ASTHMA

AND

GASTROESOPHAGEAL REFLUX

INTERNAL MEDICINE GRAND ROUNDS

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Particular attention should be paid to the diet of asthmatic patients...Experience generally compels them to...take the heavy meals in the early part of the day and not retire to bed before gastric digestion is completed...Severe paroxysms may be induced by overloading the stomach.

--Sir William Osler, 1892

INTRODUCTION

The tracheobronchial tree begins as an budding diverticulum from the foregut in the earliest stages of embryonal development (1). Though ultimately serving entirely different functions, the two components of the aerodigestive tract continue to share the same communication with the external environment via the pharynx and a common visceral innervation through branches of the vagus nerve. The teleological failure to anatomically dissociate the two systems necessitates adaptive reflexes to coordinate normal acts such as swallowing and provides the substrate for potential pathophysiological interactions between the gut and the respiratory tract.

This review will focus on the relationship between asthma and gastroesophageal reflux (GER) in adults, though other respiratory complications of gastrointestinal disease will be briefly discussed and mention will be made about considerations unique to children and infants. The evidence favoring a pathophysiological relationship between asthma and GER includes 1) the higher prevalence of GER in asthmatics than the general population, 2) the development of asthmatic symptoms coincident with esophageal acid reflux during ambulatory esophageal pH monitoring, 3) the reproduction of asthmatic symptoms and/or altered airways conductance in response to provocative challenges using esophageal infusions of hydrochloric acid, and 4) the improvement in asthmatic symptoms and/or reduced use of medication in response to treatment of GER. An examination of the strength and weakness of these data are particularly timely given new advances in the treatment of gastroesophageal reflux including the availability of the potent acid-suppressive drug omeprazole and the developing experience with laparoscopic techniques of fundoplication which coincide with current concerns about the apparent rise in asthma mortality.

RESPIRATORY COMPLICATIONS OF GASTROINTESTINAL DISEASE

Associations between respiratory disease and the digestive system have long been common in the medical literature. Earlier reports tended to focus on the effects of malnutrition. For example, late nineteenth century opinion considered that tuberculosis might have its origin in digestive dysfunction.

> "According to Professor Peter, cases of consumption frequently have their origin in disordered digestion, which lowers the vitality to such a degree as to make the (human) organism susceptible to the disease..."(2)

The majority of observers, however, emphasized the complications of gastroesophageal reflux and subsequent aspiration. GER has been associated with a number of very different respiratory conditions, though in some of these the evidence for a causal relationship is somewhat tenuous.

Aspirational Syndromes

Simpson described a patient in 1858 who died subsequent to aspiration of gastric contents after receiving an anaesthetic (3). Mendelson provided his classic description of the consequences of gastric aspiration in obstetric patients in 1946 and emphasized that the clinical manifestation depended upon whether the aspirated material was predominantly solid or liquid (4). Although Mendelson described the clinical syndrome of aspiration of liquid gastric contents as being an "asthma-like" condition, we now understand this to represent laryngospasm and subsequent non-cardiogenic pulmonary edema, rather than a manifestation of asthma per se.

Numerous reports chronicled infectious complications from the aspiration of retained material from the dilated esophagus of patients with achalasia, either putrid lung abscess (5) or what Belcher termed "dysphagia" pneumonitis (6). In 1962 Kennedy shifted this focus from obstructive esophageal lesions and emphasized the pulmonary complications which he associated with an incompetent lower esophageal sphincter with subsequent reflux and aspiration, so called "silent" gastroesophageal reflux (7). Others noted the frequent association of hiatal hernia with such conditions (8,9) and the improvement in respiratory symptoms which often followed surgical repair of hiatal hernia (7,10-15).

These observations prompted the popularization in the 1960's and 70's of the surgical repair of hiatal hernias as treatment not only for gastrointestinal symptoms, but as primary treatment of associated lung disease (9). This evolution was spurred in large measure by the favorable reports of such an approach from several Dallas thoracic surgeons including Paulson, Urschel, and Davis (13-17). Despite often including large numbers of patients, these early reports were largely anecdotal in nature. There were no control groups in these early series and the nature of the patients' underlying lung diseases were poorly characterized. Treatment response was generally based on subjective indices. The majority of these patients were said to have bronchitis, bronchiectasis, recurrent pneumonia or persistent cough. One is left to speculate on the precise role of the hiatal hernia repair per se in these patients who had non-asthmatic conditions, as relief of pulmonary symptoms frequently occurred in those who underwent simultaneous resection of "involved pulmonary segments" along with the hiatal hernia repair itself (7,13-15).

Chronic Cough

Cough lasting for more than 3 weeks in patients with normal chest radiographs who do not have chronic bronchitis can ultimately be attributed to either chronic sinusitis or asthma in 67-75% of cases based upon response rates to empiric treatment for these conditions (18,19). Of the remaining group, the next most common putative diagnosis is GER, accounting for 11-21% (18,19). Ambulatory pH monitoring often shows these patients have abnormal esophageal acid exposure (20-23), with the predominant abnormality being impaired acid clearance (23). Cough is thought to be induced through an esophageal-tracheobronchial vagal reflex (22).

In most reported series the presence of GER was not suspected clinically and required further evaluation such as ambulatory pH monitoring (20). Irwin et al claim that these patients have a typical clinical profile. Such patients have a normal chest X-ray, are non-smokers, are not taking angiotensin converting enzyme inhibitors, and do not have overt evidence of sinusitis or asthma. Irwin has suggested that the specificity (as confirmed by response to treatment) of this "profile" nears 100% based on small numbers of patients (20). Despite this observation, these authors recommend ambulatory pH monitoring in patients meeting this profile to confirm the presence of GER prior to initiating therapy. Others, however, have reported success with a more empiric approach (18).

The response to therapy directed at GER in patients has been highly variable. Though usually described as being ultimately successful, most series use the resolution of cough during GER therapy as the definition of GER-induced cough (18-21). Unfortunately for the clinician the practicality of this association is limited due to the variable nature of reported GER treatment regimes and the observation that the cough resolution may require prolonged therapy, up 6 to 12 months (18,19,21,24,25). There is a tendency for cough to recur in as many as 15% when GER treatment is stopped (25).

Pratter's algorithmic approach would seem the most practical. Patients with chronic cough and normal chest films are given (in step-wise fashion) empiric treatment for sinusitis followed by empiric treatment for asthma. This is successful in 67% of cases. Those who fail this initial approach and who have symptoms of GER are then given a 2-week trial of ranitidine 150 mg twice daily along with instructions on life-style changes. Only those who fail this and/or have no GER symptoms are then

APPROACH TO CHRONIC COUGH

INITIAL EVALUATION	Hx, Px, PFT's, CXR
STEP ONE	TREAT FOR SINUSITIS
STEP TWO	TREAT FOR ASTHMA
STEP THREE	TREAT FOR G.E.R.
STEP FOUR	BRONCHOSCOPY

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tested with pH monitoring and then treated with 8 weeks of omeprazole 20 mg daily; this was necessary in only 3/45 patients (18).

Reflux Laryngitis

Gastroesophageal reflux has also been implicated as the cause of otherwise unexplained hoarseness, so-called "reflux laryngitis". Such patients typically present with symptoms of chronic hoarseness, burning throat discomfort, globus, or nocturnal choking episodes. Laryngoscopy may be normal, but often demonstrates erythema, edema, or ulceration of the posterior larynx. This constellation of findings, while said to be typical of reflux laryngitis, is non-specific and other lesions such as carcinoma in situ and granulomas have been described (26).

Delahunty and Cherry were able to demonstrate that the daily application of gastric juice to the vocal cords of dogs over 6 weeks induced granuloma formation; no pathologic change was found in dogs whose vocal cords were treated similarly, but with saliva rather than gastric juice (27). Several series have shown that the prevalence of abnormal esophageal acid reflux exposure (defined by esophageal pH monitoring) is substantially higher than normals in patients who are referred to otorhinolaryngologists because of the suspicion that they have reflux-induced laryngitis (28-32). The prevalence in these series was from 55 to 79%. This very high prevalence in these studies is clearly in large measure the result of the referral pattern and selection criteria which favored finding a strong relationship. Others, however, in attempting to determine the prevalence of abnormal esophageal acid reflux in otherwise unselected patients with hoarseness of over 3 months duration have found a significantly lower prevalence of 34%; the prevalence in patients with any laryngeal symptom (hoarseness, globus, burning throat, nocturnal choking) was only 17% (33). These studies would suggest that while an association between GER and laryngitis exists, its frequency may be somewhat overstated. Indeed, other potential contributing factors, especially cigarette smoking and excessive voice use, co-exist in many of these same subjects (26,33,34).

