Topical Review

(A) Symptomatic bronchial hyper-responsiveness and asthma

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Introduction

Bronchial responsiveness constitutes the phenomenon of the occurrence of airways obstruction upon physical, chemical and pharmacological stimuli (1–3). The clinical presentation in asthmatic individuals includes wheeze, cough and/or dyspnoea upon exercise and inhalation of e.g. cold air, fog and perfume. The prevalence of bronchial hyper-responsiveness (BHR) in the population varies from 6 to 35% (4–14) and is strongly associated with the presence of respiratory symptoms. Even though BHR is generally accompanied by respiratory symptoms, population studies have shown that it may also occur in subjects without any respiratory symptom, so-called asymptomatic hyper-responsiveness (6–9,12,15).

There is increasing evidence that an inflammatory process in the airway wall is one of the underlying pathophysiologic mechanisms of BHR in asthma. This inflammatory process may directly or indirectly cause smooth muscle contraction, airway wall oedema, and stimulation of the nervous system, leading to symptoms of cough, wheeze and dyspnoea. It is still unclear whether an inflammatory process is also present in asymptomatic individuals, and if so, whether it has similar cellular components. Furthermore, it is important to assess whether asymptomatic hyper-responsiveness has any prognostic importance as an early sign of disease development.

Epidemiology of Asymptomatic Bronchial Hyper-responsiveness

Epidemiologic studies in children (8,9) and adults (7,16,17) have shown that BHR is significantly associated with respiratory symptoms such as wheeze, breathlessness during the day or night, chest tightness, chronic (productive) cough and nocturnal cough. Bronchial responsiveness has a continuous unimodal, log-normal distribution in the general population with asthmatic subjects at the more responsive end of the distribution (6,9,11,18,19). Thus, the more responsive a subject is, the more likely it is that he or she experiences respiratory symptoms. However, even among subjects with a very low value of PC_{20}, some are asymptomatic (6,18,19). In the various studies, the sensitivity of a BHR test, i.e. the fraction of symptomatic individuals identified by a positive bronchial challenge test, ranges from 0.29 to 0.61 in a random sample of the population (9,16,19,20). At the other end of the distribution, some subjects with high values of PC_{20} nevertheless reported respiratory symptoms. In various studies, the specificity, i.e. the fraction of asymptomatic individuals identified by a negative bronchial challenge test, varies from 0.58 to 0.90. The accuracy, defined as the number of symptomatic individuals with BHR and asymptomatic individuals without BHR divided by the total number of individuals,
ranges from 0.56 to 0.85. As a result of this wide overlap between asymptomatic and symptomatic subjects, the predictive value of a positive bronchial challenge test for the presence of respiratory symptoms appears to be low (Fig. 1).

In 1947, Curry et al. found BHR to be present in subjects without respiratory symptoms (21). Recent population studies have confirmed the presence of BHR in asymptomatic subjects (Table 1), the prevalence varying from 2.2 to 14.3%. The wide range may be due to the use of different methods for assessment of BHR. Most studies have used histamine as the provocative stimulus, other stimuli being methacholine and cold air. Although histamine and, particularly, methacholine act directly, and cold air acts indirectly on the smooth muscle (24), the degree of bronchial responsiveness to methacholine correlates well with the degree of bronchial responsiveness to cold air (25), and the observed differences in prevalence cannot simply be explained by the use of different stimuli (Table 1).

The range in prevalence rates may also result from varying definitions of asymptomatic state (8,9). The inclusion of a doctor's diagnosis of asthma besides other respiratory symptoms decreased the prevalence from 6.5 to 5.5% in one study (9), and from 7.2 to 6.7% in another study (8). Asymptomatic BHR ranged from 4.5% in subjects reporting never to have experienced respiratory symptoms or rhinitis, to 9.3% in subjects without a medical history of asthma.

The use of different recollection time periods, i.e. reporting respiratory symptoms in the 12 months prior to the study, or ever in the past, does not seem to influence the prevalence rates (20).

