The Pathophysiology of Asthma

James C. Hogg, M.D.*

For the purpose of this discussion, the pathophysiologic features of asthma will be divided into muscle spasm, airways inflammation with edema, and mucus hypersecretion. While all three are relatively constant features of asthma, their proportionate contribution to the abnormal physiology may vary considerably with the state of the disease. For example, smooth muscle spasm is probably the feature that accounts for rapid reversibility of the airways obstruction, while inflammatory edema and mucus plugging of the airways are more likely to account for the more slowly reversible or irreversible forms of the disorder.

**Smooth Muscle Spasm**

In models of asthma, such as allergic bronchoconstriction in the guinea pig, the smooth muscle contraction is not associated with airway edema or mucus plugging of the airways so that this highly typical reaction can be assumed to be due solely to smooth muscle constriction. This contrasts sharply with human asthma deaths from asthma which are always associated with edema of the airway walls and mucus plugging of the airway lumen. This does not mean that smooth muscle spasm does not occur in chronic asthma, but only that its contribution to the overall airway obstruction may wane as the disease becomes more severe.

The airway smooth muscle is greatly influenced by the nervous system (Fig 1). The control comes both from the cholinergic system which constricts bronchial smooth muscle and the beta adrenergic system of nerves which relaxes bronchial smooth muscle. While the alpha adrenergic system contracts bronchial smooth muscle, these nerves are relatively sparse in the airways. The reaction is therefore due to circulating mediators acting on alpha adrenergic receptors in the smooth muscle. A third system of nerves, the so-called non-adrenergic inhibitory system, has been described more recently and this system, as its name suggests, is thought to relax the airway smooth muscle by an as yet unidentified mediator.

Several theories of asthma have developed which relate to one or another aspect of the neural control of...
the airway smooth muscle. One theory\(^5\) has stressed the possibility of a partial beta blockade, another abnormal cholinergic mechanism,\(^6\) and a third theory has suggested a basic abnormality of the non-adrenergic inhibitory system.\(^7\) Finally, it has also been suggested that airways of asthmatic subjects may be associated with smooth muscle that functions as a single unit so that the whole network contracts when part of it is stimulated.\(^8\)

The smooth muscle contains readily identified mast cells and it seems likely that these cells are responsible for the fact that the muscle can be sensitized in vitro so that it will react to antigen challenge. The importance of mediator release from these mast cells in the normal control of smooth muscle is unclear at the present time, but it seems likely that they are important in allergically-mediated bronchoconstriction.

**Inflammation of Airways**

While the bronchoconstriction observed following acute antigen challenge in the guinea pig is not associated with airway edema, inflammatory edema probably plays an important role in human disease. Analysis of the protein in the bronchial mucus plugs from asthmatic patients\(^7\) shows large amounts of albumin and large numbers of inflammatory cells which strongly suggest that an inflammatory exudate enters the airways lumen.

The study of nonimmunologically-induced inflammatory reaction in the airways of animals has provided several insights into the development of acquired airways hyperreactivity. A single exposure to cigarette smoke in the guinea pig\(^8\) can produce an airways inflammatory reaction that has both an exudative and proliferative phase (Fig 2). The exudative phase is associated with an increased wet-to-dry weight ratio of the airway wall (Fig 2A) due to the inflammatory edema and an immigration of inflammatory cells into the interstitial space and through the epithelium to lie on the mucosal surface (Fig 2B). This inflammatory reaction is associated with an increased mucosal permeability which is maximum at a half-hour following the smoke exposure and returns to normal by 24 hours. This change in permeability can be readily measured by the tracer horseradish peroxidase (HRP) and this method has shown that the increase in permeability is associated with increased exposure of the irritant receptors (Fig 3).

Empey\(^9\) and colleagues have shown that the lower airways can become hyperreactive to nonspecific stimuli such as histamine during an acute upper respiratory tract infection. They\(^9\) have shown that the hyperreactivity to histamine seen with respiratory virus infections can be blocked by atropine and speculated that the inflammatory reaction caused by virus sensitized the afferent receptors and exaggerated the reflex component of the histamine response. Nitrogen dioxide,\(^10\) ozone\(^11\) and cigarette smoke\(^12\) have been shown to enhance bronchial reactivity to both histamine and methacholine, presumably because of increased reflex activity. Empey and colleagues\(^9\) attributed the acquired hyperreactivity to mucosal damage and speculated that this unspecified damage might be due to inflammation of the mucosa. It seems likely that the
inflammatory reaction is the common feature of the damage produced by viral infection, NO, and ozone inhalation. Our studies suggest that an important feature of this nonspecific inflammatory reaction is increased mucosal permeability which exposes both the irritant receptors and muscle to stimuli.

As the change in mucosal permeability provides increased access to both irritant receptors and airway smooth muscle (Fig 1) the hyperreactive response associated with increased permeability could involve more than one mechanism. For example, histamine is capable of stimulating both the irritant receptors to produce reflex bronchoconstriction and of stimulating the airway smooth muscle directly. Methacholine, on the other hand, only stimulates the smooth muscle and is not usually associated with irritant receptor stimulation. This fact has been elegantly demonstrated by Vidruk et al who recorded from single nerve fibers and can be clearly seen from the data of Michoud and her colleagues on intact animals. They compared antigen, methacholine and histamine challenge to Ascaris-sensitive monkeys and showed that while the antigen and histamine caused an increase in airways resistance and rapid, shallow breathing, methacholine only caused increased airway resistance without stimulating the irritant receptors to produce rapid, shallow breathing. This fact is further brought out by the study of Holtzman et al who showed that the ganglionic blocker hexemethonium could block histamine but not the methacholine response.

