

SERIES: ALLERGY

The role of allergy in the development of airway inflammation in children

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allergens, allergy,
asthma

Summary The primary immune response to allergens is the prototypic T-helper cell type 2 (Th2) response. This occurs prenatally, favoured by the normal Th2-skewed immune response of pregnancy. The immune system matures during the early years of life. The immune responses, primarily determined by genetic susceptibility, are also influenced by exposure to allergens and infections, which may reverse their direction. Although wheezing is observed before 2 years of age, this is usually not attributable to allergy, and the majority of the wheezers do not develop asthma. The development of allergic asthma can be considered to be a two-stage process. The first stage involves the development of allergen-specific immunological memory against inhaled allergens. This happens in childhood and polarises the immune response towards a Th2 phenotype. These individuals are therefore more prone to developing allergic inflammation. Stage two involves the consolidation and maintenance of this polarised Th2 response, leading to a state of chronic airway inflammation. This second phase is influenced by various factors, for example respiratory viral infections, repeated indoor and outdoor allergen exposure, environmental tobacco smoke and air pollutants. The persistent airway inflammation leads to tissue remodelling and airway hyperresponsiveness, the clinical *sine qua non* of asthma.

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INTRODUCTION

The prevalence of allergic asthma is increasing, not only in the developed world, but also in developing countries and this is particularly true of the paediatric population. In the USA, the prevalence of asthma increased by 75% from 1989 to 1994, a trend evident among all races, both genders and all age groups, although the most substantial increases occurred in children aged 0–4 years (a 160% increase) and 5–14 years (a 74% increase).¹ Furthermore, poorer urban children appear to be disproportionately affected. Airway inflammation is a characteristic feature of asthma, and the clinical manifestations of asthma depend on the severity of inflammation.

Allergic airway inflammation is an important aspect of the pathophysiology of asthma. The focus of the inflammatory

mechanisms underlying asthma is the alteration of the balance between the T-helper type 1 (Th1) and Th2 lymphocytes. There is now overwhelming evidence to suggest that allergen-induced airway inflammation is orchestrated by the activation of Th2 cells. Various factors contribute to this Th1/Th2 cell imbalance. A Th2 phenotype favours atopy and promotes airway inflammation in asthma. Atopic individuals bear a complex hereditary constitution facilitating the increased production of IgE towards common environmental allergens. By way of gene–gene interactions, this inherited ability leads to alteration of the immune system and susceptibility to allergic disorders. Allergy to airborne allergens is increasingly common, but despite the fact that everyone inhales these allergens, only a small proportion of individuals manifest allergic disease. To evaluate the role of allergy in the development of allergic airway inflammation, it is essential to trace the development of allergic disorders, their inception and the various factors that govern the development of allergy.

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GENETIC INFLUENCES

The genetics of allergic disorders are not fully understood but there is enough evidence to suggest that susceptibility to allergic disorders is genetically mediated. Studies indicate that chromosome 5, carrying the gene encoding interleukin-4 (IL-4), and chromosome 12, with the gene for interferon gamma (IFN- γ) are possible candidates.² The problem of the genetic control of allergy is complicated by polymorphism in the IL-4 gene cluster but not in the IFN- γ gene.^{3,4} Polymorphisms in the coding region of the IL-13 gene are associated with asthma and atopy. Studies have shown that atopy is also associated with polymorphism of the gene coding for the beta-chain of the high-affinity Fc ϵ RI IgE receptor and alteration in the α -chain of the IL-4 receptor, which could lead to altered IL-4 signalling.^{5,6} The triggering mechanism could, however, lie in the gene–environment interaction, leading to allergic inflammation in the susceptible population. It is well known that an increased exposure to indoor and some outdoor allergens is an important risk factor for the development of asthma and allergic sensitisation. The susceptibility of only some individuals to mount an allergic inflammatory response to these trigger factors is the result of genetic predisposition.

