The Pathology of Asthma*

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Asthma is a condition that has defied definition1 but is known to be associated with reversible airways obstruction and hyperreactivity to a variety of irritants. In discussing its pathologic features, it is useful to consider the nature of inflammatory reactions that occur in mucosal membranes (Table 1). Florey and associates2 showed that inflammatory reactions in these tissues had some features that were common to inflammation anywhere and other features specific for mucosal surfaces. The general features of inflammation include vascular dilatation and increased vascular permeability with the formation of an exudate that includes both protein and migrating inflammatory cells. The two features (Table 1) that Florey established as being specific for inflammation of mucosal surfaces are mucous hypersecretion3 and shedding of the epithelial lining cells into the airway lumen. These features have been repeatedly demonstrated in the inflammatory reactions in the airways of patients who die of asthma.4,7

PATHOLOGIC FEATURES OF ASTHMA

The present knowledge of the structural derangements in asthmatic lungs is based primarily on the study of post-mortem lungs. The greatest part of the information has come from the relatively few patients who suffer from asthma who die in status asthmaticus. A smaller number of studies have examined lungs from patients who have had asthma but died of another cause.4 It therefore seems unlikely that we have a truly accurate picture of the changes that occur in the airways of patients who have mild to moderately severe asthma.

That the airways from patients who die of asthma show all of the general features of the inflammatory reaction is documented. The histology shows congestion of blood vessels with a swollen and edematous submucosa. There is also considerable evidence of increased vascular permeability in that plasma proteins can be readily demonstrated in the mucous plugs in the airway lumen. The cellular component of the inflammatory reaction is also readily demonstrated and shows that the eosinophil is the dominant cell that migrates into the tissue.

The features of the inflammatory reaction that are specific for mucosal surfaces can also be readily demonstrated in asthmatic lungs. The fact that mucous hypersecretion must occur is indicated by the mucous plugs that fill the peripheral airways of the lungs.9 These plugs probably result from both excess production and poor clearance of material lining the airways. The normal surface lining of the airways consists of a mucous layer may be continuous. The aqueous layer appears to be controlled by active ion transport across the epithelium, where chloride moves toward the lumen and sodium towards the submucosa, with water moving into the surface layer along the resulting concentration gradient.10 This ion transport and fluid movement is enhanced by vagal stimulation and catecholamines,11,12 and the amount of liquid present in the fluid layer represents a balance between the amount secreted onto the airway surface and the amount lost to the inspired air as it is warmed and humidified. The mucous layer is 95% water and 5% glycoproteins13 and is produced by bronchial epithelial glands and the goblet cells. When an inflammatory reaction is induced in the airways, the fluid on the luminal surface is increased, because the vascular and epithelial permeability associated with the inflammatory reaction allows the exudate to form on the airways surface. In patients who die of asthma, the serum proteins and inflammatory cells that form the exudate can be readily demonstrated in the airway lumen.14 The mucous glands are increased in size and the goblet cells greatly increased in number, both of which suggest increased mucous production. The excess fluid proteins and cells that enter the lining layer further contribute to airway filling by interfering with normal clearance mechanisms. Mucus that is either too viscid or too watery is known to be transported at less than optimal velocity, and serum proteins15,16 and DNA17 from degenerating cells are known to influence the viscoelastic nature of the mucus. The excessive plugging of the airways seen in patients with chronic asthma is therefore likely to be related to a combination of factors. These include the accumulation of inflammatory exudate on the airway surface as well as the excess production of mucus by goblet cells and glands and decreased clearance of the airways surface.