Cross-sectional epidemiologic studies may, therefore, show that whatever the definition of BHR and the symptomatic state, a considerable number of subjects with BHR are asymptomatic.

Several factors have been put forward to explain asymptomatic hyper-responsiveness. First, the threshold level for BHR may be too high and has to be reduced. However, the overlap in bronchial responsiveness makes it impossible to make a clear distinction between symptomatic and asymptomatic subjects. Even when a lower threshold level is used to define BHR, BHR will still be present in asymptomatic subjects.

Second, the presence of BHR can be transient in time (26–28). Factors such as viral respiratory infections (29,30), occupational sensitizers (31,32) and allergen exposure (33) may be responsible for the temporal increase in bronchial responsiveness in asymptomatic subjects. In standardized lung function testing, however, it is recommended to measure bronchial responsiveness at least 2 weeks after a viral respiratory infection (34). Furthermore, most subjects sensitive to occupational sensitizers or allergen exposure will report respiratory symptoms. Thus, it seems plausible that other factors beside these transient factors play a role in asymptomatic hyper-responsiveness.

Third, asymptomatic BHR may be explained by factors, other than respiratory symptoms, associated with BHR. Population studies have shown that the prevalence of BHR tends to be higher in older subjects (35,36), females (35,37), subjects who are atopic (4,6,35–40), who smoke cigarettes (4,6,36,40), or have pre-existent bronchial obstruction (36–38,41–43). How far symptom status may influence these relationships has been examined in few studies. One study showed a greater increase of bronchial responsiveness with age in symptomatic subjects (35). Another study showed that symptomatic children with BHR were more frequently sensitized to house-dust mite and pollen than asymptomatic children with BHR (44). The relationship between BHR and gender (35), smoking status (35) and
<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of participants</th>
<th>Age (years)</th>
<th>BHR definition and stimulus</th>
<th>Prevalence of asymptomatic BHR</th>
<th>Prevalence of BHR</th>
<th>% of hyper-responsive subjects who are asymptomatic</th>
<th>Prevalence of respiratory symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woolcock et al. (6)</td>
<td>916</td>
<td>18–88</td>
<td>$\text{PD}_{20} \leq 3.9 \mu$ mol histamine or &gt;15% rise in $\text{FEV}_1$ after salbutamol or rimiterol ($n=12$)</td>
<td>2.2</td>
<td>11.4</td>
<td>19.3</td>
<td>55.7 (c–g)</td>
</tr>
<tr>
<td>Pattemore et al. (9)</td>
<td>2045</td>
<td>7–10</td>
<td>$\text{PD}_{20} \leq 7.8 \mu$ mol histamine</td>
<td>5.5</td>
<td>15.9</td>
<td>34.7</td>
<td>32.8 (a,h,i)</td>
</tr>
<tr>
<td>Salome et al. (8)</td>
<td>2363</td>
<td>8–11</td>
<td>$\text{PD}_{20} \leq 7.8 \mu$ mol histamine</td>
<td>6.7</td>
<td>17.9</td>
<td>37.4</td>
<td>34.4 (a,c,d)</td>
</tr>
<tr>
<td>Toelle et al. (22)</td>
<td>210</td>
<td>7–12</td>
<td>$\text{PD}_{20} \leq 7.8 \mu$ mol histamine</td>
<td>7.1</td>
<td>12.8</td>
<td>55.5</td>
<td>17.6 (h)</td>
</tr>
<tr>
<td>Cockcroft et al. (20)</td>
<td>500</td>
<td>20–29</td>
<td>$\text{PC}_{20} \leq 8 \text{ mg ml}^{-1}$ histamine</td>
<td>7.4</td>
<td>11.6</td>
<td>56.9</td>
<td>10.4 (a,k–o ever)</td>
</tr>
<tr>
<td>Sears et al. (13)</td>
<td>766</td>
<td>9</td>
<td>$\text{PC}_{20} &lt; 25 \text{ mg ml}^{-1}$ methacholine</td>
<td>8.4</td>
<td>23.0</td>
<td>36.9</td>
<td>27.1 (c,d)</td>
</tr>
<tr>
<td>Asher et al. (12)</td>
<td>1084</td>
<td>6–11</td>
<td>$\text{PD}_{20} \leq 7.8 \mu$ mol histamine or $\geq 20%$ rise in $\text{FEV}_1$ after salbutamol ($n=1$)</td>
<td>8.7</td>
<td>20.1</td>
<td>43.3</td>
<td>26.5 (b–d)</td>
</tr>
<tr>
<td></td>
<td>769</td>
<td>6–11</td>
<td>$\geq 20%$ rise in $\text{FEV}_1$ after salbutamol ($n=1$)</td>
<td>8.7</td>
<td>18.8</td>
<td>46.3</td>
<td>23.6 (b–d)</td>
</tr>
<tr>
<td></td>
<td>718</td>
<td>6–11</td>
<td>$\text{PC}_{20} \leq 8 \text{ mg ml}^{-1}$ histamine</td>
<td>9.3</td>
<td>14.9</td>
<td>62.4</td>
<td>19.7 (b–d)</td>
</tr>
<tr>
<td>Fitzgerald et al. (23)</td>
<td>229</td>
<td>9</td>
<td>$\text{PC}_{20} \leq 8 \text{ mg ml}^{-1}$ methacholine</td>
<td>10.9</td>
<td>34.5</td>
<td>31.6</td>
<td>22.3 (q)</td>
</tr>
<tr>
<td>Weiss et al. (11)</td>
<td>213</td>
<td>6–24</td>
<td>$(\Delta \text{FEV}_1/\text{VC}) &gt; 9%$ cold air</td>
<td>11.3</td>
<td>22.1</td>
<td>51.1</td>
<td>40.4 (a,c)</td>
</tr>
<tr>
<td>Rijcken et al. (7)</td>
<td>1935</td>
<td>14–64+</td>
<td>$\text{PC}_{10} \leq 16 \text{ mg ml}^{-1}$ histamine</td>
<td>14.3</td>
<td>24.5</td>
<td>58.5</td>
<td>29.2 (b,e–g,k,r)</td>
</tr>
</tbody>
</table>

