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Airway inflammation and late asthmatic reactions

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Sensitized subjects may develop symptoms of asthma after exposure to isocyanates at work [1, 2]. After challenge with isocyanates in the laboratory, they develop immediate, late and dual asthmatic reactions [3]. Dual and late asthmatic reactions are more frequent than early reactions after challenge with isocyanates [4], and like allergen-induced dual and late reactions, have probably more relevance to the history of asthma than immediate reactions. Late asthmatic reactions are usually more severe, last longer, respond to steroids but not to bronchodilators and are more resistant to therapy. Subjects sensitized to toluene diisocyanate (TDI) who develop dual or late reactions continue to have asthma upon cessation of exposure [5]. The mechanism of the late asthmatic reaction is unknown. TDI may cause late asthmatic reactions and increase bronchial responsiveness by causing an acute inflammatory reaction in the airways.

Sensitized subjects were examined during late asthmatic reactions induced by exposure to TDI in the laboratory. The late asthmatic reactions were associated with a transient increase of bronchial responsiveness [6], an increase of neutrophils, eosinophils [7], leukotriene B_4 (LTB_4) and albumin [7] in bronchoalveolar lavage fluid. These reactions were prevented by pretreatment with prednisone [8] but not with the non-steroidal, anti-inflammatory agent indomethacin [9]. Aerosolized steroids alone, *e.g.* beclomethasone [10, 11], completely inhibit late asthmatic reactions induced by TDI. Theophylline [10] has only a partial effect. Verapamil [10], ketotifen [12], salbutamol alone, atropine [13] and cromolyn [10] have no protective effect.

These studies support the hypothesis that bronchoconstriction and airway inflammation are involved in the late asthmatic reaction induced by TDI, and that polymorphonuclear leucocytes are required for hyper-responsiveness to occur. One of the inflammatory mediators (*i.e.* LTB_4) (1a) has been measured during late asthmatic reactions induced by TDI. The structure and source of all chemotactic factors which attract neutrophils and eosinophils into the airspaces and of the mediators released by these cells must be identified.

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Bronchoalveolar lavage in allergic asthma

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Bronchoalveolar lavage (BAL) has improved knowledge of the defence mechanisms of the human lung and the inflammatory and immune mediated changes involved in the pathogenesis of diseases of the pulmonary parenchyma [1]. In addition, it has been used in disorders of the airways such as allergic occupational and intrinsic asthma and chronic bronchitis, in which the bronchial components of lavage may produce more useful information than the alveolar components. Fluid containing mainly components from the airways compartment can be obtained by bronchial lavage (BL).

In bronchial asthma, inflammation is thought to play a major role in perpetuating bronchial hyperreactivity and obstruction. Clinical and morphological observations on biopsy or autopsy specimens support this hypothesis but the relative importance of the various inflammatory cells and the mediators released by them is not established.

In patients with allergic asthma, BL and BAL have made it possible to study: 1) the cell populations, antibodies and mediators present in the bronchial tree which may contribute to airway hyperreactivity and inflammation; 2) the mechanisms of allergic asthmatic response after bronchial exposure to the sensitizing allergen; 3) the action and efficacy of drugs.

Inflammatory cells present in the asthmatic lung vary with stage, severity and type of disease. In mild asthmatics studied during disease quiescence BAL showed a mild increase in % eosinophils and neutrophils [2, 3]. In BL from asymptomatic patients, CRIMI *et al.* [4] found increased albumin and specific IgE's, correlating well with the results of bronchial challenge. These data suggest that airways inflammation with increased alveolar capillary permeability is present in asthmatics even at a time of quiescence. Mast cells, which are believed to play a major role in response to allergen, were found in BAL of mild asthmatics during clinically asymptomatic periods [5–8]. Also, the level of histamine in BAL of asthmatics was higher than in BAL of controls [7] and correlated with bronchial hyperresponsiveness [6, 7]. However, RANKIN *et al.* [9] found that levels of histamine in BAL of asthmatics did not differ from controls or correlate with mast cell or basophil count. WENZEL *et al.* [10] showed that pulmonary activation of mast cells occurs after allergen challenge in subjects with atopy and asthma and, to a lesser degree, in those with atopy alone.

Mast cells do not, therefore, seem to be constantly involved in patients with day-to-day asthma but are probably recruited in response to allergen inhalation or other stimuli. Conflicting results may depend on the stage and severity of disease. When bronchial hyperresponsiveness was systematically determined a significant negative correlation was found between methacholine PC_{20} and % mast cells, eosinophils and epithelial cells recovered from BAL.

The combination of bronchial provocation test (BPT) with BL and/or BAL provides new insights into events following allergen inhalation. Exposure to specific antigen causes increased permeability of bronchial mucosa resulting in visual evidence of oedema and migration of more proteins into the bronchial lumen [11]. METZLER *et al.* [12] showed an increased % neutrophils and eosinophils in BAL within 4 h of BPT, whilst eosinophils alone were still increased 24 h later; all but one patient developed a dual response to bronchial challenge. DE MONCHY *et al.* [13] showed an increased % eosinophils

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