Treating Asthma as an Inflammatory Disease*

G. Walter Canonica, MD

Asthma is a chronic inflammatory disease involving many different cell types and cellular elements. Evidence suggests that, in the long term, this inflammation leads to remodeling of the airways, airflow obstruction, and the bronchial hyperreactivity symptoms of asthma, and is present even in patients with intermittent disease. Patients with allergic asthma and those with seasonal allergic rhinitis are believed to have minimal persistent inflammation, and the two diseases often occur together. Early intervention with inhaled corticosteroids (ICS) is believed to modify the disease process and may limit long-term remodeling. ICS remain the cornerstone and "gold standard" of treatment for asthma. ***(CHEST 2006; 130:21S–28S)***

Key words: allergic rhinitis; asthma; corticosteroids; inflammation; remodeling

Abbreviations: ICAM = intercellular adhesion molecule; ICS = inhaled corticosteroids; IgE = Ig E; IL = interleukin; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist

Asthma is a chronic inflammatory disorder of the airway involving many different types of cells and cellular elements. The chronic inflammation leads to an increase in airway hyperresponsiveness with recurrent episodes of wheezing, coughing, and shortness of breath.[1] Inflammation is evident, even in patients with intermittent asthma.[2] Airflow limitation is widespread, variable, occurs throughout the tracheobronchial tree, and is usually reversible spontaneously or with treatment. However, if poorly controlled, it can be irreversible. Airway remodeling is a long-term consequence of inflammation, but early treatment limits the damage from inflammation, and inhaled corticosteroids (ICS) suppress inflammation.

*From Allergy and Respiratory Diseases, DIMI Department of Internal Medicine, University of Genoa, Genoa, Italy.

This work was partially supported by Associazione Ricerca Malattie Immunologiche e Allergiche.

Dr. Canonica reports having received honoraria for educational presentations, and/or funding for research, and/or travel expenses, and/or for service on advisory boards from A. Menarini, Alk Abello, Almirall, Altana, Astra Zeneca, Boeringher Ingelheim, Chiesi Farmaceutici, Gentili, GlaxoSmithKline, Lofarma, MSD, Novartis, Pfizer, Schering Plough, Stallergenes, UCB Pharma, and Uriach.

Manuscript received on July 2, 2005; revision accepted on March 20, 2006.

Correspondence to: G. Walter Canonica, MD, Allergy and Respiratory Diseases, DIMI, Department of Internal Medicine, University of Genoa, Genoa, Italy; e-mail: canonica@unige.it

DOI: 10.1378/chest.130.1__suppl.21S

Inflammatory Process

Asthma is a chronic airway disorder characterized by hyperreactivity to various stimuli, airway inflammation, bronchospasm, and airway obstruction. Triggers of asthma include antigens, viruses, pollutants, and occupational agents. These triggers stimulate an inflammatory cascade involving many cells and mediators. This cascade is complex and interactive and varies between patients, within individual patients and with age, but leads to inflammation, bronchial hyperreactivity, airflow obstruction, and symptoms of asthma. The small airways, with internal diameters

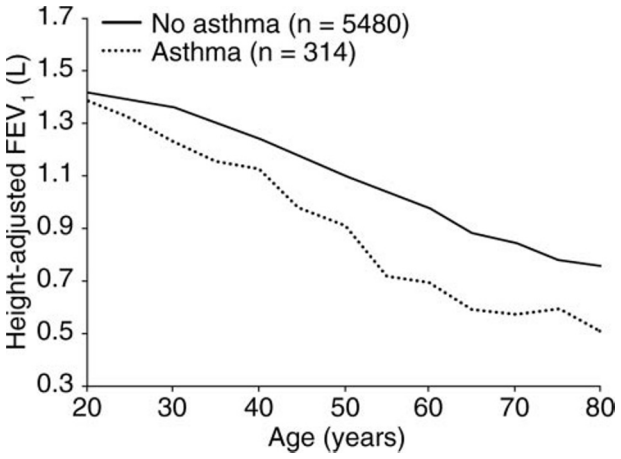

FIGURE 1. Changes in FEV_1 with the presence or absence of asthma in male nonsmokers in the Copenhagen City Heart Study. Reproduced with permission.[5]

