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 FEF_{25-75} 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
Harvey 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.

REFERENCES
3 Wright RA, Miller SA, Corello BF. Acid-induced esophagobronchial-cardiac reflexes in humans. Gastroenterology 1990; 99:71-3

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 secretion8 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
at 3 months, 1 year, and 2 years by measurement of FEV₁ and peak expiratory flow. Although the study was neither blinded nor placebo controlled, there was a trend toward a greater response to inhaled steroids in those patients treated earliest in their disease. The group with asthma symptoms less than 6 months had the greatest improvement in FEV₁: 0.53 L at 2 years. Among the other groups, there was considerable overlap, and although there was an increase in FEV₁ in all groups at 1 year, it was not sustained to the same degree in the subjects with asthma for greater than 6 months at the 2-year interval. Only the subjects with asthma greater than 10 years when treated with ICS for the first time showed a worsening of the FEV₁ at the end of 2 years. Given the paucity of side effects and the suggestive data in this and other publications, it is reasonable to start ICS in patients who require the daily use of an inhaled β₂-agonist, use one or more canisters of a β₂-agonist per month, or have evidence of nocturnal symptoms.

However, can we conclude from this study that ICS should be prescribed at the first diagnosis of asthma in every patient to provide the greatest benefit and to prevent the development of chronic airflow obstruction? Although in our practice we have a very low threshold for prescribing ICS, we have not yet reached this point because most patients wheeze rarely, do so in response to well-recognized stimuli, and never have progression of their disease to the point of daily symptoms or fixed airflow obstruction. Furthermore, it is important to account for the seasonal nature of asthma symptoms in some subjects. We have many patients for whom we prescribe ICS during their “allergic” months. However, it is unclear if they might require even less therapy if inhaled steroids had been prescribed at the time of their first symptoms.

Although ICS have become an essential part of our therapeutic package for treating airway inflammation, the second unsolved issue is one of cost-effectiveness. In moderate to severe asthmatics who have required emergency department treatment of asthma, it is logical to hypothesize that the cost benefit of use of ICS is great if they prevent costly hospital visits.¹³ For milder asthmatics, it is quite possible that the greater use of ICS could prevent progression of disease to the point of hospitalization in a number of patients and therefore result in less overall cost; an issue that will require a large international placebo controlled trial. The article by Selroos et al does suggest the intriguing therapeutic option that a “course” of inhaled steroids soon after symptoms begin may be helpful in controlling disease for long periods. For the mild asthmatic, until this issue and the potential long-term side effects of ICS (at various doses) are studied further, the use of ICS should be evaluated on an individual basis. At present, we lean toward the use of ICS in any case that has other than mild sporadic symptoms; particularly in individuals with strong family histories of moderate asthmatics. This message is one that is largely unprecipitated by many physicians, as ICS is underprescribed in some patient populations who lack access to physicians with adequate knowledge of the pathophysiology of asthma.¹³

But how much and for how long for the mild asthmatic? These are questions that will likely only be answered when we identify genetic or phenotypic markers of airway inflammation that can be correlated with progression of disease. When we have this information in hand, then studies can be designed to identify the effects ICS have on the phenotypic expression of airway hyperresponsiveness. Until then, we will have to settle for “enough, for long enough” so that the physician is confident that inflammation has been suppressed.

Robert Tarpy, MD
David M. Center, MD
Boston

References
Image-Guided Drainage of Complicated Pleural Effusions and Adjunctive Use of Intrapleural Urokinase

What Would Hippocrates Think?

More than 2,000 years ago, Hippocrates recognized that complete evacuation of the pleural cavity was necessary to effectively treat empyema thoracis. He later described incision and insertion of metal tubes into the pleural space to drain an empyema.\(^1\) Significant progress in the treatment of empyema was not made until the 20th century. In the 1940s, antibiotics became available and the incidence of empyema dramatically decreased. Complete pleural drainage combined with appropriate antibiotic therapy is now the standard treatment for empyema, but mortality rates as high as 40% are still being reported.\(^2\)

The problem with empyema drainage is that all complicated pleural effusions are not alike. During the early stages, the pleural fluid collections are fairly liquefied and easy to drain. With incomplete drainage, the fibrin content and the cellular components within the pleural fluid increase, loculations and adhesions develop, and the fluid becomes more viscous. The pleural process can progress to an organized fibrous pleural peel, which requires surgical decortication for adequate treatment. Therefore, the goal of therapy is to establish early and complete pleural cavity drainage before a pleural peel develops.