Esophageal pH monitoring in patients with laryngitis has not only suggested that there may be a higher frequency of acid exposure in some patients, but that the pattern of reflux is atypical, the predominance of reflux episodes occurring in the upright position(28). Of those patients with abnormal acid exposure (i.e. abnormal pH studies), laryngitis patients are also thought to have an unusually low frequency of concomitant GER symptoms such as heartburn and a lower prevalence of abnormal Bernstein test responses (26,28,35). This has lead to speculation that these individuals have a less sensitive esophageal mucosa, and thus lacking the usual warning symptoms, have repeated reflux up into the proximal (upper) esophagus and pharynx where direct acid damage to the larynx occurs (26). Studies attempting to document this mechanism by measuring pharyngeal pH have been conflicting,

potentially because of technical artifact induced by drying of the pH probe in the pharynx (26). Others have used dual-site esophageal pH monitoring, with pH probes placed in the distal and proximal esophagus in an attempt to investigate the role of acid reflux. Jacob found that, in support of the concept that reflux leads to direct laryngeal injury, the degree of proximal (upper) esophageal acid exposure was greater in a group of subjects with GER and laryngitis (36). However, proximal acid reflux is not invariably present in those with laryngitis; only 40% had greater proximal reflux than subjects with GER but without laryngitis.

The data from clinical trials of anti-reflux therapy are limited and have yielded extremely variable results (26,30,37). In general these studies suggest that such treatment is effective in reducing symptoms of GER per se, but that improvement in laryngeal symptoms occurs less frequently. Further, it has been suggested that in order to yield symptomatic laryngeal improvement, treatment may need to be prolonged and may require more intense therapy such as higher doses of H_2-receptor blockers or omeprazole (26). The role of anti-reflux surgery has not been well characterized in these patients.

Other Non-Asthmatic Pulmonary Conditions

Pulmonary fibrosis has been ascribed to GER (38,39). The evidence for this is solely that hiatal hernia and/or radiographic evidence of reflux were found in middle-aged, overweight men with what would otherwise be termed idiopathic pulmonary fibrosis who happened to be referred for upper GI series (38). This association should likely be ignored given the expected frequency of these findings in a similar group without lung disease, that episodes of aspiration are unlikely to be distributed uniformly throughout the lungs (much less to the distal airways), and our present understanding of idiopathic pulmonary fibrosis.

Gastroesophageal reflux has been implicated in respiratory distress and apnea of newborns based on improved symptoms in infants treated medically or surgically for reflux (40). However, others have discounted this relationship, especially with respect to sudden infant death syndrome. Esophageal reflux is particularly common in infants (3,41,42) and tends to diminish as the child matures, irrespective of GER therapy. Infants also demonstrate reflex apnea in response to laryngeal stimulation, but Ariagno et al could not find a meaningful relationship between acid reflux and reflex apnea (43). Two adult patients have been described who were thought to have GER-associated "central apnea"; one of these, however, was subsequently given the diagnosis of amyotrophic lateral sclerosis (44). Thus, it is not at all clear whether GER can legitimately be considered a cause of apnea, in either infants or adults. GER has also been said to be a cause of chronic dyspnea, though this is based on 4 patients (45).

Asthma and Gastroesophageal Reflux

Sir William Osler was one of the earliest to associate the digestive system specifically with asthma. He observed in his 1892 textbook that asthmatic patients learned to eat their largest meal of the day at noon as taking a large supper would often lead to nighttime accentuation of their respiratory symptoms (46). In keeping with Kennedy's concept of "silent" GER as a cause of pulmonary complications, numerous investigators reported a similar association between GER and asthma (10-12,47-50). Noting the frequent occurrence of hiatal hernia in these patients and the improvement in asthmatic symptoms that followed surgical repair, it was postulated that the mechanism by which GER aggravates the asthmatic condition was via "micro-aspiration" of refluxed acid material into the tracheobronchial tree. This form of gastric aspiration was distinguished from "flooding" of the tracheobronchial tree which was thought to lead to other clinical entities such as pneumonitis, lung abscess, and bronchiectasis (48).

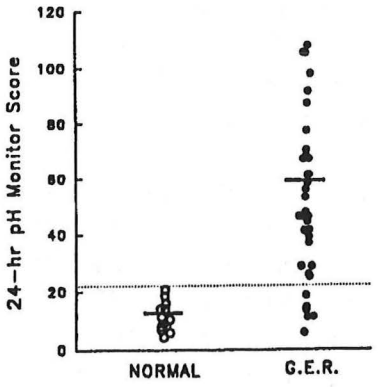
Bray had noted in 1935 that dietary indiscretion could exacerbate an asthmatic condition, postulating that this was due to gastric over-distension which would then "irritate the vagus and so set up a reflex bronchial spasm" (51), presaging the second mechanistic concept linking GER and asthma, namely a vagally-mediated reflex interaction as espoused by Mansfield (52-54).

EPIDEMIOLOGY

Through the use of prolonged ambulatory esophageal pH monitoring we have learned that episodic reflux of acid gastric material ($pH < 4$) into the distal esophagus occurs in virtually all individuals (55). In otherwise healthy, asymptomatic adults these episodes do not produce symptoms, are infrequent (1-2 times per hour) and the refluxed acid is rapidly cleared and/or neutralized by saliva (within 1-2 minutes). Thus, the episodes are of short duration and the total amount of time the esophagus is exposed to acid represents less than 4% of the day. Furthermore, these episodes occur mainly in the upright position and/or after meals and rarely during the night. The primary mechanism for these episodes is transient relaxation of the lower esophageal sphincter (56-58). This pattern is referred to as normal or physiologic GER.

Symptoms suggestive of gastroesophageal reflux such as heartburn or regurgitation occur at least monthly in 25-35% of the general population (59-62). Daily symptoms occur in 4-7% (59,60). Others may use antacids to relieve gastrointestinal discomfort related to GER, though not actually noting heartburn or regurgitation, while others may have atypical symptoms thought to referable to GER such as nocturnal cough or laryngitis. Taken as whole, it is generally believed that 10% of the community has symptomatic gastroesophageal reflux (63).

Some individuals experience episodes of acid reflux which may be more frequent owing to more frequent lower esophageal sphincter (LES) relaxation or generalized LES hypotonia or which may be more prolonged due to abnormal clearance, especially if esophageal dysmotility is present. This can be detected by esophageal pH monitoring and the severity can be gauged based upon the frequency of acid reflux events (number of instances where pH dips below 4), the average and greatest duration of the episodes (an index of clearance), and the total amount of time the esophagus is exposed to acid (% of time pH is < 4; acid contact time). These pH-monitoring variables can be scored and compared to normal, asymptomatic subjects (55,64-66). Excessive acid exposure as defined by these pH monitoring techniques is currently regarded as evidence of abnormal pathologic gastroesophageal reflux (GER).



Johnson and DeMeester, Am J Gastro 62:325 (74)

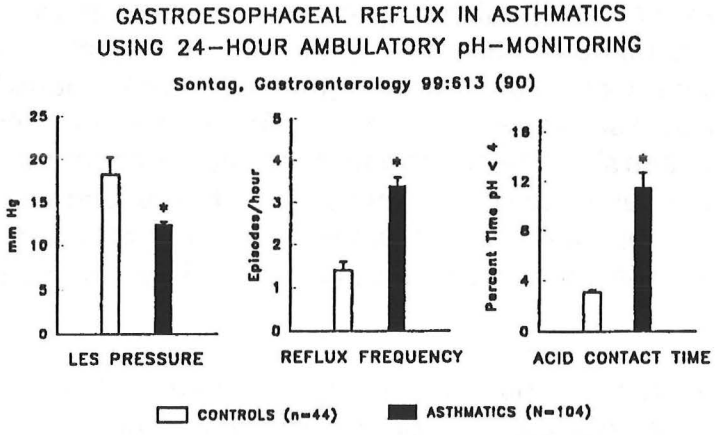
If an individual has an esophageal mucosa which is sensitive to acid and/or has abnormally excessive exposure to refluxed acid, then he may experience symptoms and/or develop actual tissue injury (esophagitis) which may lead to complications such as bleeding, ulceration, stricture formation, Barrett's epithelium, or carcinoma. Gastroesophageal reflux associated with symptoms, esophagitis, or complications is referred to as gastroesophageal reflux disease (GERD). About 85% of patients who have symptoms suggesting GER will have significantly abnormal results on esophageal pH monitoring(65). Smoking cigarettes and use of alcohol accentuate the frequency of GER (9,67,68). The prevalence of esophagitis in patients with GER is estimated to be 30-55% (55,62), though a significant number will not have typical symptoms of acid reflux.