The fact that the inflammatory reaction present in the airways of asthmatic patients is associated with epithelial cell loss can also be readily demonstrated.18 Cytologic examination of the sputum of asthmatic patients shows clumps of epithelial cells.19 This observation was first made by Curschmann20 over a century ago, and the cell clumps have more recently been called Creola bodies because they were described in the sputum of a man by that name.21 This loss of cells results in a proliferation of the basal cell layer and a recovering of the lining by metaplastic squamous and goblet cells. The increased epithelial cell turnover is a constant feature of inflammatory reaction in the airways and may be responsible for the thickening of basement membrane of the

Table 1—Inflammatory Reaction in Mucous Membranes

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<th>Features common to any inflammatory reaction</th>
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<tr>
<td>Vascular dilatation</td>
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<td>Increased vascular permeability</td>
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<td>Formation of an exudate</td>
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<table>
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<tr>
<th>Features specific for mucous membranes</th>
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<tbody>
<tr>
<td>Mucous hypersecretion</td>
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<tr>
<td>Shedding of epithelium</td>
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<tr>
<td>Smooth muscle contraction†</td>
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*Adapted from Florey.9
†Not mentioned by Florey.10

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airways of patients with asthma. This seems highly likely, because it is well known that basement membrane thickening is associated with increased cell turnover in other systems.25,26

Perhaps the most important feature of the airways of asthmatic patients is that the smooth muscle contracts in an excessive fashion to produce airways obstruction. While Dunnill4 has attributed the airways obstruction to edema, studies of allergic bronchoconstriction in guinea pigs20 have shown that the animals can die of airways obstruction following antigen challenge before any significant edema forms. This strongly suggests that the smooth muscle in asthmatic airways either functions abnormally or is increased in amount. Dunnill and associates20 reported that smooth muscle accounted for 11.9 ± 3.4% of the wall thickness in asthmatic patients as opposed to 4.6 ± 2.2 in nonasthmatic lungs. This increase in muscle has been shown to result because of hyperplasia,14 but hypertrophy of individual muscle fibers may also contribute. Unfortunately, it has been difficult to show that the increased airways reactivity is related to the excess of smooth muscle. While several attempts have been made to correlate smooth muscle function in vivo and in vitro to explain airways reactivity, none have been successful.25,26

In summary, the available data suggest that the inflammatory reaction is the underlying process responsible for the histologic appearance of the airways in asthma. This reaction can account for the mucous hypersecretion and epithelial cell loss as well as for the airway edema. It also seems highly likely that the mediators released as part of the inflammatory reaction play an important role in causing the bronchoconstriction and accounting for the increased airways reactivity. The challenge for the future is to try to understand the underlying mechanism for each of these features of the inflammatory reaction and develop strategies to combat them.

REFERENCES

5 Dunnill MS, Massarella GR, Anderson JA. A comparison of the quantitative anatomy of the bronchi in normal subjects and status asthmaticus in chronic bronchitis and in emphysema. Thorax 1969; 24:176
7 Naylor B. The shedding of the mucosa of the bronchial tree in man. Thorax 1962; 17:99
9 Bagier L, Boentgen studies of the pathological physiology of bronchial asthma. AJR 1936; 39:353
13 Nadel JA, Davis B, Phipps RJ. Control of mucous secretion in ion transport in airways. Annu Rev Physiol 1979; 41:369
16 Houston JC, de Navasquez S, Trounce JB. A clinical and pathologic study of fatal cases of status asthmaticus. Thorax 1953; 8:207
18 Sanerkin NG, Evans DMD. The sputum in bronchial asthma: pathophenomenic patterns. J Pathol Bact 1965; 89:536-41
19 Teel EE. Biochemistry and immunology of sputum in asthma. Postgrad Med 1971; 47:171
20 Curchamann H. Ueber Broncholithis Exsudativa und ihr Verhaltnism zum Asthma Nervosum. Dtsch Arch Klin Med 1883; 32:1
22 Vanco R, Benditt EP. Manifestations of diabetes mellitus—they possible relationships to an underlying cell defect. Am J Pathol 1974; 75:204

Comparison of the Histopathology of Immediate and Late Asthmatic and Cutaneous Responses in a Rabbit Model


In allergic human subjects, immediate responses to antigenic challenge occur 15-30 minutes after the exposure, while late responses occur hours after the encounter.14 The pattern of responses for an allergic individual can be identified by challenge of the target organ: the skin by intradermal injection and the airways by bronchial provocation testing with serially timed observations after the encounter.2

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