In 1951, Tillet et al\(^3\) postulated that instillation of a fibrinolytic agent into a complicated effusion would facilitate pleural drainage by lysing fibrinous adhesions and loculations and reducing the viscosity of the fluid. Unfortunately, this concept did not gain widespread acceptance. Rather, complicated pleural collections continue to be managed by surgeons who insert large (28F to 36F) bore chest tubes at the patient’s bedside. Success rates for surgically placed chest tubes without the use of intrapleural fibrinolytic therapy range from 35 to 75%.\(^4,5\) As many as 35% of these patients eventually require open surgical drainage or decortication because closed tube drainage is ineffective at alleviating the pleural process.\(^6\) In addition, up to 75% of surgical placed tubes are incorrectly positioned.\(^7\) Lung lacerations, intraparenchymal tube location, damage to large central vessels, and tube malfunction have also been reported.\(^8\)

With the use of cross-sectional imaging techniques to guide insertion of small bore catheters into specific pleural collections, vanSonnenberg et al\(^9\) successfully drained empyemas after surgically placed tubes had failed. Success rates with image-guided pleural drainage procedures approximate 80% and reported complications have been very rare.\(^10\) Failure of image-guided chest tube drainage is most often secondary to viscous fibrinopurulent material occluding the catheter, multiloculated collections, and/or the presence of a fibrous pleural peel. Multiple drainage catheters and frequent tube manipulations and exchanges are often needed.

With hopes of improving the results of image-guided catheter drainage of empyemas, several investigators have begun using adjunctive intrapleural fibrinolytic therapy. These small clinical series have suggested that intrapleural fibrinolytic therapy is beneficial and can be used without adversely affecting systemic coagulation parameters.\(^11-14\) Because of the allergic reactions associated with the use of streptokinase, urokinase has become the preferred fibrinolytic agent.

In this issue of CHEST, Moulton et al (see page 1252) report on a large series of 118 consecutive patients who underwent image-guided catheter drainage of complex pleural fluid collections. Intrapleural urokinase therapy was used in 83% (98/118) of the patients; prior surgical tube thoracostomy had failed in 35% (41/118). Complete resolution of the pleural process and full clinical recovery occurred in 94% (111/118) of the patients. The mean duration of catheter drainage was only 6 days. No complications occurred. Fibrinolytic therapy was used successfully without adverse sequelae as early as 5 days after a traumatic hemothorax, within 2 days of spontaneous closure of a bronchial pleural fistula, and 6 days after a pulmonary lobectomy. At least 4 months of imaging follow-up was available on 60% (67/111) of the successfully treated patients, and no residual pleural fluid or significant pleural disease was identified. An “apparent” pleural peel resolved in several patients. This finding is probably explained by the inability of cross-sectional imaging to differentiate between fibrinous debris adherent to the visceral pleura coupled with adjacent inflammation and a true fibrous pleural peel.\(^15\)

Although the FDA has approved fibrinolytic therapy only for use in the treatment of venous thromboembolic and coronary artery disease, it appears that image-guided chest tube drainage of complicated pleural fluid collections coupled with adjunctive intracavitary fibrinolysis should be used earlier and more aggressively. With this treatment approach, improved

12 National Asthma Education Program: Expert Panel Report. Guidelines for the diagnosis and management of asthma. USHHS Publ No. 91-3042
13 Gottlieb DJ, Beiser AS, O'Connor GT. Poverty, race, and medication use are correlates of asthma hospitalization rates: a small area analysis in Boston. Chest 1995; 108:28-33

1190

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21724/ on 04/02/2017