ORIGIN OF AIRWAY INFLAMMATION

Allergic airway inflammation can manifest at any age but tends to occur in the first decades of life. This relates to the maturation of the immune system. IgE production starts in the 11th week of gestation and specific IgE has been reported in cord blood but specific IgE responses are usually observed from the first month of life onwards. These IgE responses are towards food proteins, especially cows' milk and hens' eggs.⁷ This is also true in babies who have been completely breast fed. When children are followed from birth, it is unusual to have a positive skin prick test reaction to inhaled allergens before 2 years of age. There have, however, been reports that a strong infantile IgE response to food proteins is associated with subsequent sensitisation to aero-allergens and is also a marker of atopy.⁸ With regard to allergic disorders, atopic dermatitis is the first manifestation to appear, the highest incidence being seen during the first year of life. Allergic rhinoconjunctivitis is not observed during the first 2 years of life despite some children having allergen-specific IgE.

Wheezing during infancy is commonly observed but longitudinal studies indicate that most of these children do not develop asthma (i.e. they are transient wheezers). School-age children with asthma have a history of recurrent respiratory tract infections during early childhood.⁹ This is commonly associated with viral infections, especially with respiratory syncytial virus (RSV). RSV bronchiolitis in the first year of life is a strong risk factor for the development of

asthma and atopy¹⁰ and studies suggest that atopy may become manifest soon after exposure to RSV in the first year of life.¹¹ It is possible that there is a different pattern of immune response to viruses in persistent wheezers and transient wheezers in virus-induced lower respiratory infections: persistent wheezers show an IgE and eosinophil-mediated immune response whereas transient wheezers show an eosinopenic response.¹² This eosinophilic infiltration can be blocked by anti-IL-5 antibody, indicating a Th2 dominance that primes the airways for the allergic response. During the first 3 years of life, the manifestation of wheeze is not related to an elevated IgE level, allergen sensitisation or a family history of atopy and asthma but persistent wheezers show an increasing association with aero-allergen sensitisation with age.¹³ These findings imply that viral infections and respiratory allergies may have a synergistic effect on lower airway pathophysiology as both cause airway inflammation and airway hyperresponsiveness that greatly increase the likelihood of persistent wheezing.

INFLUENCE OF THE INTRA-UTERINE ENVIRONMENT

The predisposition to allergic airway disease could be partly caused by differences in the intra-uterine priming process. The fetus is considered to be a non-self paternal antigen and would be expected to be rejected by the mother's immune system as in transplant allograft. In transplantation models, it is believed that Th1 lymphocytes are responsible for acute rejection and Th2 lymphocytes maintain tolerance. There is evidence to suggest that the materno-fetal interface is immunologically active, with a predominance of Th2 cell cytokines. Upon stimulation, fetal cord blood cells tend to respond predominantly with the cytokines identified with the Th2 type. Placentally derived IL-4 is particularly responsible for generalised immune deviation to a Th2 cell response to generate allergic humoral response.¹⁴ The purpose of this skewed polarisation is believed to be protection of the placenta against the toxic effects of Th1 cell cytokines, in particular IFN- γ . Thus, at birth it is normal to have an immune system primed for Th2 cell responses against environmental allergens.

In non-atopic individuals, the initially low-level Th2 cell immunity is converted into Th1 immunity during childhood, whereas the process fails in atopics, leading to a consolidation of the Th2 polarised response involving the production of IL-4, IL-5, IL-9, IL-10 and IL-13. These children consolidate their fetal responses against one or more inhaled allergens and develop skin test positivity.^{15,16} These Th2 cell polarised responses are causally associated with the expression of childhood asthma and predisposition to allergic airway inflammation. This has been supported by a prospective study evaluating allergen-specific T-cell responses from the cord blood of children aged 2 years, which showed an upregulation of IL-4 and IL-13 in children with a positive family history of atopy. Conversely, children

with a negative family history of asthma demonstrated a downregulation of IL-4 and IL-13.¹⁷ There is also a relative deficiency in IFN- γ production during early life in subjects with a high risk of atopy, which supports immune deviation towards an atopic Th2 phenotype.¹⁸

It therefore seems that the immune systems of children are primed for the allergen-specific Th2 phenotype and it is the consolidation of these fetal Th2 cell responses that make the children prone to allergic airway inflammation. Non-atopic children have a rapid transition from the predominant Th2 cell response at birth to a more balanced Th1/Th2 response, whereas this response is delayed in atopic children, leading to a persistence of the fetal Th2 reaction. The exact mechanisms and molecular basis of the persistence of the fetal Th2 phenotype is not clear but one factor that is recognised as a principal trigger for the postnatal upregulation of Th1 cell function is microbial stimulation. This sets the stage for the hygiene hypothesis as a possible explanation for the increased prevalence of allergic disorders in developed countries.

