Update on the “Dutch hypothesis” for chronic respiratory disease

Jørgen Vestbo, *Eva Prescott
Medical Department, Amager Hospital, Italiensvej 1, DK-2300 Copenhagen S, Denmark and *Institute of Preventive Medicine, Kommunehospitalet, DK-1399 Copenhagen K, Denmark

Introductory article

Airways responsiveness and development and remission of chronic respiratory symptoms in adults

X Xu, B Rijcken, JP Schouten, ST Weiss

Background. Many patients with chronic obstructive lung disease show increased airways responsiveness to histamine. We investigated the hypothesis that increased airways responsiveness predicts the development and remission of chronic respiratory symptoms. Methods. We used data from 24-year follow-up (1965–90) of 2684 participants in a cohort study in Vlagtwedde and Vlaardingen, Netherlands. Increased airways responsiveness was defined as a PC_{10} value (concentration of histamine for which challenge led to a 10% fall in forced expiratory volume in 1 s) of less than 8 mg/ml. Information on respiratory symptoms was collected by means of a standard questionnaire every 3 years. Logistic regression was used to control for age, area of residence, cigarette smoking status, and sex. Findings. Participants with increased airways responsiveness (1281 observations) were more likely than those without increased airways responsiveness (5801 observations) to develop the following symptoms during any 3-year follow-up interval: chronic cough (odds ratio 1.9 [95% Cl 1.2–2.9]), chronic phlegm (2.0 [1.3–3.0]), dyspnoea (2.3 [1.5–3.5]), asthmatic attacks (3.7 [2.2–6.1]), and persistent wheeze (2.7 [1.7–4.4]). The estimate of the odds ratio for the development of any of the six symptoms was 1.7 (1.2–2.3). Participants with increased airways responsiveness were less likely than those without this characteristic to show remission of these respiratory symptoms. The estimate of the odds ratio for the remission of any of the six symptoms was 0.42 (0.28–0.61). Interpretation. These prospective analyses show that increased airways responsiveness is positively associated with the development of chronic respiratory symptoms and negatively associated with the remission of these symptoms in adults. (Lancet 1997; 350:1431–34)

The “Dutch hypothesis” was originally put forward by Orie et al. They postulated that airway hyper-responsiveness (AHR) and atopy were markers of a basic disturbance or constitution which predisposed to the development of chronic non-specific lung disease characterised by cough, sputum production, dyspnoea, and often airflow limitation. This disease, later termed CARA in Dutch, included both chronic asthma and what we would today label as chronic obstructive pulmonary disease (COPD). Retrospективly, it seems that this lack of distinction between asthma and COPD—at a time when most British, other European, and American studies made a clear distinction—was a major hindrance for communication between the Dutch group and others. Also, the “Dutch hypothesis” was not a term proposed by Orie et al but by others contrasting it with the “British hypothesis” which focused on chronic mucus hypersecretion as a marker of recurrent airway infections causing chronic airflow limitation.

The core point at the beginning of the 1960s was that the Dutch hypothesis pointed to endogenous factors which might play an important role in the development of COPD. This contrasted with the view that exogenous factors—particularly tobacco smoke—were the overwhelming causes of COPD.

Atopy, airways hyperresponsiveness, and the risk of COPD

The role of atopy has gradually been separated from that of AHR, at least in epidemiological studies. In several studies total IgE has been used as a marker of atopy. In general, smokers have an increase in total IgE and also in blood eosinophil count compared with non-smokers. In the absence of clinical asthma there is, however, no indication that atopy interacts with tobacco...
FEV1 is not without pitfalls, an association between metric values or peak flow, measurements of par-Ve the decline in FEV1 has been made by Rijcken and It is worth noting that the clinical diagnosis of COPD seems to have been favoured over methacholine in with increased airways responsiveness were less likely to report remission of symptoms than those without increased responsiveness.

The strength of the study lies in its sample size, its two distinct cohorts, and the appropriate use of advanced statistical methods. It does, however, have one limitation. The results were said to be uninfluenced by the exclusion of “asthmatics” but no definition of the latter was provided. Presumably the authors relied on self-reported physician made diagnoses. The relationship between AHR and the clinical symptoms of asthma is likely to have introduced some bias. We would have expected, conversely, some weakening of the demonstrated associations after exclusion of asthmatic subjects. The authors have nevertheless collected and analysed invaluable data which strengthen the overall credibility of AHR as an important aetiological factor in chronic respiratory disease.

