaken only for medical purposes in a specialist centre when the diagnosis of occupational asthma remains uncertain after other investigations have been completed. Inhalation tests are not justifiable when undertaken solely for medicolegal purposes