Factors in clinical expression of allergic airways disease
Lopuhaä, C.E.

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CHAPTER 8

Summary
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Inhalant allergy is considered to play an important causal role in the development of asthma. Several epidemiological studies have indicated a relationship between asthma and allergic sensitisation. There is, however, a considerable discrepancy between the prevalence of sensitisation to inhaled allergens (40-50%) and allergic asthma (5-10%) in the general population in industrialised countries. The majority of sensitised persons do not develop asthma and some are even spared from upper airway symptoms. In the small proportion of sensitised people who develop asthma, this is generally accompanied by symptoms of the upper airways.

Although allergic sensitisation is a prerequisite for the development of allergic disease, the allergic effector phase is another important determinant for manifestation of disease. Allergic sensitisation is defined here as production of IgE antibodies to environmental allergens. The processes following the interaction of IgE antibodies and inhaled allergens are regarded as the allergic effector phase.

Several factors are known to influence the development of allergic disease. Environmental as well as genetic factors appear to be relevant for both allergic sensitisation and the allergic effector processes. In addition to allergen exposure, other environmental factors like socio-economic status, sibship size, early childhood infections and dietary habits are considered to be involved. Allergic sensitisation and allergic diseases appear to be clustered in families, suggesting a genetic propensity to develop asthma. This was recently confirmed by the results of genetic linkage studies.

Exposure to allergen in allergic individuals induces a biphasic reaction characterised by early IgE-mediated mast cell degranulation with release of soluble mediators like histamine. This early reaction is generally followed by recruitment and activation of several inflammatory cell types among which the eosinophilic granulocyte is the most prominent. Products of these activated inflammatory cells are believed to cause the symptoms during this late phase.

In this thesis several aspects of the allergic effector processes that may be important for the development of asthma in sensitised individuals have been studied.

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In chapter 2 we investigated the influence of prenatal famine on the occurrence of allergic sensitisation and obstructive airways disease in adulthood. Fetal life is characterised by a Th2-skewed immunity, which is associated with the development of allergic sensitisation. Moreover, there is an association between the levels of IgE in cord blood and IgE-mediated allergy in childhood. Prenatal conditions may therefore influence the development of allergic diseases.

The “fetal origins” hypothesis proposes that adaptation of fetal growth rate caused by variation in the supply of nutrients and oxygen may cause permanent changes in structure and function of organs. This is particularly likely to happen in tissues exposed during periods of rapid cell division. The permanent changes in structure and function of tissues are considered to influence the occurrence of diseases in adulthood. The Dutch famine was a period of severe food shortage in the western part of the Netherlands that lasted from November 1944 to May 1945. In a cohort of 912 individuals born between November 1943 and February 1947 in Amsterdam the association of prenatal exposure to famine and the prevalence of inhalant allergy and obstructive airways disease at the age of 50 years was examined. The participants were asked about their medical history. In addition, lung function and serum levels of total IgE and allergen specific IgE directed against house dust mites, grass pollen and cat dander were measured. We were not able to demonstrate an influence of prenatal famine on spirometric values and parameters for allergic sensitisation in adulthood. However, medical history showed a significantly increased prevalence of symptoms of obstructive airways disease in participants exposed to famine during mid and early gestation. As the bronchial tree shows a rapid development in this particular period of gestation, maternal factors may affect function of the lower airways in fetal life leading to an increased propensity to develop asthmatic symptoms in adulthood.

In chapter 3 the results of a study on the occurrence of allergy to environmental allergens in a developing country is described. The prevalence of allergic diseases is significantly higher in industrialised western countries than in less developed nations. In this study the epidemiological associations between parasite infections, IgE antibodies and skin reactivity to inhalant allergens are investigated. Infections with helminths as well as infections with malarial parasites have proven to influence the immune system of the infected host. These infectious diseases may play a role in the difference in prevalence of allergic diseases between western industrialised countries and less developed nations. The study showed a parallel increase with age in the prevalence of
helminthic infections, allergic sensitisation to house dust mite and levels of total IgE in children attending primary school. However, the skin reactivity to house dust mites declined with age. Despite sensitisation to allergens, as detected by the presence of IgE antibodies in serum, skin reactivity to these allergens appeared to be low in subjects with parasite infections. The results suggest that not production of IgE antibodies, but processes relevant for the allergic effector phase after the allergen-IgE-antibody interaction are modulated by the systemic effects of helminthic infections.