Compared to the general population, a substantially higher prevalence of GER has been associated with a variety of respiratory disorders in infants and children (41,69-73) and in adults with laryngitis (28), chronic cough (74), chronic bronchitis in non-smokers (75), and asthma (74-76). This has been taken as evidence favoring a pathophysiologic effect or interaction between GER and these disorders. On the other hand, GER has also been observed to be more frequent in a number of other situations where it is unlikely to be causing or contributing to the underlying disorder: pregnancy (59), idiopathic pulmonary fibrosis (77), chronic bronchitis in smokers (75), in patients seen in outpatient clinics (59), and in hospitalized patients (59). Further, the frequency of abnormal GER as defined by esophageal pH monitoring increases with age in adults (64). Thus, GER is common and is frequently associated with a variety of disorders; determining a causal interaction is decidedly more problematic.

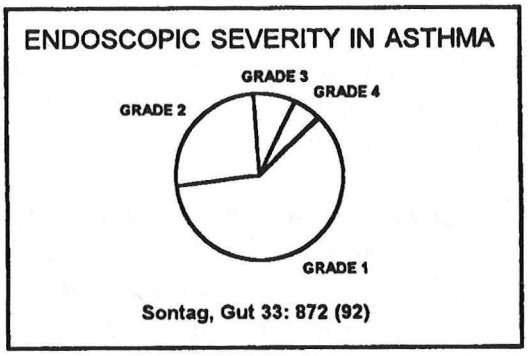
The frequency of GER in asthmatics is generally considered to be significantly higher than in the general population. The reported rates are clearly influenced by such factors as subject selection, age, smoking and alcohol use; however, the usual estimates suggest that 50 to 80% of adult asthmatics have GER (61,74,76,78,79) as compared to about 10 to 35% of the general population (see above).

Symptoms of GER such as heartburn or regurgitation are reported more frequently by asthmatics. In a randomly selected sample in Sweden, 50% of asthmatics reported these symptoms as compared to 25% of the general population (61). Kjellen found that 35% of asthmatics had typical GER symptoms (79). In a group of 27 asthmatics referred for esophageal pH monitoring because of the clinical suspicion that their asthma might be related to GER, Gastal found that 44% had significant GER (74).

Sontag et al studied 104 consecutive patients with asthma who were not selected on the basis of symptomatic status (76). All were studied with 24-hour ambulatory pH monitoring as well as esophageal manometry. As a group, asthmatics were found to have significantly decreased LES pressure, more frequent acid reflux, greater acid contact time, delayed clearance, and had abnormalities in both the upright and supine positions. As compared to a concomitant control group, 82% of asthmatics had evidence of abnormal GER. The results were independent of bronchodilator use, smoking status, or use of alcohol. Although the statistical method used to classify patients with respect GER has been questioned (80), the results are based upon receiver-operating characteristic (ROC) analysis of the asthmatic and control groups in the study which gave threshold values very similar to those traditionally used (65). The patients studied were derived from a Veteran population and thus represented an older group of asthmatics (mean age was 52 years) and others have found a higher prevalence of GER by 24-hour monitoring in patients over 45 years of age (64). Nonetheless, Sontag's study used an internal control group of similar age and sex distribution to define threshold values and these cut-offs were similar to the profile previously described for subjects over 45 years (64).



The overall prevalence of esophagitis in asthmatics with GER is said to be about 40% (78,81,82), which is not too dissimilar from that reported for GER in general (see above). Of note, however, asthmatics tend to have milder degrees of esophagitis; over 85% have only grade 1 or 2 lesions (82). In keeping with observations in others with GER, asthmatics with esophagitis do not necessarily have symptoms suggestive of reflux (58,83,84); indeed, many do not.



Taken together, these data suggest that abnormal GER is present in the majority of patients with adult asthma, but these patients are as likely as not to actually have typical symptoms suggestive of GER. And while these patients may often have mucosal injury (esophagitis), the majority do not; those who do have mild degrees of injury. These observations support, but clearly do not prove, a possible pathophysiologic relationship between asthma and GER. Perhaps more importantly, the very high prevalence of GER in adult asthmatics, the poor sensitivity of symptomatic status for predicting the presence of GER, and the general absence of severe histologic complications all have important implications with respect to diagnosis and management; this will be discussed in greater detail below.

PATHOPHYSIOLOGY

The frequent coexistence of GER and asthma suggest the possibility that the two might share common precipitating factors such as smoking or the accentuation of nocturnal physiologic changes. Additionally, asthma and GER might interact such that one causes or exacerbates the other. The physiologic changes which occur during an asthmatic episode and some of the common asthmatic medications might be expected to favor GER.

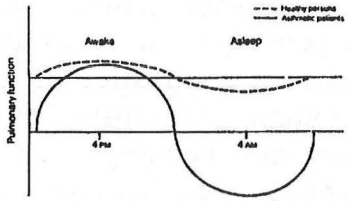
Conversely, it has been suggested that the reflux of gastric material into the esophagus might trigger acute bronchospasm, either directly via aspiration of small amounts of acid material into the tracheobronchial tree or through a vagally mediated reflex where acid-sensitive esophageal receptors stimulate afferent activity which then causes "cross-traffic" activation of vagal efferents to bronchial smooth muscle. A third mechanism does not require GER to trigger acute bronchospasm; GER might instead heighten bronchial reactivity to other stimuli via vagally mediated changes in resting bronchomotor tone and/or responsiveness. Thus, GER might potentiate rather than directly cause, airway narrowing. There is supportive data for each of these three potential mechanisms.

Nocturnal Physiology

The majority of severe asthmatic attacks (85), episodes of respiratory failure (86), and deaths (87) occur at night. It is often said that nocturnal worsening of respiratory symptoms is an important clue to the presence of GER-associated asthma (78,88-91). However, it is also true that there are a number of physiologic alterations during sleep and/or at night which may contribute to worsening asthma independent of a direct of effect of GER.

Normal subjects display circadian variation in lung function. Expiratory airflow as judged by FEV_1 or peak expiratory flow rate (PEFR) is best around 4 pm and at its worst around 4 am; the variation in normals is small and of negligible significance, only about 8% difference between the highest and lowest values. Asthmatics also display this same circadian pattern, however, baseline function and variability are both significantly worse than in normals. Asthmatics can have peak-trough daily swings of up to 50% (88,89,92).

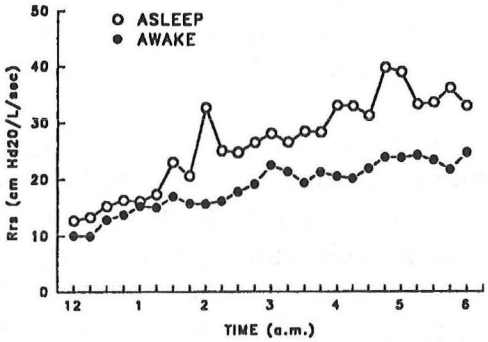
CIRCADIAN VARIATION IN PULMONARY FUNCTION IN NORMALS AND ASTHMATICS



Jarjour, J Respir Dis 15: S19 (94)

This nocturnal worsening in asthmatics is not a function of being recumbent; the same circadian variation was found in a group of asthmatics who were kept supine throughout the entire day, regardless of whether they slept (93). This variation is related to sleep rather than clock-time, as demonstrated in asthmatics who switched back and forth from day to night work shifts (93). Of particular interest, this circadian variation, while related to sleep, is not purely a function of sleep. Ballard noted that there was a progressive rise in airways resistance in asthmatics through the night in a group of asthmatics even when they remained fully awake. The increase in airways resistance was more pronounced when these subjects slept (94).