ROLE OF EARLY MICROBIAL INFECTION

T-cell responses are influenced by the cytokine profile. Th1 cell cytokines generated during an infectious response influence the development of asthma and atopy, microbial infections being potent and highly Th1 cell-selective stimuli for the adaptive immune response. Bacteria are potent inducers of IL-12 secretion from dendritic cells, neutrophils, macrophages and natural killer (NK) cells, which leads to a cytokine milieu rich in IFN- γ that suppresses Th2 cell responses.¹⁹ It has been shown that *Mycobacterium bovis* BCG infection can suppress the development of allergen-induced airway hyperresponsiveness and airway eosinophilia in mice.^{20,21} Studies in children brought up in a farm environment found that there was a lower incidence of hay fever, asthma and allergic sensitisation²² but these studies were all cross-sectional and their results need to be proved by prospective research. These findings suggest, however, that environmental exposure to microbial antigens and bacterial compounds helps the development of immune tolerance through the stimulation of Th1 cells and/or the suppression of Th2 cells, thus preventing the development of allergic disorders in children. Moreover, bacterial lipopolysaccharides stimulate the production of IL-12 (which is a powerful Th1 lymphocyte inducer) by dendritic cells, skewing the bias towards Th1 cells.

Commensal micro-organisms that colonise the gastrointestinal tract during infancy provide the major stimulus for the postnatal upregulation of Th1 lymphocyte function.²³ In experimental models maintaining the infant animals in a germ-free environment, the Th2 cell polarity of the fetal immune system could be maintained, the germ-free animals being resistant to tolerisation or immune deviation to the Th1 response on exposure to mucosally derived antigens.²⁴

These observations raise the possibility that, in humans, postnatal gastrointestinal colonisation may be causally implicated in the different prevalence of atopy encountered in different populations.

Helminthic infections induce very pronounced Th2 cell responses and hence would be expected to promote atopy through the induction of IL-4.²⁵ However, despite the extensive prevalence of helminthic infection in developing countries, the prevalence of allergic diseases is relatively low. The dosage of allergen has been incriminated as one of the factors. Helminthic infections of low intensity can non-specifically potentiate the synthesis of IgE antibody against environmental allergens and thus enhance allergic reactivity. In contrast, the excess polyclonal IgE stimulation by more intense helminthic infection can suppress the allergic response by saturating the Fc ϵ receptors on the mast cells and thus competitively inhibit the binding of allergen-specific IgE.²⁶

There is an increasing body of evidence to suggest that the diabolical interference by microbes in early life may reverse the Th response by upregulating the Th1-type and depressing the Th2-type response. This could greatly reduce the probability of atopy and subsequent allergic airway inflammation in later life.

ROLE OF ALLERGENS IN THE INITIATION OF AIRWAY INFLAMMATION

Allergic individuals have circulating allergen-specific lymphocytes and IgG, IgM, IgA and IgE antibodies. Allergen-specific Th2 cells produce IL-4 and IL-13, and promote the production of specific IgE. Allergic sensitisation in atopic children, as indicated by allergen-specific IgE, can then result in target organ-specific damage. This can manifest as allergic rhinitis in the upper airways and asthma in the lower airways. One of the least understood aspects of the development of allergic inflammation is target organ specificity. There is little information on why some individuals manifest upper airway inflammation and others develop dermatitis despite having an equivalent level of allergen sensitisation. This becomes more complicated in the case of asthma. Although the vast majority of older school-age asthmatics (80–90% compared with only 30% of those under 5 years of age) are sensitised to one or more inhalant allergens, only a subset of allergic individuals develop persistent airway disease. This has been demonstrated by a study in Australia,²⁷ where, by school age, up to 40% of children display sensitisation to one or more aero-allergens, this remaining stable through adulthood. Only 25–30% of the sensitised atopics, however, progress to develop asthma. It therefore seems that additional co-factors must be operating in this disease process.