As the mast cell is important in initiating the inflammatory reaction in allergic asthma, the relationship of the mast cell to the airway lumen is of critical importance in the initiation of these attacks. Studies on mast cell distribution are not easy because their fixation requires alcohol rather than water-based fixatives and these are seldom in routine use. Salvato and colleagues have demonstrated that mast cells are depleted in asthma and those that remain are markedly degranulated. Guerzon and associates have shown that there are relatively few mast cells in the mucosa compared to the large concentration of mast cells in the submucosa of the airways (Fig 1). While there are a very important number of mast cells on the surface of the airway lumen, this number can be over-estimated by washing and brushing techniques which also harvest mast cells from the mucosa. For example, Guerzon et al estimated approximately one mast cell for every 10 epithelial cells, while Patterson found 1/200 epithelial cells in lung washings. We have previously proposed the hypothesis that large antigen molecules that penetrate the mucosa slowly must first react with the small number of mast cells on the epithelial surface and that chemical mediators released from these mast cells are responsible for stimulating irritant receptors and opening the epithelial tight junctions. This increase in permeability allows the antigen to penetrate to the larger number of mast cells that are located deeper in the airway wall (Fig 1).

As the inflammatory reaction is responsible for the epithelial damage leading to hyperreactive airways, it is important to evaluate the epithelial changes that
occur with airways inflammation. An important histologic feature of the asthmatic lung is the change in the epithelial basement membrane. Callerame et al showed that the mean width of the basement membrane from asthmatic subjects was 17.5 μ while that from normal subjects was only 7 μ and attributed the thickening of the basement membrane to the deposition of immunoglobulins. Data from Hulbert et al on airway inflammation shows that the basement membrane (Fig 2D) begins to increase in thickness in association with the increased epithelial mitotic activity (Fig 2C). This suggests that the increased thickness of the basement membrane may be due to increased epithelial cell turnover in the same way that the basement membrane of the diabetic microvasculature thickens in relation to the increased endothelial cell turnover. Curschman was the first to note that asthmatic patients had a large number of epithelial cells in their sputum and this has been amply confirmed by other investigators who have demonstrated squamous cells, as well as compact clusters of columnar cells known as Creola bodies in the sputum. The loss of the mucous cells has been attributed to muscle spasm and submucosal edema, but it also seems likely that direct toxic injury to epithelial cells, perhaps by products of the eosinophil, could play a role in damaging the epithelial cells. The increased cell turnover of the epithelium brought about by increased cell death is also associated with active division of the basal cell layer with metaplasia to goblet and squamous cells.

**MUCUS PLUGGING OF THE AIRWAYS**

At autopsy, the lungs from patients that die because of asthma are hyperinflated and tend not to collapse after the thorax is opened because the segmental and subsegmental airways and the bronchioles are filled with inflammatory mucus plugs. These plugs contain mucous, serous and cellular elements. The eosinophilic leukocyte is the cell that tends to predominate in these plugs, but other inflammatory cells and a large number of epithelial cells can also be found. The submucosa shows evidence of an inflammatory reaction which consists of a congested microvasculature and an edematous interstitial space containing the same inflammatory cellular infiltrate as the airways lumen. The reason for the excess mucous in the airways is probably related to both increased production and decreased clearance, but the relative importance of these two mechanisms is unclear. The machinery for increased production is present in that there is both hypertrophy of the bronchial mucous glands, as well as goblet cell metaplasia and hyperplasia of the mucosal lining. The fact that these mucus plugs have a high protein content with much of this protein being albumin suggests that an inflammatory exudate may be important in their formation.

The importance of these mucus plugs in the pathogenesis of the disease is relatively unclear. While patients that die of asthma all have extensive mucus plugging of their airways, the precise role in less severe forms of asthma is not known. Bronchographic studies of patients with chronic asthma showed that the airways of living asthmatic patients were often occluded by mucus, but this form of investigation is both unsuitable and unwise in these patients. While it has long been known that the sputum of asthmatic patients contains plugs, the study of sputum does not provide direct evidence on the severity of the airway obstruction caused by the plugs.

In summary, asthma is a disease characterized by muscle spasm, airway inflammation and mucus plugging of the airways, but the relative importance of these abnormalities varies with the state of the disease. For example, when an asthmatic attack is easily and completely reversible by drugs that relax smooth muscle, it seems likely that smooth muscle spasm is the major cause of the airways obstruction. Similarly, when patients die of asthma and their airways are solidly plugged, it seems reasonable to conclude that the plugs are the cause of death. The transition between these two extremes represents the battleground between inconvenience and life-threatening disease and we believe that inflammation of the respiratory mucous membrane is the process that determines how this battle proceeds.

**REFERENCES**

5. Szentivanyi A. The beta adrenergic theory of the astopic abnormality in bronchial asthma. J Allergy 1966; 42:203
7. Sanerkin NG, Evans DMD. The sputum in bronchial asthma: pathopneumonic patterns. J Path & Bact 1965; 59:535
16 Salvato G. Asthma and mast cells of bronchial connective tissue. Experientia 1962; 18:330
18 Guerzon GM, Pare PD, Michoud MC, Hogg JC. The number and distribution of mast cells in monkey lungs. Am Rev Respir Dis 1979; 119:59
23 Vracko RV, Bendett ET. Manifestations of diabetes mellitus: their possible relationship to an underlying cell defect. Am J Path 1974; 75:204
27 Dunnill MS, Messarella CR, Anderson JA. Thorax 1969; 24:176
29 Rigler L. Bronchial asthma. AJR 1938; 39:353