AIRWAYS RESISTANCE (Rrs) INCREASES OVERNIGHT IN ASTHMATICS



Ballard, J Appl Physiol 67:243 (89)

A number of other physiologic parameters follow a similar circadian pattern. Serum catecholamines (88), vagal tone (95,96), and cortisol levels (97) vary in concordance with changes in airflow in

asthmatics. However, drops in airways resistance can be only be partially ablated with continuous infusion of physiologic doses of corticosteroid (98) or during vagal blockade (99).

Lung volume (functional residual capacity) decreases during sleep in both normals and patients with obstructive lung disease (100); as lung volume decreases, airways resistance increases (101). Vagal afferents which respond to changes in lung volume, hypoxia, and hypercapnia are known to affect airways resistance, largely through changes in laryngeal cross-section (102-105). In addition, sleep alters breathing pattern, ventilation, and respiratory drive during sleep (106). Thus, normal physiologic events during sleep contribute to increased total airways resistance; this effect may be accentuated by any stimulus which alters vagal tone in asthmatics.

Sleep also influences GER. Clearance of esophageal acid is impaired during sleep in both normals and patients with GER (107). This is the result of changes in swallowing frequency; there is no change in peristaltic patterns attributable to sleep (107,108). Although acid clearance is impaired during sleep, the majority of reflux episodes in normal subjects with physiologic reflux occur during waking hours. Patients with GER, on the other hand, have more frequent and more prolonged episodes when supine, especially during sleep (see above). Transdiaphragmatic pressure tends to increase during sleep (106,109), so that gastric pressure becomes significantly more positive relative to esophageal pressure, an effect which would favor GER. Thus, sleep does not induce reflux per se, but does accentuate acid exposure in those with GER.

Asthmatic Potentiation of GER

The crural diaphragm serves to partially modulate the competence of the lower esophageal sphincter (LES) and thus prevent acid reflux, especially during periods of increased abdominal pressure (58,110,111). During an acute exacerbation of asthma, there is significant air-trapping, hyperinflation, and acute shortening the diaphragm. This alteration in diaphragm configuration could theoretically influence its ability to protect the lower esophagus from GER; however, the functional significance of the diaphragm in this regard has been questioned (112).

Hyperinflation increases elastic resistance and creates an inspiratory load which necessitates greater inspiratory effort, the result of which is that esophageal pressure becomes much more negative relative to gastric pressure during inspiration. This would tend to favor GER, especially in someone with a hypotonic LES. Additionally, this effect would be compounded by the patient's active expiratory efforts which are mainly generated by contraction of abdominal muscles, resulting in excessive gastric pressures. Cough would also predispose to GER via pressure effects. Some have postulated that a similar mechanism could relate GER and exercise-induced asthma

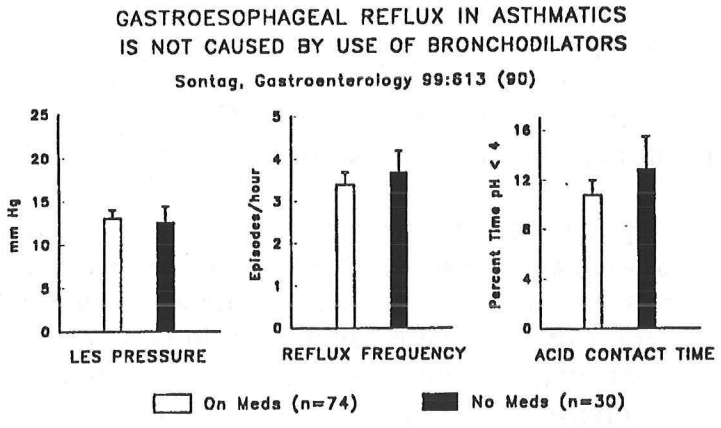
(113). There is some anecdotal support for the postulate that asthma may worsen GER; treatment directed at control of asthma was said to diminish the frequency of symptomatic episodes of GER in a small group of patients (54,114). Additionally, the use of nasal continuous positive airway pressure (CPAP), which raises thoracic pressure (and presumably esophageal pressure) is reported to decrease the frequency of GER, even in patients with GER who do not have obstructive sleep apnea (115-117)

Ethanol predisposes to GER by decreasing LES pressure as well as by reducing esophageal peristalsis (68). Nicotine in cigarette smoke also lowers LES pressure and tends to worsen GER (34,67). Smoking clearly has adverse effects on asthmatic status, even with passive exposure. Thus, the presence of these common risk factors in an individual patient might contribute to worsening of asthma, GER, or both.

Many of the drugs used to treat asthma have effects of potential significance relative to GER. Theophylline (in concentrations of 10-20 μg/dl) has been shown to cause relaxation of the LES in normals and in asthmatics (118). Theophylline also increases basal gastric acid production (119), but has no significant effect on esophageal motility (120).

Adrenergic agents have differing effects on LES pressure. LES contraction occurs with α-agonists and relaxation with β-agonists (120). Adrenergic agents used in asthma do not significantly effect acid secretion (119) or esophageal motility (120). The β-agonists have far less effect on esophageal function than does theophylline (121).

These observations would suggest that bronchodilator therapy should accentuate GER, especially theophylline. Berquist et al reported that theophylline caused a reduction in mean LES pressure and this was associated with increased symptoms of heartburn and increased the frequency of positive Bernstein tests in 15 normal subjects (72). In contrast, numerous studies in asthmatics, including studies by this same group of investigators, have failed to demonstrate any significant worsening of GER symptoms or results of esophageal pH monitoring in association with bronchodilators, both β-agonists and theophylline (76,82,122-126). It has been



suggested that the differences in effects of these drugs in normals as compared to asthmatics can be explained by the offsetting effects. The potentially negative effect of these drugs on LES function and acid secretion is balanced by their beneficial contribution to improving asthma, thereby lowering transdiaphragmatic pressure differences.

These observations suggest that it is unlikely that asthmatic physiology or therapy plays a major role in causing GER. More importantly, while current practice is to emphasize avoidance strategies and anti-inflammatory therapy as the basis for asthma therapy, β-agonists and theophylline should not be with-held from patients who need them based upon concerns for their effects on GER.

Micro-Aspiration Induction of Asthma

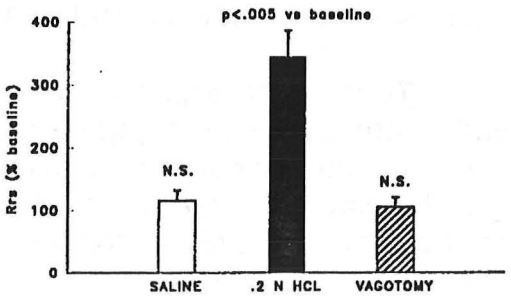
As noted above, one potential mechanism by which GER might trigger asthma would be via the aspiration of small amounts of refluxed material with direct irritation of the airways and reflex bronchoconstriction. It is well established that mechanical stimulation of the upper airway (larynx or tracheobronchial tree) leads to significant increases in airways resistance (127). Experimental installation of fluids (including water or saline) into the trachea also causes a rise in resistance (128). These effects are via parasympathetic reflexes as they can be ablated by vagal blockade.

GASTROESOPHAGEAL REFLUX AND PULMONARY ASPIRATION

modified from Deschner, Am J Gastro 84:1 (89)

The most frequently cited study in support of the micro-aspiration theory is by Tuckman et al who measured airways resistance changes in response to tracheal acidification in anesthetized cats (129). Total lung resistance increased 4-5 fold following the installation of very small volumes (as little as 0.05 ml) of 0.2 N HCl into the upper trachea. The effect occurred rapidly, was enhanced with increasing acidity, was not present when similar volumes of saline were used, and was ablated by vagotomy; all of which suggests a vagally mediated reflex in response to pH sensitive tracheal receptors. The relevance of these data with respect to asthma are uncertain, however. The duration of the effect on airways resistance was extremely short-lived, occurring within the first 20 seconds after installation of acid

AIRWAYS OBSTRUCTION INDUCED BY TRACHEAL ACIDIFICATION IN CATS



Tuchman, Gastroenterology 87:872 (84)

and being completely gone by 40-60 seconds. Human subjects with more responsive airways might have a more sustained response, though this has not been shown directly.