*a, asthma diagnosis by a physician; b, ever asthma attacks; c, ever wheeze or tightness in the chest; d, ever night cough; e, ever shortness of breath on rest; f, ever shortness of breath on exertion; g, chronic cough or phlegm; h, wheeze or exercise wheeze in previous 12 months; i, nocturnal cough, attacks of breathlessness or asthma in previous 12 months; k, wheeze on most days or nights; m, ≥2 periods of wheezing resulting in shortness of breath; o, wheezing apart from a cold; p, rhinitis; l, cumulative history of symptoms consistent with asthma; r, episodes of bronchitis in the previous 3 yr. BHR, bronchial hyper-responsiveness.
pulmonary function (35,38) appeared to be independent of the presence or absence of respiratory symptoms. Other factors that may relate differently to BHR depending on symptom status are parental smoking and a positive family history of asthma. The association between parental smoking and bronchial responsiveness has been reported to be less strong (45) in asymptomatic children than in asthmatic symptomatic children, or even absent in asymptomatic children (46). In asymptomatic children, an increase in bronchial responsiveness to cold air was associated with a positive family history of asthma, while this association was not present in symptomatic children (47). Thus, the relationship between BHR and age, atopy and parental smoking appears to be stronger in symptomatic than in asymptomatic subjects, in contrast to the association between a family history of asthma and BHR, which appears to be stronger in asymptomatic subjects.