of < 2 μm, are major sites of inflammation and airway obstruction.[3,4] These sites are characterized by frequent hypertrophy of airway smooth muscle, new vessel formation, increased numbers of epithelial goblet cells, and deposition of interstitial collagen beneath the epithelium; these morphologic changes may not be completely irreversible. These changes, which occur with chronic inflammation, are involved in remodeling of the airways, which is discussed more fully later in this article. Mucus plugging causes further constriction of the airway lumen. The effects of long-term asthma on lung function were shown in the Copenhagen City Heart Study,[5] in which a sample of male nonsmokers in the general population who identified themselves as having asthma had substantially greater declines in FEV_1 over time than those who did not have asthma (Fig 1).

Figure 2 shows the inflammatory cascade involved in airway inflammation.[6] The inflammatory process of asthma appears to involve mast cells, eosinophils, epithelial cells, macrophages, and activated T-cells, which can influence airway function through secretion of preformed and newly synthesized mediators that act directly on the airway or indirectly through neural mechanisms.

Allergic Asthma

The mast cell is a key player in the early allergic response that typically starts within minutes of exposure to an appropriate antigen. Acute symptoms peak within 10 to 15 min and typically resolve within 60 min of exposure to an adequate dose of antigen. Studies by Brightling et al[7] and Carroll et al[8] indicate that there is microlocalization of mast cells in the airway smooth muscle, suggesting that interactions between mast cells and smooth-muscle cells are critical for the development of the disordered airway function found in asthma. The mast cell surface-bound Ig E (IgE) is cross-linked by the antigen, leading to mast cell activation and release of potent mediators, such as histamine, leukotrienes, prostaglandin D_2, bradykinin, and platelet-activating factor. This results in airway smooth-muscle contraction, edema, and enhanced mucous secretions leading to airflow limitation and acute asthma symptoms, such as nasal discharge, sneezing, bronchoconstriction, and skin weal and flare. Typically, an early phase response may induce a 25% reduction in

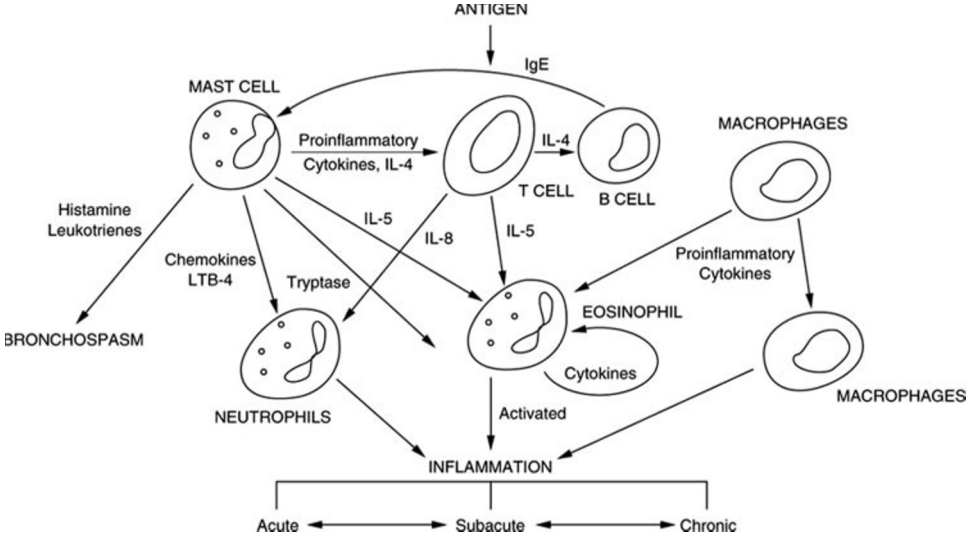

FIGURE 2. The inflammatory cascade in asthma. Reproduced with permission from the National Asthma Education and Prevention Program.[6] LTB-4 = leukotrience B_4.