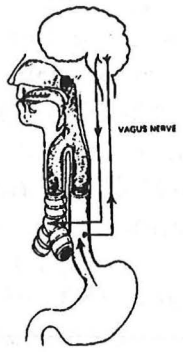
In order for micro-aspiration to trigger asthma, gastric material would have to reflux into the distal (lower) esophagus, traverse up to the proximal (upper) esophagus, into the hypopharynx, and then be aspirated into the trachea. Numerous investigators have attempted to document this reflux and aspiration of gastric material using scintigraphic techniques. A radio-labeled meal is ingested and the subject is allowed to sleep. The subject is later scanned and uptake over the lungs is taken as evidence for aspiration. Several studies have reported positive scans in subjects with asthma (75,130-134) and have correlated results of esophageal pH monitoring with aspirator status (130). Others have been unable to document nocturnal aspiration. (135) and the majority of these studies find that only a minority demonstrate aspiration, averaging only 20-35% of those tested. These studies have many potential problems. Gastric emptying of labeled meal requires that subjects be given the test meal immediately before retiring, a condition that would predispose to reflux and aspiration; indeed, one study showed evidence of aspiration in 38% of controls (131). Rapid clearance from the tracheobronchial tree and/or stomach, as well as problems with high background activity in the abdomen, create technical problems which would tend to cause a loss of sensitivity for detecting aspiration.

Another approach has been to look for evidence of reflux and aspiration by pH-monitoring using dual probes. One probe is placed in the distal esophagus, as is standard. The second probe is then placed more proximally, e.g. in the upper esophagus, pharynx, or even in the trachea via cricothyroid puncture. The simultaneous drop in pH at both locations would favor the likelihood that aspiration of acid material occurs. Using dual probes with one in the trachea, Donnelly was able to demonstrate simultaneous acidification in esophagus and trachea in 3 asthmatics in whom reflux surgery was planned (136). Pharyngeal probes have been unreliable due to drying of the probe (137). Dual probes in the proximal and distal esophagus in larger groups of asthmatic subjects have shown that while occasional acidification of the proximal (upper) esophagus occurs in those with GER, the frequency of such events is quite low and these events do not correlate with symptoms or changes in peak expiratory flow (74,138-141).

Thus, while aspiration of refluxed acid material may occur in some subjects with asthma, it would appear that this is very infrequent and that this is not an adequate explanation for a causal relationship between the two. This is particularly true for adult asthmatics; it is likely that aspiration is more common and likely contributes to a greater extent to respiratory symptoms in infants and in young children (3,109,142).

Neural Triggering of Asthma

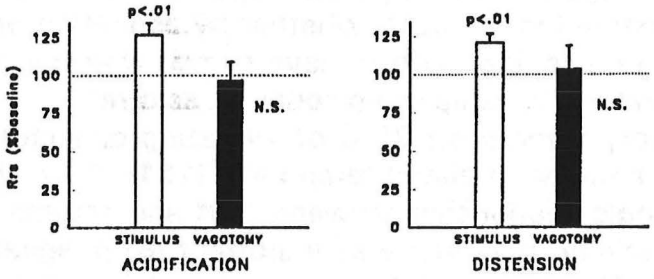
REFLEX MODULATION OF AIRWAY SMOOTH MUSCLE
FROM G.E.R. STIMULATION OF ESOPHAGEAL RECEPTORS



modified from Deschner, Am J Gastro 84:1 (89)

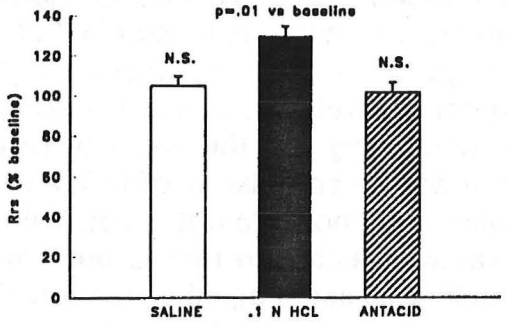
Mansfield has popularized the concept that asthma can be triggered indirectly through stimulation of receptors in the lower esophagus without aspiration and that this reflex is vagally mediated (54). Wright has shown that esophageal infusion of either saline or 0.1 N HCl can cause a vagal reflex in normal subjects which included a decrease in both heart rate and FEV_1 (143). Mansfield created esophagitis in dogs through daily infusion of HCl into the esophagus and then later measured airways resistance in response to esophageal stimulation. He noted that specific airways conductance fell significantly following either esophageal acidification using infusion of 100 ml of 0.1 N HCl or esophageal distention using a balloon filled to 60 ml with air as compared to esophageal infusion of saline. These changes were ablated by vagal blockade (53).

AIRWAYS OBSTRUCTION INDUCED BY
ESOPHAGEAL STIMULATION IN DOGS



Mansfield, Ann Allergy 47:431 (81)

AIRWAYS OBSTRUCTION INDUCED BY
ESOPHAGEAL ACIDIFICATION IN ASTHMATICS



Mansfield and Stein, Ann Allergy 41:224 (78)

Mansfield and Stein demonstrated a statistically significant increase in airways resistance in 15 asthmatics following esophageal infusion of 0.1 N HCl which was continued until the subjects complained of their typical GER symptoms (52). These subjects did not have any response to saline infusion and airways resistance returned to baseline after ingesting antacids. This has been taken as evidence favoring a causal relationship between GER and asthma. Unfortunately, the change in airways resistance seen with esophageal acidification, while statistically significant, is very small and of questionable significance; other measures of airflow obstruction such as FEV_1 or peak expiratory flow were unchanged. Further, this study does not preclude an effect of unrecognized aspiration as large volumes were used in supine subjects.

Numerous other studies have attempted to induce acute changes in asthmatics using esophageal perfusion challenges. Davis showed that such infusions could provoke acute bronchospasm in sleeping children with asthma (144). The results in adults, on the other hand, have been mixed. Several investigators were unable to produce any measurable effect of esophageal acidification on lung function in asthmatics (145-147). One the other hand, worsening expiratory airflow could be induced in the majority of asthmatic subjects in a number of other studies (75,140,148-150). Of note, however, those studies which showed a positive result could only demonstrate an effect on the most sensitive indicators of airflow limitation such as total airways resistance, peak expiratory flow, or the average flow rate between 25 and 75% of vital capacity; none was able to convincingly demonstrate an effect on more clinically relevant parameters such as FEV_1 or to provoke clinically overt bronchospasm. While there was a tendency for studies to show more of an effect in sleeping subjects, in subjects with clear symptomatic association of GER and asthmatic episodes, or in asthmatics with demonstrated esophageal acid sensitivity (i.e. a positive Bernstein test), these differences clearly did not explain the discrepant outcomes among these various investigations.

Neural Enhancement of Bronchial Reactivity

These observations would suggest that, while individual exceptions likely occur, the frequency with which GER actually triggers clinically evident episodes of acute bronchospasm has been somewhat overstated in the past, whether by aspiration or through reflex neural mechanisms. Along these lines, others have shown that there is a poor correlation between the temporal relationship of episodes of acid reflux on pH monitoring and the onset of respiratory symptoms; 75% of wheezing episodes occur before an episode of reflux or are entirely unrelated temporally (151). This of course does not rule out a pathophysiologic relationship between GER and asthma, as factors related to reflux, but not to acidity, may serve as important esophageal stimuli, e.g. esophageal distention (53,143) or reflux of non-acidic material such as bile (152).

Perhaps the most compelling evidence favoring an actual pathophysiologic role for GER in asthma are the numerous studies of both the medical and surgical therapy of GER which have shown notable improvement in asthmatic symptoms and control, and that asthmatic symptoms have been observed to recur upon cessation of GER therapy (see below). Of note, in virtually all of these studies, while GER therapy invariably leads to rapid control of GER symptoms, the improvement in respiratory symptoms and control requires many weeks to months. This, too, argues against theories which postulate that refluxed acid per se triggers asthma, and suggests that the underlying mechanism relates to changes in basal bronchial sensitivity or tone which occur in response to the cumulative effects of acid exposure. In this sense,

GER might increase bronchial smooth muscle tone or reactivity via neural mechanisms. As such, GER would potentiate asthmatic responses to virtually any other trigger or stimulus (153).