Allergen sensitisation is a key issue influencing the development and progression of asthma in children.²⁸ In the German multi-centre allergy study,²⁹ it was observed that

children who had asthma at 7 years old had been sensitised very early in life and had a persistent sensitisation compared with children who did not have asthma at age 7. Transient sensitisations did not increase the risk of asthma at 7 years, whereas persistently sensitised children had a significantly higher risk of being asthmatic. Among the risk factors for persistent sensitisation included a family history of atopy or asthma, greater risk being derived from a maternal history of atopy, and exposure to tobacco smoke *in utero*. A recent study showed higher specific airway resistance in non-wheezy 3-year-old children if they were atopic or had a family history of atopy.³⁰

There is an inverse relationship between house dust mite concentration and age of first wheezing, as well as a strong correlation between wheezing at age 11 and house dust mite sensitisation.³¹ Furthermore, dust mite exposure and allergen-specific IgE have been associated with emergency hospital visits for asthmatic symptoms.³² Lau *et al.* found a

clear relationship between allergen exposure during infancy, as judged by the concentration of house dust mite allergen in carpet dust and subsequent sensitisation to house dust mite. This was evident at 3 years of age, the relationship being further strengthened by the age of 7. Interestingly, this relationship was observed even for low concentration of house dust mite. There was, however, no clear correlation between allergen exposure and the development of childhood asthma,³³ although as half of all children with asthma at age 7 have non-atopic asthma, this is perhaps not surprising. Lau *et al.*'s result implies, however, that the strong association between asthma and sensitisation to dust mites depends on the individual's susceptibility to an increased risk of asthma. Factors other than increased allergen exposure could contribute to the development of asthma. This is further substantiated by a study from New Mexico, where children growing up in a high-altitude desert area, with a lower prevalence of atopic

