Chronic rhinosinusitis (CRS) is presently classified into two subgroups: CRS without and CRS with nasal polyps. A variety of inflammatory mediators, including cytokines and chemokines, as well as adhesion molecules and matrix metalloproteinases, are upregulated in both subgroups of CRS; remodeling is also observed in both. However, there are also characteristic differences. Whereas CRS without nasal polyps has more neutrophil infiltration, in CRS with nasal polyps (especially when associated with allergy/asthma) eosinophil infiltration is strikingly increased. Although several features of remodeling (eg, squamous metaplasia, basement membrane thickening, collagen deposition, hyperplasia of mucous glands, and goblet cells) are features seen in both subgroups of CRS, epithelial shedding as observed in asthma is not seen in either subgroup. Furthermore, pseudocyst formation seen in CRS with nasal polyps is not seen in CRS without nasal polyps.

Etiology
The development of rhinosinusitis depends on a variety of factors including, but not limited to, host factors (eg, cystic fibrosis, immotile cilia syndrome, allergic or immune conditions, anatomic abnormalities, systemic disease, endocrine disorders, metabolic conditions, neurologic mechanisms, tumors) and environmental factors (eg, infectious or viral agents, trauma, noxious chemicals, iatrogenic conditions). Histopathologically, acute rhinosinusitis is predominantly viewed as an exudative process associated with necrosis, hemorrhage, and/or ulceration, in which neutrophils predominate; however, chronic rhinosinusitis is predominantly a proliferative process associated with fibrosis of the lamina propria, in which lymphocytes, plasma cells, and eosinophils predominate along with, perhaps, changes in bone. However, a variety of findings have been reported, including varying degrees of eosinophils in tissues and secretions as well as polyp formation and the presence of granulomas, bacteria, or fungi.

Although the precise etiology of the inflammation associated with CRS is not fully understood, the presence of bacteria within the nose and paranasal sinuses is well documented [3,4]. Yet there is much diversity in the type of pathogens identified primarily due to the
time, manner, and mode of sample collection, treatment methods (including use of antibiotics or surgery prior to sample collection), and differences in bacterial culture techniques. In patients with CRS without any underlying infection, the probability of bacterial colonization must be considered because bacterial colonization might exacerbate a noninfectious inflammatory process in CRS through bacterial allergic mechanisms. Calenoff et al. [5] identified bacteria-specific immunoglobulin (Ig) E in 57% of patients with CRS, compared with only 10% in subjects with allergic rhinitis.

Besides CRS, it is suggested that bacterial allergy might play a role in chronic inflammatory diseases involving the respiratory or GI tracts, including asthma, nasal polyposis, and chronic gastritis [6,7]. It is well recognized that bacteria (e.g., *Staphylococcus aureus*), possess the ability to elicit exotoxins, and that these can be pathogenic in humans (e.g., toxic shock syndrome toxin 1 [TSST-1]) [8]. The term “superantigen” is used to describe these bacteria produced particles due to their ability to activate subpopulations of the T-lymphocytes (5% to 30%) in contrast to typical antigens (< 0.01%) [9]. T-cell superantigens bind to human leukocyte antigen (HLA) class II histocompatibility complexes on antigen-presenting cells (APC) as well as T-cell receptors (TCR) on T-lymphocytes at sites separate from antigen-binding sites. The result is that conventional antigen-specificity is bypassed and a profound superantigen-induced activation of T-lymphocytes leads to mitogenesis and cytokine production. Superantigens can also act as classic antigens, because antibodies to superantigens are often present. Superantigen-producing bacterial strains have been implicated in the pathogenesis of atopic dermatitis, Kawasaki disease, psoriasis, and rheumatoid arthritis [10].

The mechanisms by which superantigens might induce an inflammatory response are currently under intense investigation. Schubert [11] hypothesized a potential unifying role for bacterial superantigen in the pathogenesis of CRS, and proposed that microbial persistence, superantigen production, and host T-lymphocyte response are fundamental components unifying all common chronic eosinophilic-lymphocytic respiratory mucosal disorders. In this model, coexisting immune responses, including type I hypersensitivity and cellular antigen-specific immune responses combined with superantigen-induced T-lymphocyte activation, may contribute to the apparent heterogeneity of the disease. Schubert’s hypothesis is intriguing, especially because it might explain why limited bacterial colonization would have a profound effect on the local inflammatory response. Bachert et al. [12] reported staphylococcal superantigen-specific IgE antibodies to the superantigens staphylococcal enterotoxin A (SEA) and staphylococcal enterotoxin B (SEB) in nasal polyp tissue. Further studies are clearly needed to examine this type of noninfectious immune response to bacterial superantigens in patients with CRS.

**Inflammatory Mechanisms in CRS**

CRS is characterized by goblet cell hyperplasia, limited subepithelial edema, cell infiltration, and the presence of fibrosis. The presence of bacteria within the nose or paranasal sinuses can give rise to a chronic infectious inflammatory process, cause persistence of disease, or might exacerbate a noninfectious inflammatory process through bacterial colonization. In humans, the histologic appearance of inflamed mucosa and inflammatory cells in sinus exudates depend somewhat on the allergic status of the patient. In the sinus fluid of patients with CRS, the main inflammatory cells are neutrophils, as normally observed in acute rhinosinusitis, but a low percentage of eosinophils, mast cells, and basophils may also be observed [13–15]. High concentrations of histamine, leukotrienes (LT) C_{4}, D_{4}, and E_{4}, and prostaglandin D_{2} were found, suggesting mast cell or basophil activation in chronically inflamed sinuses [15–17].

The presence of interleukin (IL)-1β, intercellular adhesion molecule (ICAM)-1, and E-selectin has been reported in tissues from patients with CRS [13]. IL-8 was found to be increased in the nasal discharge of patients with CRS to significantly higher levels as compared with that in patients with allergic rhinitis [18]. The presence of IL-8 not only in epithelial cells and gland duct cells but also in polymorphonuclear cells of patients with CRS suggests that once chemoattracted into the inflamed mucosa, these polymorphonuclear cells can further amplify the inflammation by inducing the recruitment of neutrophils into the sinus mucosa. Apart from IL-8, neutrophils also produce IL-1, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α in vitro [19,20], further contributing to the chemotaxis and activation of other inflammatory cells.

However, in patients with allergy and/or asthma and chronic hyperplastic sinusitis, the paranasal tissue was found to be extensively infiltrated by eosinophils, and the extracellular deposition of major basic protein (MBP) was associated with damage to the sinus respiratory epithelium [21]. In general, although nonallergic patients show some evidence for neutrophilic inflammatory process, allergic patients tend to show fewer neutrophils and somewhat more eosinophils in the inflammatory process [16,22]. The relative abundance of eosinophils and fewer numbers of neutrophils in those patients with CRS and coexisting asthma suggest that this type of inflammatory response may be independent of infection and may represent an allergic inflammation [23–26]. However, it is also likely that infection impacts upon this disease process. In CRS with nasal polyps, eosinophilic inflammation is markedly increased as compared to CRS without nasal polyps. On clinical grounds, there appears to be a continuous spectrum of illness ranging from chronic infectious rhinosinusitis to relatively pure noninfectious inflammation.

In addition to upregulated cytokines and chemokines in CRS, there is an upregulation of adhesion molecules like ICAM-1 and E-selectin on endothelial cells, which