In further support of this concept, Wilson et al (154), Ekstrom and Tibbling (155) and Herve et al (156-158) have all shown that esophageal acidification is related to and/or induces a heightened state of bronchial reactivity. Herve's group demonstrated that esophageal acidification lead to increased bronchomotor reactivity to methacholine challenge as well as to isocapnic hyperventilation (158). Harding has recently provided data which suggest that esophageal acid worsens expiratory airflow without evidence of aspiration and that peak expiratory flow continues to decline even after effective esophageal clearance of acid; this supports the concept that neural reflexes modulate bronchomotor tone (141).

TREATMENT OF GER-ASSOCIATED ASTHMA

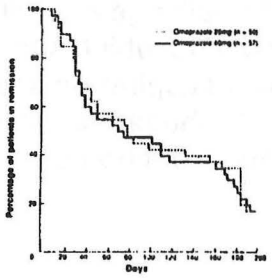
Treatment of GERD

A complete discussion of the management of GERD is beyond the scope of this discussion; a brief review is necessary, however, in order to relate therapy of GER to patients with co-existing asthma. Conservative measures including the use of as needed antacids (159) and elevation of the head of the bed (160) have been shown to be effective in controlling or reducing the symptoms of heartburn, regurgitation in a significant number of patients with GERD. Other life-style changes (see table) geared towards diet, avoidance of smoking and alcohol, weight loss, and avoidance of drugs which may reduce LES pressure represent the primary modality in the stepped approach to treating most patients with uncomplicated GERD (58,83). These measures are effective in approximately 28% of patients, including the promotion of esophagitis healing (161-165).

A significant number of patients require additional medical therapy using acid-reductive drugs, prokinetic agents, or both. Histamine (H-2) blockers including cimetidine and ranitidine have been shown to improve symptoms and heal esophagitis. The overall effectiveness of these agents is variable, though GERD control can be achieved in about 60% of patients (161-164,166). The success or failure of H-2 blockers is largely dependent upon the degree of acid suppression achieved. Divided dosing and higher doses are required as compared to the management of duodenal ulcer. When actual tissue injury has occurred as the result of GER (i.e. esophagitis), the success of therapy is also determined by the length of therapy; greater healing occurring with more prolonged treatment (166). The addition of a prokinetic agent such as metoclopramide or cisapride may have a role in combination with H-2 blockers in some patients (167).

Omeprazole, which has significantly greater acid suppression as compared to H-2 blocking agents, is the most effective medical therapy for GERD; successful results can be achieved in over 80% of patients treated for an adequate duration (165,166). Unfortunately, omeprazole therapy is currently still very expensive (168). One of the major problems with medical therapy, including omeprazole, is the relapse rate following discontinuance of the drug. While omeprazole can control symptomatic GERD in 80% of patients treated for 8 weeks, as many as half will experience return of symptoms within 2 months and most, if not all, will recur within one year without further therapy (165).

SYMPTOMATIC RELAPSE FOLLOWING DISCONTINUANCE OF OMEPRAZOLE THERAPY FOR G.E.R.D.

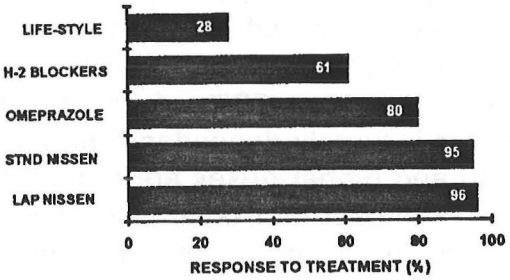


Hetzel, Gastroenterology 95: 903 (88)

Thus, most patients will require indefinite maintenance therapy. Unfortunately there is an approximate 20-40% long-term failure rate and cost is a particularly important issue for maintenance therapy. Potential long-term consequences of prolonged acid suppression on gastrin levels, gastric mucosal changes, B-12 malabsorption, and tumor induction have also been raised (169-175), although no significant clinical problems have been identified in published follow-up of patients receiving long-term omeprazole (176).

Two comparative trials have suggested that surgical fundoplication is superior to medical therapy for maintenance therapy (177,178). Unfortunately these studies were done prior to the availability of omeprazole and adequate acid suppression was likely not achieved in the medical therapy groups. Nonetheless, standard Nissen fundoplication is said to be nearly 95% effective in controlling GERD. No reliable data exist on the long-term outcome in surgical patients, though long-term failures may occur in 10-20%. The use of surgery for control of GERD has been tempered by the morbidity and potential mortality of surgery, especially when viewed as treatment for a "benign" condition.

SYMPTOMATIC RESPONSE TO G.E.R. TREATMENT



More recently, laparoscopic techniques have been employed to perform the Nissen fundoplication (39,179-182).

Laparoscopic Nissen procedures are associated with shorter lengths of hospitalization (2-4 days post operative) as compared to standard operations, though total morbidity is similar. The most notable complication has been persistent dysphagia. Pitcher, et al reported this problem in 5-7% of their recently reported experience with 68 patients (179). The problem occurred early in their experience when a smaller dilator was used in a few of the patients around which to form the fundoplication. Since resorting to a larger dilator in all cases, the prevalence of persistent dysphagia has declined; the same group has now done 136 procedures with no persistent dysphagia in over 100 of the most recently performed cases (183). There have thus far been no reported deaths attributed to laparoscopic fundoplication. The effectiveness of laparoscopic surgery has been the same as with conventional surgery, the reported studies have achieved control of GERD in 96% overall. Long-term follow-up is not available, though failures would be expected as this is essentially the same surgical procedure done by a different technique. These favorable results have been achieved in centers which perform the procedure regularly; as with other laparoscopic surgery, local availability and expertise are important (184,185).

Medical Therapy of GER-Associated Asthma

Kjellen reported that the use of life-style modifications in a group of patients with both asthma and symptoms of G.E.R. lead to improvement in both the reflux symptoms as well as symptomatic asthma improvement in 51% of patients. Use of bronchodilator drugs decreased, but they were unable to show any improvement in pulmonary function testing (186). Others have not found the same magnitude of improvement; the overall rate of improvement with life-style modification alone is about 30%. Nonetheless, given that the prevalence of GER is so high in asthmatics (50-82%), it would seem prudent to instruct all asthmatics on typical GER life-style modifications.

LIFESTYLE THERAPY FOR G.E.R.

- STOP SMOKING
- RESTRICT ALCOHOL
- ELEVATE HEAD OF BED
- AVOID LATE OR LARGE MEALS
- WEIGHT LOSS
- DIETARY RESTRICTIONS
  - fat, caffeine, chocolate
- AVOID MEDICATIONS AFFECTING L.E.S.
- USE ANTACIDS prn

Goodall treated 20 patients with asthma and symptomatic GER using cimetidine (1000 mg/d in divided doses). They found symptomatic improvement in 14 of 18 patients. Small, but statistically significant, improvements were noted in p.m. peak expiratory flow measurements, but no difference was found with respect to spirometry (187). In a similar study using ranitidine 150 mg b.i.d., Harper demonstrated improvement in asthma symptoms in 9 of 14 subjects treated for 8 weeks; they were able to show a modest improvement in FEV_1 as well (188). In another study using ranitidine 150 mg b.i.d., but for only 4 weeks, Ekstrom was able to show only modest improvement in nocturnal symptoms

and medication use; there was no effect on spirometry, lung volumes, or bronchial reactivity to methacholine (189). Virtually all of these studies were associated with prompt improvement of associated reflux symptoms. Overall, treatment with H-2 blockers has lead to improvement in asthma symptoms in about 46% of patients; effects on measurable lung function have been modest or nil.

MEDICAL G.E.R. THERAPY FOR ASTHMA

STUDY	TREATMENT	DURATION	IMPROVED
Ekstrom,1989	Ranitidine 150mg bid	4 weeks	6/46 (13%)
Ford, 1994	Omeprazole 20mg/d	4 weeks	0/11 (0%)
Harper, 1991	Ranitidine 150mg bid	4 weeks	2/14 (14%)
		8 weeks	9/14 (64%)
Goodall, 1991	Cimetidine 1000mg/d	6 weeks	14/18 (78%)
Harper, 1995	Omeprazole 20-40mg	12 weeks	22/30 (73%)
Larrain, 1991	Cimetidine 1200mg/d	24 weeks	20/27 (74%)

There is very little available data regarding the use of prokinetic agents to treat GER-associated asthma in adults, though some benefit has been shown in children (190-192). Treatment results in children have been highly variable (72,73,193-195). The pathophysiology of GER and asthma in infants and young children is likely considerably different than that in adults (3,41,69-71,142,196) and should not be used to guide adult therapy.