Finally, asymptomatic subjects may not recognize variable airway obstruction as breathlessness. To examine whether asymptomatic subjects perceive breathlessness differently from symptomatic subjects, Brand et al. (48) compared the Borg score reported by these two groups during histamine-induced bronchoconstriction. At the same degree of bronchoconstriction, symptomatic hyperresponsive subjects were more likely to show an increase in the Borg score during a 20% fall in FEV₁ than asymptomatic hyperresponsive subjects (Fig. 2), independent of age, gender, smoking habits, FEV₁ and atopy (P=0.049). In a study conducted by Stenton et al. (49), a comparison was made between respiratory symptoms reported by questionnaire, BHR to methacholine, and the recognition of bronchoconstriction. After a decrease in FEV₁ of 20% or more, subjects were asked whether they had ever felt like that before. Recognition of this feeling was associated with the severity of bronchial responsiveness, i.e. all subjects in the most responsive category, and only 27% in the least responsive group recognized the feeling of bronchoconstriction. Two-thirds of the subjects with intermediate bronchial responsiveness and who reported respiratory symptoms, such as wheeze, chest tightness, breathlessness and cough, did not recognize the feeling of bronchoconstriction. Further, there were also subjects who reported no respiratory symptoms but recognized the feeling of bronchoconstriction.

The clinical relevance of asymptomatic hyperresponsiveness is unclear. Longitudinal population studies have shown a faster decline of pulmonary function in subjects with BHR compared to subjects without BHR, independent of symptom status, smoking, atopy, pre-challenge FEV₁, age, gender and height (50–52). Further, the severity of bronchial responsiveness was positively associated with the degree of pulmonary decline (10). From these data, the question was raised whether BHR might be a predictor for the subsequent unfolding of respiratory symptoms (Table 2).

A study in 236 children, aged 8–11 years, assessed the predictive nature of BHR and wheeze for childhood respiratory illness during 1 yr of follow-up (44). Children with BHR but no wheeze at baseline had more frequent respiratory symptoms and more severe bronchial responsiveness during 1 yr of follow-up than those who did not have BHR and wheeze at...
TABLE 2. Longitudinal studies into the relationship between bronchial hyper-responsiveness and the subsequent development of respiratory symptoms

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Age (years)</th>
<th>Follow-up (yrs)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peat et al. (44)</td>
<td>236 children, divided into four groups according to wheeze in the previous 12 months and BHR</td>
<td>8–11</td>
<td>1</td>
<td>AS with BHR had intermediate wheeze and BHR compared to SS with BHR and AS without BHR.</td>
</tr>
<tr>
<td>Hopp et al. (53)</td>
<td>13 AS who developed asthma during follow-up</td>
<td>5–18</td>
<td>6:30 ± 5:0 Mean: 10:6</td>
<td>Almost all subjects who developed asthma showed BHR at their initial visit (n=16). The other four subjects had siblings with asthma. SS and AS who developed asthma had similar bronchial responsiveness at initial visit.</td>
</tr>
<tr>
<td></td>
<td>26 age- and sex-matches controls from AF and NF</td>
<td></td>
<td>7:69 ± 4:5 AF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 SS who developed asthma during follow-up</td>
<td>5–44</td>
<td>7:0 ± 1:7 NF Mean: 14:5</td>
<td></td>
</tr>
<tr>
<td>Jones et al. (54)</td>
<td>55 AS with BHR</td>
<td>4–11</td>
<td>6</td>
<td>Thirty-two (58%) of the AS with BHR developed asthma, and eight (13%) of the AS without BHR. Of these eight children, six had siblings with asthma.</td>
</tr>
<tr>
<td></td>
<td>55 AS without BHR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhong et al. (55)</td>
<td>31 SS and 50 AS with BHR and 88 age-matched controls without BHR</td>
<td>11–17</td>
<td>2</td>
<td>Ten (20%) of the AS with BHR developed asthma compared to two (2%) of the AS without BHR. The subjects who developed asthma had more severe bronchial responsiveness compared to those who remained asymptomatic.</td>
</tr>
<tr>
<td>de Gooijer et al. (56)</td>
<td>17 SS 19 AS with family history of atopy 15 AS</td>
<td>8–11</td>
<td>27</td>
<td>The prevalence of BHR was decreased in all groups. Asymptomatic BHR in childhood was not associated with development of respiratory symptoms in adulthood.</td>
</tr>
<tr>
<td>Prieto et al. (57)</td>
<td>66 AS with allergic rhinitis</td>
<td>16–51</td>
<td>36–70 months Mean: 43:8</td>
<td>The risk of becoming symptomatic was similar between AS with BHR and AS without BHR.</td>
</tr>
</tbody>
</table>