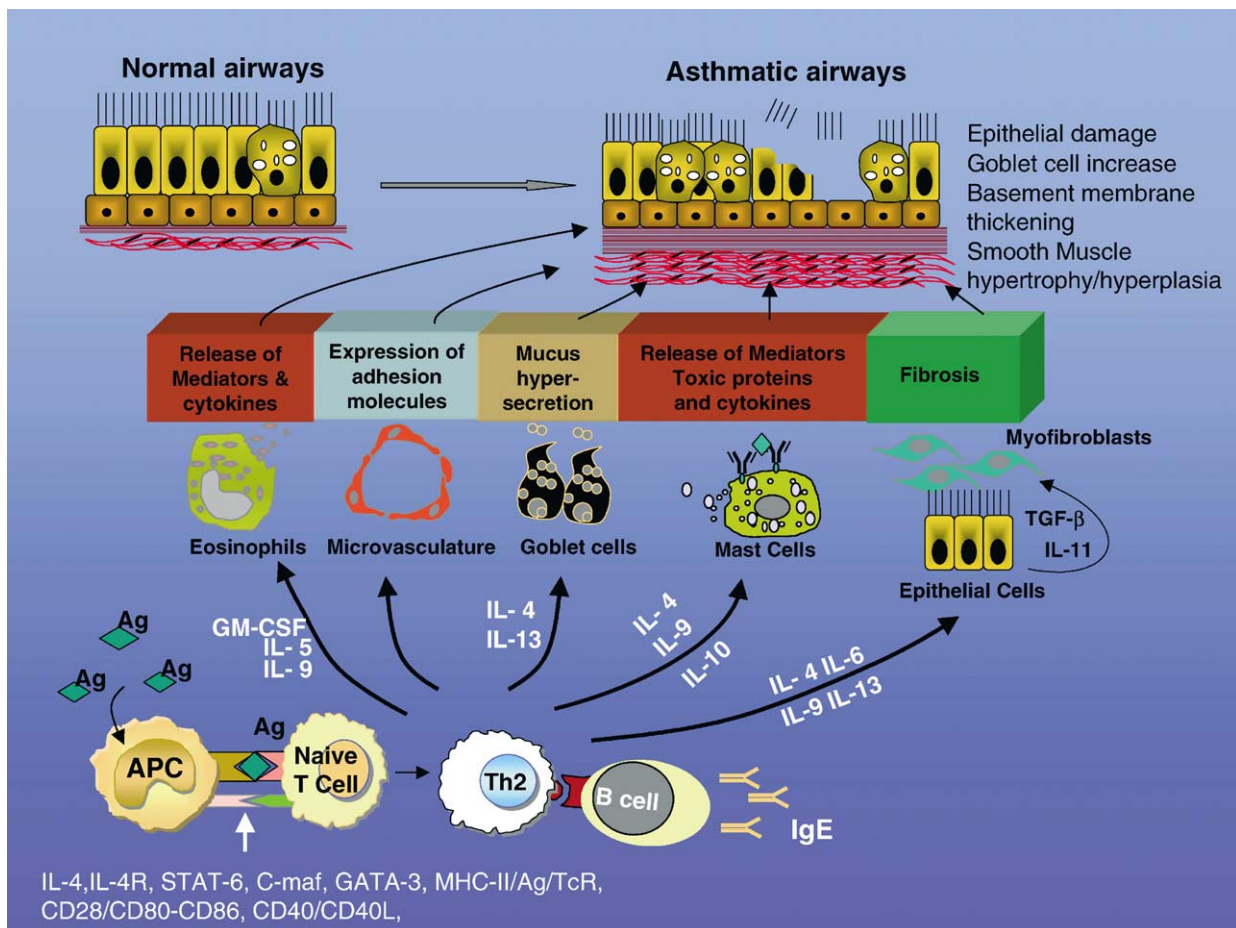


Figure 1 The initiation of the allergic inflammation involves the presentation of the processed allergen to the naïve T-cells by antigen-presenting cells (APC). In the presence of an appropriate cytokine milieu, a T-helper type 2 (Th2) cell polarisation is favoured. Re-exposure to allergen results in the cross-linking of IgE on mast cells and basophils, leading to the early response in which pro-inflammatory mediators and cytokines are released. This is followed by the recruitment of eosinophils, monocytes, neutrophils and other inflammatory cells, causing airway oedema and mucous plugging. Recurrent exposure to allergen leads to a state of chronic inflammation characterised by smooth muscle hypertrophy and tissue remodelling. TGF- β , transforming growth factor-beta; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ag, antigen; STAT-6, signal transducer and activator of transcription; C-maf, transcription factors; GATA 3; MHC-II/Ag/TcR, Major Histocompatibility Complex, Antigen, T-cell receptor; CD.

sensitisation to house dust mites, had a higher prevalence of asthma when compared with children who were born elsewhere and moved into this community.³⁴

The assumption was that there is a linear relation between allergen exposure and the prevalence and severity of sensitisations and symptoms. This is true with regard to dust mite allergen exposure but does not hold good for exposure to cat allergen. Exposure and sensitisation to dust mite in early life has a direct relationship to the development of asthma. This is not, however, the case with exposure to cat allergen, for which an increased exposure leads to a tolerant response with a decreased risk of asthma. A study of children with cat allergen sensitisation has shown that the risk of sensitisation is reduced with the highest exposure to cat allergen. Exposure to higher doses of cat allergen can produce an IgG and IgG4 antibody response without sensitisation or risk of asthma. This modified Th2 cell response could be regarded as a form of immunological tolerance.³⁵ Another explanation could be that the presence of the pet could lead to an increase in the level of endotoxins and bacterial products, which could shift the immune response to a Th1 phenotype. Unfortunately, studies conducted in this area are cross-sectional in nature, and properly conducted prospective trials are needed to evaluate any possible causal relationship.

ALLERGIC INFLAMMATION IN AIRWAYS

Th2 cell-mediated airway inflammation depends on the interaction between the T-lymphocytes and the micro-environment of the airways. The development of a Th2 cell

profile is regulated by IL-4. The production of IL-12 skews the immune response towards a Th1 phenotype. It is still not clear which factors determine whether IL-4 or IL-12 predominates. Bacterial endotoxins, intracellular bacteria and certain viral infections (hepatitis A and measles) stimulate IL-12 production and deviate the immune response towards the Th1 phenotype. If IL-4 is produced, the immune response deviates towards a Th2 phenotype.¹⁹ In the presence of IL-4 and IL-13, the B-cell undergoes class-switching to produce IgE.³⁶ IL-4 and IL-13 also induce the release of pro-inflammatory cytokines and adhesion molecules. The priming of the B-cell results in the production of allergen-specific IgE, which coats the mast cells through the high-affinity IgE receptors FcεRI.