Published data relating omeprazole treatment in asthmatics is somewhat limited. Depla reported a patient who had marked improvement in symptoms, peak expiratory flow, and FEV_1 after omeprazole 20 mg/day for 3 months (197). Ford, et al reported no improvement in 11 patients with asthma and documented GER; however, patients only received four weeks of treatment (198). Recent data from Harding has suggested that omeprazole therapy led to significant improvement in asthmatic symptoms, peak expiratory flow, and FEV_1 in 73% of a group of 50 asthmatics with documented GER (199). Treatment was tailored to achieve normalization of acid contact time by pH monitoring; 27% of their patients required doses of omeprazole of over 20 mg/day.

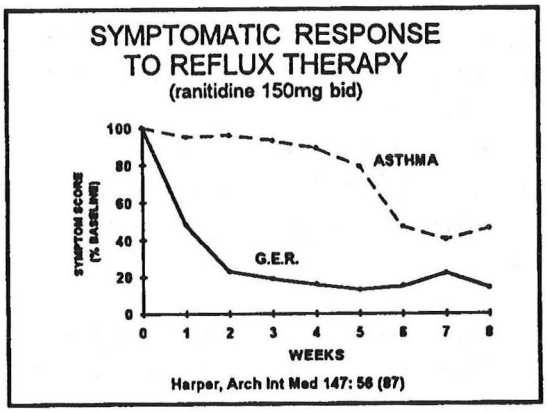
Medical therapy can thus be expected to lead to improvement in some asthmatics. In general, such therapy is consistently less effective in controlling asthma than it is for GER per se. Efficacy is clearly a function of the intensity of acid suppression. The predominant effects of medical therapy are to improve symptoms and reduce medication use; the influence of therapy on objective measures of lung function are frequently modest and confined to the more sensitive indicators of expiratory flow limitation.

Clinical predictors of which patients with asthma will respond to treatment for GER are fairly unreliable. Features which are said to be predictive of GER-associated asthma include: patients who can clearly relate their symptoms of GER to worsening of asthma, the presence of nocturnal asthma, the absence of atopy, adult onset asthma, and severe asthma refractory to other therapy. Unfortunately, while many

patients with asthma can be shown to have GER by pH testing (76), as many as half lack typical symptoms of reflux. Further, it has recently been shown that clinical features such as those mentioned have a very poor sensitivity for identifying patients whose asthma will respond to intense acid suppressive therapy (200).

Duration of Therapy

One factor which appears to influence the efficacy of medical therapy for GER-associated asthma is the duration of treatment. Most studies report prompt improvement in symptoms of heartburn or regurgitation, often within one or two weeks. One the other hand, the asthmatic response rate tends to increase with more prolonged therapy. Patients treated for shorter intervals (e.g. 4 weeks) have shown improvement in asthma in only about 15% of cases (188,189,198) whereas prolonged treatment (8 weeks or more) is associated with improvement in 40-70% (187,188,199,201-203). This relationship is shown to best advantage in the study by Harper, et al (188). The need for prolonged therapy to achieve maximum therapeutic results with respect to asthma is analogous to the observations in patients treated with esophagitis (166).



Surgical Therapy of GER-Associated Asthma

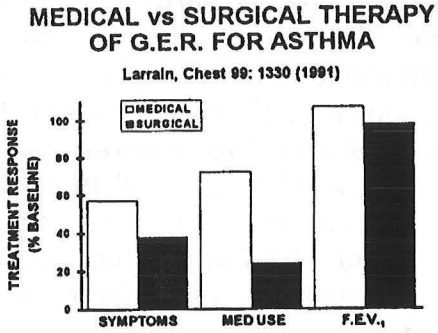
Anti-reflux surgery has been used in selected patients with GER and asthma. In a larger study of fundoplication in the management of pulmonary complications of GER, Pellegrini reported marked symptomatic improvement in all 5 asthmatics (204). Sontag's group reported 13 patients who underwent fundoplication; 6 of these became entirely asymptomatic with respect to their asthma, 6 were improved, and only 1 was unchanged. Significant reductions in asthma medications were also reported, including the elimination (2) or reduction (4) of prednisone in 7 who were previously steroid dependent (205). Tardiff reported improvement in 5 of 10 patients treated surgically, though none

EFFICACY OF G.E.R. SURGERY FOR ASTHMA

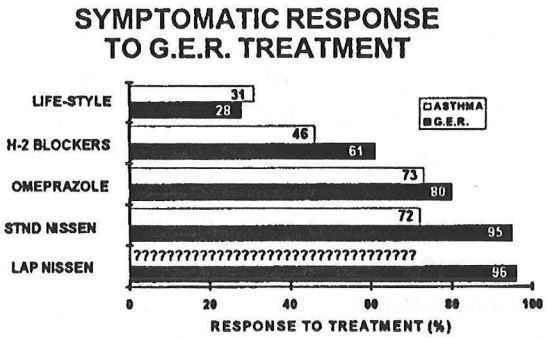
STUDY	n	IMPROVED	REMISSION
Pellegrini, 1979	5	5/ 5 (100%)	—/— (—%)
Sontag, 1987	13	12/13 (92%)	6/13 (46%)
Tardif, 1989	10	5/10 (50%)	0/10 (0%)
Perrrin-Fayolle, 1989	44	29/44 (66%)	11/44 (25%)
Larrain, 1991	26	20/26 (77%)	9/26 (35%)
Combined	98	71/98 (72%)	26/93 (28%)

became asymptomatic (206). In the largest reported surgical series, fundoplication resulted in "cure" of asthma in 25% and improvement in 41% (207).

In the only comparative trial of medical, surgical or placebo therapy, Larrain showed that both medical and surgical treatment succeeded in improving asthma symptoms and reducing medication use, though without significant improvement in objective measures of pulmonary function (202). No clear benefit of surgery over medical therapy was proven in this study. Taken as a whole, standard anti-reflux surgery appears to successfully control GER symptoms in 96% and asthma is improved in 72%. It is also noteworthy that medical therapy has not been associated with asthmatic remissions, whereas many of the surgical series have reported such patients. Long term results appear favorable, though the data of Perrin-Fayolle suggest that long-term asthma relapses occur after surgery (207).



The reports to date of laparoscopic Nissen fundoplication have not specifically addressed the efficacy of this procedure for the amelioration of asthma. The report from Pitcher, et al included 9 patients with asthma, but reliable data regarding the outcome of their respiratory status is not available (183). However, as the laparoscopic approach accomplishes virtually the same anatomic and physiologic results as the standard operation, one would anticipate similar results with respect to asthma control.



Maintenance Therapy

As noted above, relapse after cessation of medical therapy occurs commonly in GERD. Similarly, symptoms of asthma may worsen or recur when GER treatment is stopped (187,188). As such, patients with GER-associated asthma who respond initially to medical therapy will likely require prolonged maintenance therapy. Unfortunately, there is no clear answer as to what the recommended therapy should be in these situations. Although it may be possible to maintain control with less intense therapy such as ranitidine 150 mg bid, it would

appear that more intense acid suppression with prolonged use of omeprazole may be necessary in this subgroup of patients with GERD. Having identified a patient as benefiting from GER therapy, the physician and patient together will likely find it necessary to choose between long term medical treatment and surgery. This decision can only be made on an individual basis, weighing the relative risks and benefits of each approach.

DIAGNOSIS AND EVALUATION

Tests for Evaluation of GER and Asthma

A variety of diagnostic tests are available for evaluating patients with suspected GER-associated asthma. The presence of typical symptoms of GER is highly predictive of true GER (about 85%) and can be relied upon for most clinical purposes. As noted above, however, as many as half of asthmatics with GER do not have typical reflux symptoms. The "gold standard" at present for identifying the presence of pathologic GER is prolonged ambulatory pH monitoring of the distal esophagus. The procedure is relatively non-invasive and interpretation has become fairly standardized. Scintigraphic tests for GER have been used, but generally suffer from lack of sensitivity. Definitive evidence of actual tissue injury from GER requires endoscopy. However, the presence of esophagitis on endoscopy (with or without biopsy) in the immuno-competent patient can be taken as firm evidence of GER. Endoscopy, along with barium swallow, is most useful in detecting complications of GER such as esophagitis, Barrett's mucosa, and structures. Esophageal manometry is useful in detecting associated motility disorders and in measuring LES pressure. However, while average LES pressure tends to be less in patients with GER, there is tremendous overlap with normals; measurement of LES pressure is not useful in identifying the patient with GER and is best used as part of pre-surgical evaluation (see below).