AS, asymptomatic subjects; SS, symptomatic subjects; AF, asthma family; NF, non-asthma family, no history of a major allergic disease (asthma, allergic rhinitis, eczema) for three generations; BHR, bronchial hyper-responsiveness.
Inflammation

INFLAMMATION AS UNDERLYING MECHANISM OF BHR

In both human and animal studies, inflammatory changes in the airways, such as viral infections (29), allergen exposure (33), occupational (toluene diisocyanate) exposure (31) and ozone inhalation (58), have been shown to induce a temporal increase in bronchial responsiveness. Initially, information on the inflammatory process in the airways was largely based on autopsy findings of patients with severe asthma (59). The inflammatory changes which have been described include severe damage of airway epithelium, an extensive mucosal and submucosal infiltration by inflammatory cells, such as eosinophil granulocytes, and airway luminal obstruction by mucus and cellular debris (60,61).

The relevance of these airway changes in autopsy studies to day-to-day asthma was first uncertain. Later studies in airway wall biopsies of patients with stable asthma revealed qualitative changes similar to autopsy findings in severe asthma patients (60,62–70). Many cells are activated, e.g. an increased proportion of eosinophils are EG2 positive (62,64,70–72). At present, the role of neutrophils in this process is uncertain (60,61,73,74). Apart from the cellular process, it is likely that an imbalance in the neuronal control of the airways plays a role in inflammation by activation of sensory fibres which release mediators, such as substance P and neurokinins A and B (60).

The changes described in bronchoalveolar lavage (BAL) are largely concordant with the histologic findings, and include an increased number of desquamated epithelial cells (63,67), (activated) inflammatory cells, such as eosinophils (73,75,76), mast cells (67,73,77) and macrophages (78,79). Furthermore, increased concentrations of inflammatory mediators in BAL fluid have been reported, compatible with activation of these cells (73,75,76,80–83). The inflammatory process in the airways can also be assessed by cell counts in sputum (obtained spontaneously or induced by hypertonic saline), a less invasive technique compared to bronchoscopy. In asthma, percentages of eosinophils (84,85), mast cells (84) and neutrophils (84) are increased, whereas the percentage of
macrophages is decreased (84,85). Total cell counts and differential counts of intact epithelial cells and lymphocytes are not increased in asthma (84). These findings are confirmed for asthmatics with a mild exacerbation compared to smokers with chronic bronchitis, except for the numbers of neutrophils which were not different (86).

Mast cells are known as prominent effector cells in IgE-mediated asthmatic reactions (60,61,74). Their numbers do not seem to be increased in the submucosa of patients with mild asthma. However, increased numbers of mast cells have been demonstrated (87) by electron microscopic (EM) investigation of bronchial epithelium. Furthermore, evidence has been found for mast cell degranulation (60,61,63,73). The increased numbers or activation state of mast cells has been confirmed by the presence of increased concentrations of mast cell mediators in BAL fluid (80,81). Mast cells secrete a wide array of pre-formed and newly formed mediators, such as histamine, PGD2, LTC4, chymase and tryptase (60,61,74), and interleukins such as IL-4 (61,68). This interleukin has the potential to induce the immune ‘switching’ of B-lymphocytes to immunoglobulin production, and to upregulate the expression of the adhesion molecule VCAM1 on the endothelial surface (61,89–91). Eosinophils may adhere to these endothelial cells by binding to VCAM1 and ICAM-1 through specific integrin ligands (VLA4 and LFA-1, respectively), which enables their migration to the bronchial mucosa (60). IL-4 may be secreted in the course of IgE-mediated reactions, and this may imply that the mast cell has an even more important role in the regulation of the ongoing allergic reaction.