The effector phase after the interaction of IgE antibodies and inhaled allergens at the bronchial level is elaborated upon in the study described in chapter 4. Most inhaled allergens are complex mixtures of various allergenic and non-allergenic components. Recognition patterns of allergenic components may vary considerably between allergic patients. This phenomenon hampers establishing the relationship between IgE-antibody levels, allergen dose and bronchial response. Therefore, we applied a model of bronchial allergen challenge with isolated major allergens of house dust mite (Der p1, Der p2) in allergic asthma patients. Use of isolated allergens permits an accurate determination of IgE-antibody levels and precise quantification of the amount of inhaled allergen.

It was demonstrated that the level of bronchial hyperresponsiveness, as determined by inhalation of histamine, was the main predictor of the immediate allergic bronchial response. Univariate analysis showed a weak association between levels of allergen specific IgE and bronchial responses to allergen, but in multiple linear regression analysis there was no independent contribution of indices for the degree of allergic sensitisation (allergen specific IgE or skin reactivity to allergen) to the bronchial response. We conclude that -although the presence of specific IgE is a prerequisite for development of the allergen induced early asthmatic reaction-bronchial hyperresponsiveness is the main determinant of the degree of bronchoconstriction.

The degree of allergic sensitisation as determined by serum IgE antibodies or skin reactivity to allergen does not appear to explain the difference between allergic individuals with or without asthma. Nor are there indications for a persistent increased allergen exposure in patients with allergic asthma. This suggests that asthma is determined by differences in the effector phase of the allergic reaction. Bronchial inflammation, probably a result of ongoing exposure to allergen, and an increased bronchial hyperresponsiveness are two hallmarks of allergic asthma.

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However, in allergic subjects without symptoms of asthma some degree of bronchial hyperresponsiveness and bronchial inflammation can also be demonstrated. This may indicate that the difference in the allergic effector phase between allergic asthma and allergic non-asthmatic patients is quantitative rather than qualitative.

The results of a study in which we compared allergen induced bronchial inflammation and bronchial hyperresponsiveness between house dust mite allergic patients with asthma and patients with perennial rhinitis without any evidence of asthma are described in chapter 5. A similar early asthmatic reaction was induced in both groups by bronchial allergen challenge. Subsequently, late phase bronchoconstriction appeared to be more pronounced in asthmatic patients than in non-asthmatic patients. A similar increase in indices for eosinophilic bronchial inflammation (number of eosinophilic granulocytes and eosinophil cationic protein (ECP)) was found in induced sputum in both groups. Although the change in eosinophil associated parameters was quantitatively the most pronounced inflammatory event induced by allergen, it did not discriminate between asthmatics and non-asthmatics. Likewise, there was no difference in the fold increase in bronchial hyperresponsiveness. Interestingly, numbers of neutrophilic granulocytes and increases in levels of interleukin-8 (IL-8) and myeloperoxidase (MPO), which are both associated with the neutrophilic component of the inflammation, were more pronounced in sputum of asthmatics. We concluded that the differences in neutrophil associated parameters in the absence of clear differences in eosinophil related inflammation might indicate that neutrophils contribute to the development or persistence of asthma in allergic patients.

In chapter 6 the results of a study comparing allergic inflammation in the skin and the nose between patients with asthma and non-asthmatic patient with perennial rhinitis are described. Several allergic inflammatory parameters were measured in nasal washings after a nasal challenge with a fixed dose of house dust mite allergen. Parallel to the nasal challenge, intracutaneous allergen challenge was performed. Wheal and flare reactions were measured during the early allergic skin reaction, while the extent of the skin induration was measured during the late phase. In agreement with the results of the bronchial allergen challenge described in chapter 5, we did not find significant differences in allergen induced eosinophilic nasal inflammation between asthmatic patients and non-asthmatic patients with allergic rhinitis. However, in contrast to allergen induced bronchial inflammation, the neutrophilic component of the allergen induced nasal inflammation
was also very similar in both groups. In agreement with the nasal challenge, but unlike the bronchial allergen challenge, the late phase reaction after dermal allergen challenge did not reveal significant differences between asthma and non-asthmatic rhinitis. We concluded that allergen provocation in the nose and skin are adequate techniques for studying allergen induced inflammatory responses, but the development or persistence of bronchial asthma seems to depend on local factors in the bronchial tree that cannot be studied in allergic models in the skin or the upper airways.