TESTS FOR G.E.R. IN ASTHMATICS

- IDENTIFY REFLUX
  - pH MONITORING
  - SCINTIGRAPHY
  - ENDOSCOPY
- IDENTIFY TISSUE INJURY
  - ENDOSCOPY
  - BIOPSY
- EVALUATE PHYSIOLOGY
  - L.E.S. PRESSURE
  - ESOPHAGEAL MOTILITY
- DETERMINE CAUSAL RELATIONSHIP
  - pH MONITORING WITH DIARY
  - TRIAL OF THERAPY

All of these tests have their respective role in the management of patients with typical GERD. Their role in patients with suspected GER-related asthma may be somewhat different. In particular, all of the tests mentioned above may provide evidence of the existence of GER in an asthmatic. None of them, however, can actually determine a causal relationship between the presence of GER and its effect on the patient's asthma. The use of a symptom diary and recordings of peak flow

measurements during pH monitoring has the potential for making this association, but as noted earlier, the relationship between individual episodes of reflux and asthma symptoms is highly variable and likely of little use in the majority of patients. Perhaps the most clinically relevant test for an association between GER and asthma is the clinical response of the patient to a trial of intense acid suppression. Taking these issues into account, and recalling the very high prevalence of GER (but low prevalence of severe esophagitis) in asthmatics, it may be that the ideal initial diagnostic study in refractory asthmatics would be an empiric trial of adequate therapy.

Suggested Clinical Approach in GER-Associated Asthma

The management guidelines for both asthma and GERD suggest a stepped approach. This can be anticipated to achieve satisfactory control in most patients. Those who have both asthma and clinically evident GERD need not be approached any differently; treat asthma with standard asthma therapy and GERD with its own standard treatments. In so doing, the patient's overall status may improve through synergistic interactions of the two.

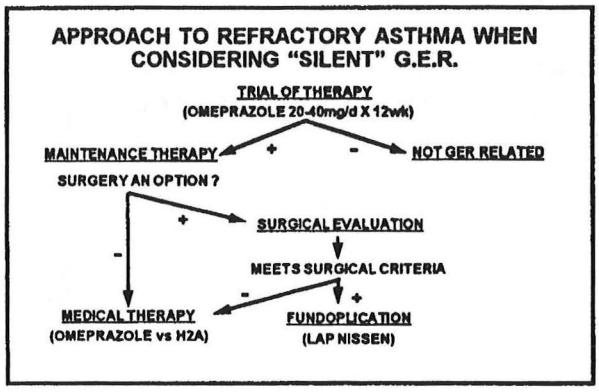
The asthmatic who does not have overt evidence of GERD may deserve special attention. Given the high prevalence of "silent" GER and the potential for improvement, even with conservative treatment, it would seem reasonable to suggest to all asthmatics that they undertake the usual GER life-style changes outlined above. Asthmatics whose respiratory disease is not well controlled should be approached in a systematic fashion, focusing on proper use of medications and avoidance and/or treatment of identifiable triggers (see table). This approach should be successful in most patients (208,209). Only after an exhaustive search for other causes of refractory asthma should "silent" GER be pursued.

REFRACTORY ASTHMA:
FACTORS TO ADDRESS

- KNOWLEDGE/USE OF MEDICATIONS
- PROPER USE OF M.D.I., ADD SPACER
- AVOIDANCE OF TRIGGERS/ANTIGENS
- AVOIDANCE OF CONFOUNDING DRUGS
- OCCUPATIONAL EXPOSURES
- SINUSITIS
- G.E.R.
- ALTERNATIVE DIAGNOSIS

For the reasons stated above, my preference in the small number of patients who reach this point would be to undertake a trial of intense acid-suppressive therapy. As the goal is to establish if the patient's asthma is related to GER and to see if treatment will result in improvement, this trial should preferably start with the most effective treatment. As such I would recommend using omeprazole 20-40 mg/day and continuing treatment for 12 weeks. During this interval, the patient's symptoms, use of medication, and peak expiratory flow should recorded frequently. Pulmonary

function tests should be done before and at the end of the trial, though as noted, this may be an insensitive indicator. If the patient's asthma does not respond to this trial of therapy, then it is highly unlikely that the asthma is related to GER.



If the patient responds to this trial of therapy, then a decision regarding maintenance therapy will need to be made. The risks and benefits of each approach should be discussed. Medical therapy has the advantages of ease of use, reversibility, and ready availability; however, the patient will likely require life-long treatment at considerable cost. While long-term suppressive therapy (including omeprazole) appears to be safe to date, concerns regarding the long-term use of omeprazole in particular have been raised (169-175) and should at least be considered. Surgery may be associated with better asthma control in some, though Harding's recent data regarding the efficacy of intense acid suppression suggests that prior comparisons with medical therapy have been inadequate. Surgery may free or reduce the patient from the need for frequent medication use; long-term costs may be less. Surgery, including laparoscopic procedures, entail some morbidity and at least the potential for mortality. Advances in this area may improve the morbidity associated with surgery; length of hospital stay has clearly already been improved. Laparoscopic surgery should ideally be performed by those with significant experience in the Nissen procedure; this will limit its availability.

MAINTENANCE THERAPY FOR G.E.R.: MEDICAL vs SURGICAL

	ADVANTAGES	DISADVANTAGES
MEDICAL	EASY TO ADMINISTER REVERSIBLE NO MORTALITY READILY AVAILABLE	NEED FOR DAILY Rx LIFE-TIME COST TUMOR INDUCTION (?) B-12 DEFICIENCY (?)
SURGICAL	BETTER CLINICAL RESULTS REDUCED MEDICATION "ONE-TIME" COST	LIMITED AVAILABILITY SURGICAL MORBIDITY POTENTIAL MORTALITY LONG-TERM FAILURE (?)

If the patient believes that surgery may be a desirable option, then at that point a more detailed evaluation is in order. These patients should have the presence of GER clearly established via endoscopy (and pH monitoring if needed). The presence of a long stricture segment precludes laparoscopic surgery and thus patients should be evaluated by endoscopy (with/without barium swallow). Esophageal manometry is needed to determine if the patient has a hypotonic LES and to identify associated motility disorders. A significant motility disorder would indicate the need for a

modification of the Nissen procedure. Patients who are not candidates for surgery should be managed medically, though the ideal maintenance treatment is as yet not known.

SURGICAL EVALUATION PRIOR TO FUNDOPLICATION

DIAGNOSTIC EVALUATION	IDEAL SURGICAL CHARACTERISTICS
ESOPHAGOSCOPY (+/- pH MONITORING)	CONFIRMED PRESENCE OF GER
(+/- BARIUM SWALLOW)	ABSENCE OF LONG STRICTURE
ESOPHAGEAL MANOMETRY	HYPOTONIC L.E.S.
	ABSENCE OF MOTILITY DISORDER

CONCLUSIONS

There is a strong association between gastroesophageal reflux and asthma. Most patients with asthma have pathologic GER, though many lack the typical symptoms of reflux. The two disorders likely interact, one with another; both have the potential for worsening each other. Although some patients undoubtedly may experience symptoms due to aspiration of refluxed material and direct irritation of bronchial tree, the most likely mechanism of interaction is through the neural modulation of bronchial tone and/or reactivity from prolonged afferent irritation from the distal esophagus.

While GER may exacerbate asthma, it is unlikely that it causes asthma de novo and it is worth remembering that the clinical effect is small in the majority of patients with co-existent disease. Nonetheless, a small, but potentially important group of patients have refractory asthma exacerbated by GER. The best test for a clinically relevant association between GER and refractory asthma is a prolonged trial of intense acid-suppressive therapy. The ideal maintenance therapy in GER-associated asthmatics is as yet not known, but surgery may be a desirable option in selected patients.

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