Mucosal inflammation and bronchial hyperreactivity

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Asthma, bronchial hyperreactivity and airway inflammation

Asthma is a chronic disease characterized by increased bronchial responsiveness ranging in degree from mild to severe. Airway inflammation has been receiving increased attention as the major mechanism in bronchial hyperresponsiveness. Many stimuli known to induce airway inflammation also increase bronchial reactivity, *e.g.* viral respiratory infections, ozone, antigens and chemicals such as toluene diisocyanate (TDI). Inflammation should be understood not only as an increase in the number of inflammatory cells, but also as including an increase in the bronchial blood flow and vascular permeability leading to mucosal oedema and epithelial shedding. The time sequence and severity of this inflammatory process in the pathogenesis of asthma is not known, although some information of the separate events has been obtained in recent studies (LAITINEN *et al.* [1]; BARNES [2]; PERSSON [3])

Neurogenic inflammation

It has been proposed that the inflammation in the airways of asthmatic patients is due to neurogenic inflammation (BARNES [2]). This is thought to be caused by neuropeptides such as substance p released by sensory nerve endings. Substance p-like immunoreactive nerves occur in the lower respiratory tracts of many species including man. These neuropeptides have been observed in association with blood vessels, smooth muscle, and ganglion cells. Sensory nerves are known to mediate inflammatory actions in the skin, eye and respiratory tract. Characteristic features of neurogenic inflammation in airways are vasodilation, increased blood flow and increase in the permeability of mucosal blood vessels to macromolecules. Several mediators have been shown to decrease vascular resistance in the canine tracheal vascular bed. These same mediators cause an increase in extravasation of red blood cells (LAITINEN *et al.* [4]). Extravasation produced by mediators is thought to be due to the formation of endothelial gaps. In bronchial biopsy specimens, vascular endothelial gaps up to one micrometer in width have been found in asthmatic patients (fig. 1), whilst the walls of bronchial vessels in healthy controls were intact.

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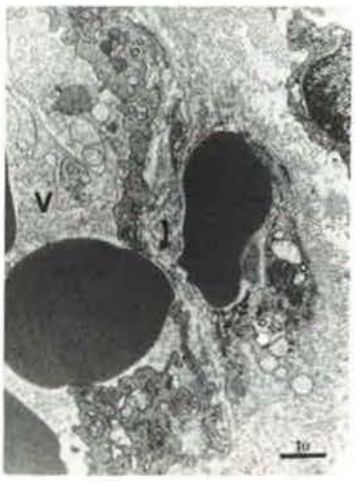

Fig. 1. – This represents a transmission electronmicrograph from the airway mucosa of a patient having clinically moderate asthma. The picture shows a venule (V) containing red blood cells in the lamina propria. In the venular endothelium can be seen a gap, one micrometer in width, indicated by the arrow. One red blood cell is located outside the venule and the other appears to be penetrating through the gap.
Original magnification x20,000; bar=1 micrometer.

Cinical evidence of the association between inflammation and bronchial hyperreactivity

Several investigators have noted that 'Creola Bodies', consisting of compact clusters of columnar epithelial cells, can often be seen in the sputum of asthmatic patients.

DUNNILL [5] described the morphology of the airways in bronchial asthma, based on necropsies in patients dying in an asthmatic attack. In the mucosa, the main findings included oedema and separation as well as shedding of the mucosal cells. Submucosal tissue was oedematous with numerous dilated capillaries, oesinophils, mast cells, lymphocytes and plasma cells. These histological changes imply that asthmatic patients dying in asthma attack have mucosal inflammation in the airways. Recently, similar histological findings have been shown in the bronchial mucosa by taking fresh biopsy specimens from the airways of asthmatic patients with increased bronchial reactivity (LAITINEN *et al.* [1]).

We have taken fresh bronchial biopsy specimens from mild to severe asthmatics with various durations of the disease, chronic bronchitics, and patients with hyperventilation syndrome as controls. To study the morphology of the mucosa in these specimens, we have developed a new elecronmicroscopical method by using Slot grids without bars and by making

photomontages of the adjacent electronmicrographs. With this method we have calculated the number of mast cells, neutrophils and eosinophils in the airway mucosa. At the time of the biopsies the patient had clinically stable asthma. They had not had viral respiratory tract infections for at least two months and no antigen challenge tests had been performed for several months.

The preliminary results showed that in the lamina propria there was no difference in the number of mast cells between the two patients groups and controls. The number of mast cells in the epithelium of asthmatics was increased compared to that of the epithelium in bronchitics and controls. The mast cells in the epithelium in asthmatics could be highly degranulated and associated with epithelial destruction. Epithelial destruction and highly degranulated epithelial mast cells were observed even in mild asthmatics with a short (<1 yr) duration of the disease.

Mast cells are widely distributed in different organs which are connected with defence mechanisms against noxious agents entering the body. In the airways mast cells are mainly situated in the connective tissue of the lamina propria, but they may also have other locations, *e.g.* in the bronchial epithelium and lumen. The special cytoplasmic granules of mast cell are associated with initiating inflammatory processes to special stimuli. There are several mediators in the granules which have experimentally been shown to generate chemotactic factors and call up inflammatory cells. Morphological studies give information of the state of the mast cell granules which may reflect their activity. In order to piece together the puzzle of the process of 'cells communicating', further studies should pay special attention to the location of mast cells in relation to other tissue structures, *e.g.* nerves, blood vessels, smooth muscle, epithelium and other inflammatory cells.

The ability of the activated mast cells to cause allergic inflammation has been studied extensively in the skin. In the nasal mucosa mast cells are related to allergic but not to infectious inflammation. Mast cell mediators with chemotactic activity for neutrophils have been described.

In our studies high amounts of neutrophils (>500 per mm^2 of mucosa) were observed in severe intrinsic asthmatics who had had the disease for several years (fig. 2). Mild to moderate asthmatics with a short duration of the disease had no or few neutrophils in the mucosa.

Fig. 2. – The bronchial biopsy specimen is taken from a clinically severe intrinsic type asthmatic having had the disease for several years. The electronmicrograph shows a damaged airways epithelium. Between the columnar and basal epithelial cells is seen homogeneous gray mass, probably presenting intercellular oedema (small thin black arrows) causing shedding of the epithelium. There are also many inflammatory cells, neutrophils and eosinophils (E with straight arrow) are also present in the capillaries and venules of the lamina propria. B=baselment membrane. Original magnification x16,000; bar=10 micrometers.

Summary

The emphasis in studying the mechanisms of bronchial hyperreactivity is on neurogenic mechanisms and inflammation of the airways. These mechanisms have important implications for the treatment of asthma. It now seems appropriate that the bronchial inflammation of asthmatic patients should be treated at an early stage of the disease more vigorously than it is at present.

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