Bronchial inflammation is reported to be associated with upregulation of the inducible form of Nitric Oxide Synthase (iNOS) in the airways, resulting in increased levels of exhaled Nitric Oxide (eNO). Thus, measurement of eNO is advocated as a non-invasive parameter for diagnosis and monitoring of bronchial asthma. In chapter 7 we investigated levels of eNO after a bronchial allergen challenge. The changes in levels eNO were studied in allergic asthma and non-asthmatic allergic rhinitis after a standardised early allergic bronchoconstriction. In agreement with literature, baseline eNO levels were higher in asthmatic patients as compared with non-asthmatic patients with rhinitis. Twenty-four hours after bronchial allergen challenge eNO increased in both groups. The increase was significantly higher in non-asthmatics, resulting in similar levels in both groups. We concluded that eNO has limited value in discriminating between allergic asthmatics and non-asthmatic allergic patients, particularly after recent exposure to allergen.

It is generally assumed that neither differences in the level of IgE antibodies to allergens like house dust mites, nor differences in actual daily exposure to house dust mites conclusively explain why asthma occurs in some house dust mite allergic individuals and not in others. Differences in the allergic effector phase seem to be particularly relevant for the development of asthma. The high proportion of individuals sensitised to occupational allergens that develops asthma may indicate that in some instances high levels of exposure may “overcome” the absence of factors in the effector phase predisposing to asthma. The latter is also underlined by the fact that significant bronchoconstriction can be induced by artificial allergen inhalation in non-asthmatic allergic patients. In the studies described here, we showed that the early asthmatic reaction after allergen inhalation in allergic asthmatics is mainly determined by the degree of the
bronchial hyperresponsiveness. It seems obvious to attribute the absence of asthma symptoms in allergic rhinitis to the lower level of non-specific bronchial hyperresponsiveness. Nevertheless, there is a considerable overlap in bronchial hyperresponsiveness between allergic patients with and without asthma. Indeed, allergen provocation induces early asthmatic reactions in asthmatics as well as in the majority of non-asthmatic rhinitis patients. Moreover, a significant proportion of non-asthmatic rhinitis patients showed late phase bronchoconstriction as well, be it less pronounced than in asthmatics. Baseline bronchial inflammation as judged by examination of induced sputum was similar with respect to indices for eosinophilic inflammation but showed higher numbers of neutrophilic granulocytes and levels of IL-8 in asthma. Baseline nasal inflammation was indistinguishable between asthma and non-asthmatic rhinitis for all parameters investigated.

After bronchial allergen challenge, differences in neutrophil numbers persisted and there was an increase in IL-8 and MPO in asthma only. The finding that the difference in allergen induced bronchial inflammation between asthma and non-asthmatic rhinitis was lacking after allergen provocation in the nose and the skin seems to indicate that there is no general difference in the effector phase processes underlying allergic inflammation. Other explanations for the development and persistence of asthma in allergic patients can be envisioned. Local factors specific for the bronchial tree could be responsible for an enhanced or altered allergen induced inflammatory response. This option appears to be supported by our finding of a difference in allergen induced bronchial inflammation, which was not detected in the upper airways. Alternatively, the difference between allergic subjects with or without asthma may not be determined by the allergic inflammation per se but by an enhanced airway narrowing due to an increased sensitivity of bronchial structural components like airway smooth muscle for the inflammatory mediators produced. This phenomenon is generally referred to as (baseline) non-specific bronchial hyperresponsiveness, but the exact underlying mechanisms remain unclear.

There appears to be a multiplicity of factors contributing to the development and persistence of asthma, including genetic factors and continued allergen exposure. Our studies demonstrated the influence of the prenatal environment on the development of lower airway function and the propensity to contract asthmatic symptoms in adult life. Moreover, we showed
that infections might modulate the effector phase of an allergic reaction as was shown by the influence of infections with helminths.

The difference in allergen induced bronchial inflammation, which we found between asthma and non-asthmatic rhinitis, may reflect a causal role for neutrophilic granulocytes in the development or persistence of asthmatic disease. Although it cannot be ruled out that this difference is a consequence rather than the cause of asthma, further research into a possible role for neutrophils in the complicated inflammation reactions in the bronchial mucosa in asthma is warranted. The absence of similar asthma-related differences in the upper airways implies that human allergen challenge models for unravelling the pathogenesis of allergic asthma should focus on the lower airways.