Asthma Pathogenesis and the Peripatetic Polymorphonuclear Granulocyte

The Phlogistic Plot Thickens

The complexity of clinical asthma is matched by the heterogeneous nature of its inflammatory cellular response, which is associated with increased bronchial hyperresponsiveness. Soon after the techniques of bronchoalveolar lavage (BAL) and bronchial biopsy were deemed to be clinically safe, investigation of the asthmatic inflammatory cascade was intensified, particularly after laboratory challenge protocols with both allergens and pollutants. The majority of these earlier studies focused on the activation of mast cells and release of mediators, some of which were chemotaxants for eosinophils to sites of bronchial allergic inflammation. Tissue damage in the bronchial conducting airway was thought to be mediated by eosinophil-derived toxic products. More recently, the role of the T-lymphocyte in orchestration of inflammatory events via cytokine networks has also been explored and espoused as a major component of allergic inflammation. Because neutrophils have not been regularly demonstrated after allergen-induced bronchial challenge protocols, the overall significance of this cell in the chronic inflammatory response of asthma generally has been deemphasized. However, in this issue of CHEST (see page 1236), Frangova et al reported significant increase in neutrophils and a neutrophil granule product, myeloperoxidase, in BAL from nonsmoking allergic and nonallergic asthmatics. The patients in this study were sampled under baseline conditions at a time when they were free of respiratory infections for at least 1 month preceding the BAL procedure; the allergic patients were investigated out of their respective pollen seasons. The number of BAL eosinophils and lymphocytes, but not epithelial cells, also correlated significantly with the number of BAL neutrophils. The degree of methacholine hyperresponsiveness in these patients did not correlate with any of the cellular components, including eosinophils. Equivalent results were obtained in allergic and nonallergic patients.

Although a single cross-sectional study such as this requires confirmation, the results are of sufficient interest to revisit the role of the neutrophil in the asthmatic inflammatory process. First, it has been demonstrated that the neutrophil is the dominant cell after both in vitro and in vivo exposure to ozone in both animals and humans. Under these experimental conditions, a number of cytokines [interleukin-6 (IL-6), the α-family of chemokines (IL-8, Gro-α, Gro-γ) and GM-CSF] derived from bronchial epithelium act as potent chemoattractants for polymorphonuclear cells, which may exert toxic effects by release of elastase, toxic oxygen metabolites, and/or serine neutral proteases (cathepsin G, trypsin, and chymotrypsin). Recent in vitro investigations demonstrated that the latter group of proteolytic enzymes are involved in the detachment of epithelial cells from the basement membranes. In addition, neutrophil products are known to increase the induction of both histamine and
electrical field hyperresponsiveness in isolated human bronchial tissues. After ozone inhalation in dogs, neutrophils are activated to produce thromboxane A₂, which appears to be essential for hyperresponsiveness in this species. Polymorphonuclear leukocytes may play a role in neurogenic inflammation, in which it has been shown that increased neutrophil adhesion in the postcapillary venule is associated with loss of neutral endopeptidase activity. Finally, increased numbers of neutrophils and extracellular deposition of elastase were associated with loss of epithelium in several fatal cases of asthma. The special kinetic conditions imposed by controlled allergen challenges in the laboratory may underestimate the contribution of polymorphonuclear leukocytes to allergic inflammation. In both animal and human challenge experiments, it has been reported that neutrophils appear within the first few hours after challenge and are less prominent 24 h later. There are as yet no systematic human studies of possible adverse events mediated by polymorphonuclear leukocytes during the early phases of inflammation. Under in vitro conditions, detachment of epithelium from the basement membrane by neutrophil-derived products may occur within 4 h. Recruitment of neutrophils in delayed asthmatic reactions might also be expected in response to mast cell release of leukotriene-B₄. Once polymorphonuclear leukocytes are attracted to the inflammatory site, they could perpetuate the inflammatory cycle by release of elastase and leukotriene-B₄, both of which could signal synthesis and exocytosis of the chemokine chemoattractant, IL-8, from epithelial cells and other neutrophils.

Very little scientific data are available about the precise role of specific inflammatory cells in the remodeling process that occurs in the bronchial basement membrane and lamina propria. Could neutrophils contribute to the irreversible obstructive component commonly observed in chronic asthma? In addition to collagen deposition by myofibroblasts in the lamina reticularis, the normal constitutive elastin component in this anatomic matrix could be destroyed by neutrophil elastase. These combined effects would decrease bronchial wall elasticity and eventually lead to irreversible bronchial obstruction.

As interest and investigation of asthmatic inflammation expands, it is now abundantly clear that multiple effector cells and their proinflammatory products are involved and that this inflammatory milieu can perpetuate itself through intercalated and often redundant mediator/cytokine pathways. Coupled with the fact that other non-IgE-mediated events (eg, immune complexes, complement components, anaphylatoxins) usually elicit a brisk neutrophilic response, the presence of polymorphonuclear leukocytes in both allergic and nonallergic asthmas, as reported by Frangova et al, should stimulate further investigation of this cell in both early and late inflammatory events of asthma.

I. Leonard Bernstein, MD
Cincinnati, Ohio

Clinical Professor of Medicine and Environmental Health Sciences, Department of Medicine, Division of Immunology, University of Cincinnati Medical Center.

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Society and Toxicology: A Double Standard?

Or of Mice and Toads... (With Apologies to Mr. Steinbeck)

As practicing physicians, we are accustomed to facilely manipulating the concepts and principles of risk assessment on a daily basis. Steeped in the tradition of the scientific method, we are most comfortable with testing and differential diagnosis establishing a course of action with at least a 95% level of confidence. It is easy for us to overlook that outside our scientific

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