T-lymphocytes play a very important regulatory role in the inflammatory processes of allergic asthma. The T-helper cell population (CD4 positive) can be subdivided into Th1 and Th2 cells with specific features of each subgroup (60,61,74,92). These subsets are also characterized by production of specific cytokines. As IL-4, IL-5 and IFN\_\gamma, are cytokines, mutually exclusive in their presence in Th1 and Th2 cells, these proteins are relevant parameters to determine. The evaluation of the presence of Th1 or Th2 cells may give a clue to distinguish the various circumstances that lead to inflammation. In general, Th1 cells are found in (viral) infections and not in asthmatic individuals with increased airway responsiveness, while conversely the presence of Th2 cells, in general, may be an indicator for an allergic component (61,92 94). In the induction phase of the allergic inflammation, B-cells (61), macrophages (61) or dendritic cells present in the bronchial epithelium (95), act as antigen-presenting cells (APC) (96) interacting with T-cells (Th0-cells), which respond by differentiating to Th2 cells, a subtype that is capable of generating IL-3, IL-4, IL-5 and GM-CSF (61,92–95). IL-3, IL-5 and GM-CSF play a role in the activation and prolongation of the survival of eosinophil granulocytes (60,74,97). The possible role of IL-4 was discussed above.

The eosinophil granulocyte is another potent inflammatory effector cell. Eosinophils are attracted to the bronchial mucosa and activated by many stimuli, such as leukotriene C4, platelet activating factor, IL-4 and IL-5. Once activated, eosinophils release newly formed mediators, including leukotrienes, PAF, 15-HETE and arginine-rich proteins, such as MBP, ECP and EPO (60,61,74). These agents may cause epithelial injury and denudation, probably due to disruption of desmosomal attachments between epithelial cells (62,67,70). This may result in an increased permeability to irritant stimuli for sensory nerves, thereby further inducing inflammatory changes as well as an increase in airway responsiveness (66,98–100).

As to the relation between these inflammatory changes and BHR in stable asthma, positive correlations have been described between the degree of bronchial responsiveness and the number of epithelial cells (63,76), eosinophils (76,101), mast cells (67,77,102), macrophages (103) and activated T-cells (104) in the BAL fluid. No relationship was observed between BHR and the number of neutrophils in BAL (63,76,77,103). Sputum cell counts were not related to bronchial responsiveness to hypertonic saline (85), histamine (105) and methacholine (86). However, a decrease in PC\textsubscript{20} histamine was significantly associated with an increase in numbers of eosinophils and mast cells after allergen challenge (105). In bronchial biopsies, the level of bronchial responsiveness was related to increased numbers of mast cells (70,106),
dendritic cells (106), T-cells expressing IL-2 receptors (70), and raised levels of HLA-DR expression (107). A similar relationship was observed between bronchial responsiveness and the cytokines IL-5 and GM-CSF independent of atopic status, while IL-2 correlated with BHR in non-atopic subjects (106). IL-3 and TNF-α showed no correlation with BHR. However, in vitro (108) and in vivo (109–111) studies in humans and in animals have shown the ability of TNF-α to increase bronchial responsiveness. Moreover, there was a positive correlation between the number of activated eosinophils in the biopsy specimens and the degree of bronchial responsiveness (64,70,72,106,112).