Airways hyperresponsiveness and other risk factors for COPD

Thus, AHR seems to be an independent risk factor for the development of FEV1 decline. As such, the Dutch hypothesis has always been the “downgrading” of asthma as a “constitutional factor” as suggested by the Dutch hypothesis. This poses the further interesting question of how the AHR risk links with other established risk factors. It is worth noting that the clinical diagnosis of COPD is usually “cross-sectional”—that is, the diagnosis is made after demonstrating irreversible airflow limitation after the apparent exclusion of a few (and rare) specific conditions that can also cause fixed airflow obstruction. It is not generally diagnosed after the longitudinal observation of an excessive decline in FEV1. The distinction from asthma is most often achieved from the clinical history, a history of smoking and other exposures such as dust and fumes, serial measurements of spirometric values or peak flow, measurements of par-enchymal lung function, or (when doubt remains) corticosteroid reversibility or the quantification of airway responsiveness. This clinical approach does not always distinguish between the several ways in which the affected individual may have acquired a low level of lung function. The different possibilities are shown in fig 1 where the normal course of growth and decline in FEV1 is shown.

One of the main obstacles for the acceptance of the Dutch hypothesis has always been the “downgrading” of the role of tobacco smoking. In the literature on COPD the attributable risk of tobacco smoking is generally believed to be 80–90%. At the same time only 15% of smokers develop COPD, a phenomenon generally ascribed to the presence or absence of various degrees of “susceptibility”. The growth phase for the lungs (or at least lung function) has recently been shown to be affected by smoking, especially in girls. From cross-sectional studies it seems that AHR is associated with a
AHR and smoking interact in causing airway obstruction. AHR alone is not enough to explain the clinical differences between smokers. There is evidence that AHR is a marker of susceptibility to smoking, which is often seen in the Dutch hypothesis. Studies have suggested that AHR in smokers is a risk factor for COPD along with smoking, rather than a demonstrable interaction between AHR and smoking. AHR as the underlying marker of susceptibility needs to be considered in conjunction with other factors such as mucus hypersecretion.

The heterogeneity of COPD and the Dutch hypothesis

The heterogeneity of COPD and the Dutch hypothesis has been the reluctance to accept a common background for diseases with such differing pathophysiology as asthma and emphysema. The Dutch hypothesis suggests that COPD may arise as a consequence of emphysema with further risk factor for COPD. Studies focusing on this point are clearly needed. Chronic mucus hypersecretion has re-emerged as a risk factor for an accelerated FEV1 decline and recent studies have suggested a more obvious impact of smoking on lung function in symptomatic than in asymptomatic subjects. Studies focusing on this point are clearly needed.

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LEARNING POINTS

- Airway hyperresponsiveness (AHR) is associated with respiratory symptoms, level of lung function, and decline in lung function.
- Changes in AHR are associated with changes in respiratory symptoms, seemingly in both asthmatic and non-asthmatic subjects.
- AHR is a risk factor for COPD, independent of age and tobacco consumption.
- The reported relationship of AHR with gender needs further evaluation.
- Future studies of respiratory epidemiology may benefit from looking at changes in the risk factor of interest as well as at changes in the outcome variable—for example, the methodology reported in the introductory article.

between asthma attacks is now discarded, and it is generally accepted that processes of airway remodelling often lead to permanent damage to the airway wall and to fixed obstruction. Thus, an increased longitudinal decline in FEV1 can be demonstrated in asthmatic subjects compared with non-asthmatic subjects, just as it can in subjects with COPD. This makes asthma a risk factor for COPD and it supports the conclusions of Lange et al that the increased morbidity of subjects with asthma is due in part to COPD.

Weiss has suggested that our emerging knowledge of the importance of perennial factors for the later risk of impaired lung function should be combined with experience from research on childhood wheeze, recognised and unrecognized childhood asthma, and the above cited studies on AHR and FEV1 decline. From this exercise we should appreciate that merely studying exposures and FEV1 decline in adult life is insufficient (Weiss, personal communication). Thus, AHR and perhaps atopy (the core components of the “basic disturbance” described by Otey et al) could link early life events with the data on decline in FEV1 in adult life—in its purest form exemplified by the seminal study by Fletcher and coworkers of London transport workers. In parallel, COPD research will enquire into the underlying mechanisms—for example, research into oxidative pulmonary stress—but whether future research will ever again lead to a single aetiological hypothesis remains to be seen.

Conclusions

We conclude that the “Dutch hypothesis” is still with us. After more than 35 years of increasing awareness of COPD and increasing research, the “hypothosis” is now being tested. Its components and the ideas behind it being tested. Its components and the ideas behind it—such as it can in subjects with COPD. This makes asthma a risk factor for COPD and it supports the conclusions of Lange et al that the increased morbidity of subjects with asthma is due in part to COPD.

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doi: 10.1136/thx.53.2008.S15

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