responses with evidence of proximal esophageal flow of the acid, they have concluded that their data strongly support the "reflex" theory rather than the "reflux" microaspiration theory.

Further evidence for a lesser importance of microaspiration in production of pulmonary symptoms secondary to GE reflux was shown in a study by Gastal et al.\(^2\) from patients evaluated in our laboratory. In this study, we compared the presence of both abnormal proximal and distal esophageal acid in 27 asthmatics, 28 patients with chronic cough, 37 patients with noncardiac chest pain, and 27 healthy control subjects. Although abnormal distal esophageal GE reflux was prevalent in both the asthmatic (44\%) and cough patients (50\%), abnormal proximal acid exposure was actually significantly more prevalent in patients with unexplained chest pain secondary to reflux who did not have pulmonary symptoms. These results supported the major importance of the reflex mechanism for GE reflux and pulmonary symptoms and suggested a lesser role for reflux microaspiration.

However, as with many interesting theories in medicine, it would appear that the bottom line has yet to be written. Subsequent studies from our laboratory have revealed that the finding of abnormal proximal esophageal acid exposure in the patient with asthma or cough can have prognostic importance.\(^6\) When evaluating the effect of antireflux therapy on pulmonary symptoms, we have recently found that those patients showing abnormal proximal acid exposure on ambulatory pH monitoring had the highest positive response rate. These data suggest that reflux microaspiration may still play a role in some patients and that ambulatory pH monitoring seeking evidence of proximal acid exposure is a valuable clue as to which patients should have aggressive antireflux therapy.

Does GE reflux play a role in the production of bronchospasm and associated wheezing or coughing?\(^3\) There is no question that this is true in many patients. Is the major mechanism by which this occurs merely distal esophageal acid exposure causing a reflex bronchoconstriction or need one always invoke high reflux and microaspiration as the cause?\(^5\) From our perspective, it would appear that this question has not been completely answered.

**Donald O. Castell, MD**

**Peter F. Schnatz, DO**

Philadelphia

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**Gastroesophageal Reflux-Induced Bronchial Constriction**

The role of gastroesophageal reflux (GER) in cardiopulmonary disease has been suspected for decades. In this issue of CHEST (see page 1220), Harding and colleagues add yet another piece to the puzzle in showing that microaspiration is not a necessary component for the development of intraesophageal acid-induced airway obstruction. Importantly, sensitive measures of airway resistance are required to demonstrate modest differences in response to acid infusion between patients with GER alone vs those having asthma in addition to GER. This raises the question whether the findings demonstrated in the study are clinically significant. Furthermore, the infusion of acid and normal saline solution into the esophagus in the supine position may not necessarily be relevant to the same procedure done in an upright position. Enhanced esophageal acid clearance and changes in different parameters of pulmonary function occur in ambulatory patients.

Findings in the study conflict with other reports that have shown no effect of intraesophageal acid infusion on pulmonary function, or changes only in individuals with gross esophagitis or acid-sensitive esophagi (positive Bernstein test).\(^1\) Reasons for these discrepancies include the number of patients studied, suboptimal testing techniques, and patient selection criteria.\(^2\) The carefully conducted study of Harding and coworkers using sensitive measurement techniques reveals clear cut differences in asthmatics with GER vs nonasthmatics with GER. Their findings are valid in our opinion.

Given that acid infused into the esophageal lumen induces changes in airway resistance, it is likely that a number of variables influence airway reactivity in GER. These include the temperature and humidity of ambient air, presence of allergens in the air, time of
day, preceding activity (exercise, eating, stress), and adrenal cortical and medullary activity.

Harding and colleagues noted a prolonged decline in specific airway resistance and peak expiratory flow, but no significant change in FEF25-75 in asthmatics with GER. These observations suggest a greater effect on central than peripheral airways. As vagally induced bronchoconstriction shows this same pattern, it would seem plausible that GER-induced increase in airway resistance is vagally mediated. This is supported by our observation that the reflex could be blocked by intramuscular atropine administered prior to intraesophageal acid infusion.3 Interestingly, Harding and co-workers observed that there was a progressive increase in airway resistance despite clearance of the acid. The duration of this progression extended to the end of their testing period. Whether this represents a continuing effect of vagal stimulation or activation of other mediators of bronchoconstriction is unclear. It would have been interesting to see if this progressive deterioration in airway resistance could have been reversed at different points in time by the administration of atropine. Further studies looking at airway function for at least 180 min poststimulation are warranted because of the heterogeneity of response to a provocative stimulus in asthmatics.

Richard A. Wright, MD
Harvy L. Snider, MD, FCCP
Louisville, Kentucky

Dr. Wright is Professor and Chief, Division of Gastroenterology/Hepatology; and Dr. Snider is Associate Professor, Division of Respiratory and Environmental Medicine, Department of Medicine, University of Louisville.

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When Should Inhaled Corticosteroids Be Started for Asthma?

The treatment of asthma has evolved over the past decade, in part, as a result of the greater appreciation of airway inflammation in the pathophysiology of asthma. Early pathologic studies1 and more recently, studies using fiberoptic bronchoscopy with bronchoalveolar lavage have increased our knowledge of the intense cellular inflammation that is present in the airway mucosa and submucosa in patients with severe asthma. Eosinophils, T lymphocytes, neutrophils, and monocytes are all present in increased numbers.2,3 Importantly, these inflammatory changes are seen in the submucosa of even mild asthmatics.4,5 In addition, molecular probes have allowed us to appreciate the complex network of bioactive cytokines: especially the TH2 subset (interleukin-3, 4, 5, and the granulocyte-macrophage colony stimulating factor) present within the inflammatory process.6

Currently, there are no medications that can specifically and selectively block the cytokine secretory process or the incompletely defined mechanisms for the initial recruitment of the earliest CD4+ T cells responsible for these cytokines.7 Along these lines, corticosteroids are potent inhibitors of cytokine secretion and lymphocyte migration,9 which may account for some of their anti-inflammatory activity in the treatment of asthma. The potential side effects of inhaled corticosteroids are at the crux of one of the major dilemmas in our treatment of asthma. It has been hoped that with the development of inhaled corticosteroids (ICS) that systemic side effects could be avoided while still reaping the benefits of the anti-inflammatory action. If the risks of ICS to the patient are small or absent, we could justify their use in large populations of individuals, even if there are no great potential benefits in every asthmatic. For example, very mild asthmatics might only require transient therapy when symptomatic.

Two previous studies10,11 have suggested that the early use of ICS even in patients with mild asthma may improve overall control and outcome in the disease. In addition, the National Asthma Education Program has suggested that ICS be considered in any patient requiring the daily use of an inhaled β2-agonist.12 In this issue of CHEST, Selroos et al (see page 1228) further investigate the question of early vs late use of ICS in 105 consecutive patients with mild asthma who are divided into six groups that depended on the duration of symptoms (<6 months; 6-12 months; 1 to 2 years; 2 to 5 years; 5 to 10 years; >10 years). All subjects were given budesonide (800µg to 2400µg) via a multidose dry powder inhaler. Efficacy was evaluated