INFLAMMATION AND ASYMPTOMATIC BHR

The above findings suggest that inflammatory changes play a role in symptomatic individuals with BHR. It can be hypothesized that the difference between symptomatic and asymptomatic hyper-responsive individuals is the result of differences in inflammatory cell numbers, composition or activation. Little is known about the relationship between BHR and the presence of inflammatory cells in the airways in asymptomatic, non-asthmatic subjects. One study in asymptomatic hyper-responsive males showed that the levels of peripheral blood eosinophil counts were intermediate between symptomatic hyper-responsive males and asymptomatic normal responsive males, independent of smoking status and age (113). No differences were observed between the groups with regard to neutrophils. These findings suggest a relationship between BHR and inflammatory changes in peripheral blood, which may reflect the situation in the airways of asymptomatic hyper-responsive subjects. This gives support to other studies finding (see above) that asymptomatic hyper-responsiveness may precede the development of symptomatic asthma. However, the two biopsy studies available are less clear whether this is the case. One study found an association of BHR with inflammatory changes in bronchial biopsies in healthy individuals with a ‘positive respiratory record’ (114), but not in subjects with asymptomatic BHR without a respiratory record. The subjects with positive respiratory records were, however, more hyper-responsive. Another study only investigated asymptomatic individuals. The authors did not find differences in numbers of neutrophils, T-cells, eosinophils and mast cells, nor in the expression of HLA-DR in bronchial biopsies of asymptomatic individuals with and without BHR. However, the combined use of the monoclonal antibodies RFD1 and RFD7 showed changes in macrophage subsets. Finally, Roisman et al. recently assessed breathlessness during a 20% fall in FEV1 upon methacholine and bradykinin challenge in hyper-responsive asthmatic individuals (115). More shedding of epithelium in airway wall biopsies was associated with less breathlessness during bronchoconstriction by either agent, possibly due to intra-epithelial nerve injury which is associated with epithelial damage in asthma. It might, thus, even be possible that asymptomatic asthma is associated with epithelial damage, which may lead to symptomatic asthma upon allergen or irritant exposure. This can be compatible with the finding that sputum of asymptomatic hyper-responsive children contained less mast cells, basophils and eosinophils compared to symptomatic hyper-responsive children, but similar numbers as in asymptomatic normal responsive children (116). Furthermore, Sur et al. (117) found that EDN and IL-5 levels in BAL fluid were significantly higher in symptomatic asthma patients than asymptomatic ones. IL-5 levels were especially high in symptomatic individuals with high numbers of eosinophils, suggesting increasing inflammation when asthma progresses from the asymptomatic to symptomatic state (Fig. 4). Altogether, the data suggest that higher environmental exposure induces the influx of cells which only asserts symptoms when epithelial damage is already present.

Discussion and Conclusions

Cross-sectional population studies investigating the relationship between BHR and respiratory symptoms have shown that BHR is significantly associated with respiratory symptoms, such as wheeze, breathlessness and chest tightness. However, a positive bronchoprovocation challenge is neither a very sensitive nor a predictive indicator for the presence of respiratory symptoms. Questionnaire responses as to respiratory complaints do not accurately reflect previous experience of
bronchoconstriction. Although the prevalence in the population is low, varying from 2.2 to 14.3%, a significant proportion of subjects with BHR is asymptomatic. There is no cut-off point of BHR to distinguish completely symptomatic from asymptomatic subjects. The variability of BHR in time, a poor perception of airways obstruction and a poorer association of BHR with older age, cigarette smoking, atopy and pre-existent bronchial obstruction in asymptomatic hyper-responsive individuals can only explain part of the phenomenon of asymptomatic hyper-responsiveness. An important finding is that asymptomatic subjects with BHR are more prone to develop respiratory symptoms than asymptomatic subjects without BHR.

It is likely that inflammatory changes in the airways are the underlying mechanisms for BHR in asymptomatic subjects as well. Current studies in asthma suggest that an intricate interaction between different types of inflammatory cells and their respective mediators plays a role in the processes that lead to increased bronchial responsiveness. Only a few studies have examined the presence of inflammatory changes in asymptomatic subjects with BHR. Although the number of eosinophils in peripheral blood was found to be increased in asymptomatic subjects with BHR compared with asymptomatic subjects without BHR, BHR was not found to be associated with overall inflammatory changes in the airways. However, one study did suggest that increasing inflammation is associated with progression of an asymptomatic to a symptomatic state. Furthermore, it is possible that handling of inhaled irritants and viral infections is different in asymptomatic individuals with and without BHR, thereby ultimately leading to a different clinical outcome. Therefore, the role of airway mucosal inflammatory processes in the occurrence of mild degrees of BHR in asymptomatic subjects should be a subject of further studies. These studies should preferably not only be of cross-sectional nature, but should also include follow-up of individuals. Only this will allow us to answer the question whether asymptomatic BHR is a risk factor for development of asthma (or chronic obstructive pulmonary disease), and whether there is a pathophysiologic inflammatory pathway in which we may interfere to prevent this unwanted development.

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