Allergy is regarded as an altered immune response characterised by an increased production of IgE in response to environmental antigens and allergens. This increased IgE circulates in the blood and enters the tissues, including airway mucosa and skin, where it is mostly bound to FcεRI receptors on the surface of mast cells and basophils and low-affinity (FcεRII) receptors on eosinophils, macrophages and platelets. Cross-linking of the cell-bound IgE molecules by polyvalent allergens results in activation of the mast cells. This releases a range of pre-formed and newly generated pro-inflammatory mediators.³⁷ These changes manifest clinically as cough and wheeze in the lung and sneezing and rhinorrhoea in the nose – the classical type I hypersensitivity reaction or early-phase response. This is followed by a relatively asymptomatic period during which a plethora of cytokines and mediators generated during the early phase reaction draw leukocytes into the tissues. The late-phase response is observed 2–6 hours after allergen

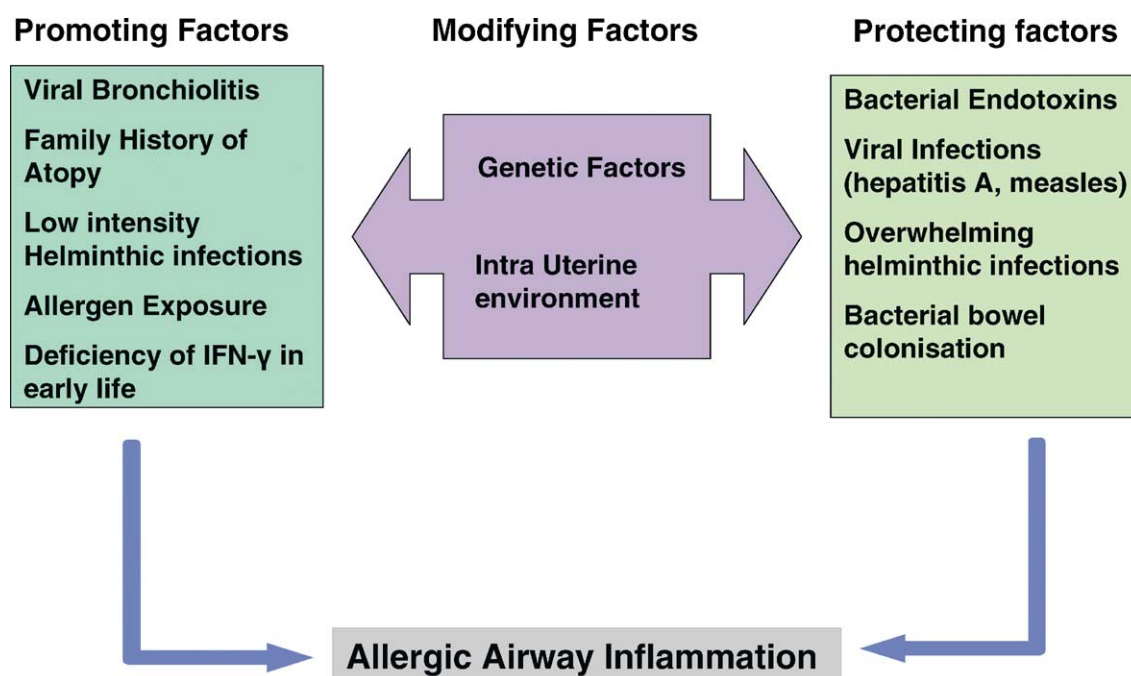


Figure 2 Factors that promote and protect against the development of allergic airway inflammation. IFN-γ, interferon-gamma.

exposure in 50–60% of individuals with asthma and rhinitis.³⁸ It is believed that IgE also plays a role in the late-phase responses.^{39,40} It has now been recognised that structural cells such as airway epithelial cells are also important sources of mediators in airway inflammation, especially in the chronic phase of the disease (Fig. 1).

CONCLUSION

The role of allergy in the development of airway inflammation can therefore be considered to be a continuum of the events of a two-stage process in which the initial sensitisation and predominance of Th2 memory cells is followed by the development of airway inflammation in genetically susceptible individuals. Various factors – including genetics, the type, timing and dosage of exposure to allergen and infection, and other environmental co-factors influence this development in both stages (Fig. 2).

PRACTICE POINTS

- Allergy contributes to 60–70% of asthma in children
- Allergen sensitisation influences the development of asthma
- Allergic disorders develop as a result of consolidation of fetal Th2 response
- Initial allergen sensitisation leads to a predominance of Th2 memory cells
- Factors like genetic makeup, nature and dose of allergens and environment influence the progression of the disease

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