HEARTBURN

University of Texas
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Internal Medicine Grand Rounds

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K.G. is a 57 year old white woman who was refered in November of 1991 by her Internist for evaluation of long standing heartburn. She gave a history of more than twenty years of burning substernal chest pain that would generally occur one to three hours after each meal and occasionally awaken her from sleep at night. The pain occurred daily, though there would be intervals lasting from weeks to months during which her symptoms subsided. She discovered twenty years ago that antacids taken in either liquid or tablet form provided immediate but temporary relief. Beginning in the late 1970's, she was prescribed cimetidine in doses ranging from 800 to 1200 mg per day. The cimetidine reduced her symptoms markedly, but never completely relieved the heartburn. Moreover, immediately upon discontinuing the drug, her symptoms would return as they had been before.

Her past history is notable for a bipolar disorder which has been well controlled with medical therapy. She gives a remote history of heavy alcohol consumption and continues to smoke one half of a pack of cigarettes daily.

Most recently, she was treated with ranitidine 300 mg twice daily for a period of 8 weeks. She noted a substantial improvement in her symptoms while on the medication; however, her heartburn returned within one week of completing the drug treatment.

Her physical examination was unremarkable with the exception of mild obesity.

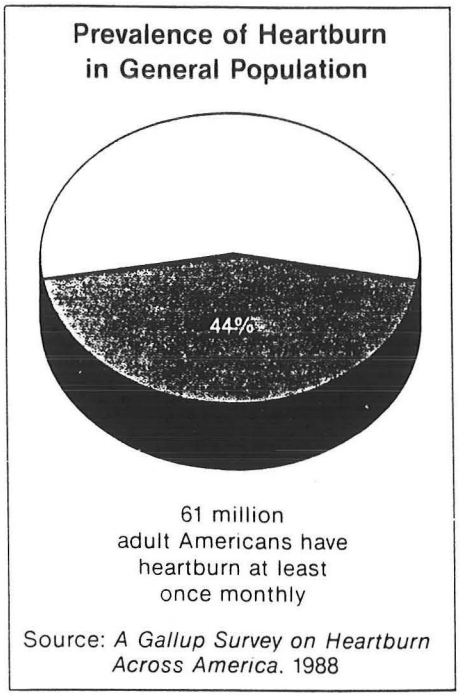
She underwent an upper endoscopy at which time a small sliding hiatal hernia was identified as well as an obvious Barrett esophagus. Additionally, deep linear erosions were present in the body of the esophagus both proximal and distal to the squamo-columnar junction. Multiple biopsies taken of the esophagus revealed acute inflammation and specialized columnar epithelium consistent with a Barrett esophagus. Additionally, moderate dysplasia was present in all biopsy specimens.

She was started on omeprazole 20 mg daily for 12 weeks and noted complete relief of all heartburn within one week of commencing the drug. She underwent a follow-up endoscopy upon completion of her 12 week course at which time the erosive esophagitis had healed leaving her with an uninflammed Barrett esophagus. The second set of biopsies (taken after the esophagitis had healed) revealed no dysplasia.

Having completed the maximum approved duration for omeprazole therapy, she was switched to ranitidine 300 mg twice daily, but relapsed with recurrent heartburn within six weeks. At the present time, she is in her third course of omeprazole therapy and continues to report excellent symptomatic relief. She is however, concerned about the high cost of the drug ($110 per month) as well as the potential risk of long-term drug therapy and the uncertain prognosis associated with her Barrett esophagus. A surveillance EGD is planned for January 199

PREVALENCE

Heartburn is ubiquitous(1). Although the complications illustrated by the above case occur in only a small fraction of the patients with heartburn, nonetheless, the sheer numbers of people with symptoms due to reflux disease warrant careful scrutiny of the problem(2). Indeed, reflux symptoms are among the most common complaints encountered by primary care physicians(3) and gastroenterologist alike(4).



In a random poll of 800 adults conducted by the Gallup Organization, 19% of the respondents stated that they had experienced heartburn more than three times in the previous month(5). A total of 44% reported heartburn at least once in the previous month. In that same survey, 18% reported that they used antacids on a routine basis but only 11% stated that they had consulted with their physician about these symptoms. Extrapolating these data to the general population, more than 60 million Americans admit to having heartburn at least once a month.

A more conventional study of disease prevalence was conducted in the 1970's at the Philadelphia Naval Hospital(6). A total of 1004 individuals took part in this survey. The individuals were selected to represent a cross section of an inpatient and outpatient population. Specifically, 335 were normal controls, 246 medical inpatients, 200 surgical patients, 121 gastroenterology clinic outpatients and 102 patients attending the obstetrics and gynecology Clinic. Overall, 11% of the patients reported daily heartburn. Another 12% reported weekly heartburn and 15% reported heartburn on at least a monthly basis. Among pregnant patients, the prevalence of heartburn was 25%.

These studies illustrate the wide variability in the frequency of symptoms(7) and point to the need for standard definitions as to which patients can be said to have "disease" as opposed to merely suffering from the "aches and pains of daily life".

DEFINITIONS

Heartburn is a useful word. It is familiar to lay people and physicians alike and does not require a lot of interpretation. The medical term for heartburn is **pyrosis** and is defined as a burning substernal or epigastric pain that typically occurs within a couple of hours of eating a meal(8). Some patients will report a positional component to the pain noting that it occurs after bending over or upon lying down. The patient will often have already noted that the pain is instantaneously (but only temporarily) relieved with antacids.

Regurgitation is defined as the effortless backward flow of liquid or food from either the esophagus or stomach into the pharynx. Effortless regurgitation should be distinguished from true vomiting which is a substantially more complicated physiologic process. Regurgitation is often accompanied by sour taste.

Water brash is defined as the abrupt sensation of having excess salty liquid in the mouth. The symptom is brought on by parasympathetic stimulation of the salivary glands resulting in hypersecretion of a sodium rich saliva. It should be noted that water brash is not synonymous with regurgitation(8).

Indigestion is a term familiar to most lay people but unfortunately lacks the specificity of a good word like heartburn. Bloating, abdominal pain, nausea and belching are all symptoms that may be lumped under the general term indigestion. If a patient complains of indigestion, they should be asked to specify exactly what they mean.

Dyspepsia is a term which is unfamiliar to most lay people and suffers from inconsistent usage among physicians. Until physicians can agree upon what it means, its usage should be discouraged.

Gastroesophageal reflux (hereafter abbreviated by the acronym **GER**) is defined as the physiological act of the reflux of liquid from the stomach into the esophagus(9). GER by itself occurs in normal people everyday , and does not imply any disease state.

Gastroesophageal reflux disease (hereafter abbreviated by the acronym **GERD**) is best defined as the presence of any symptoms or pathologic lesions due to GER. Hence, GERD is a clinical diagnosis that can be made on the basis of symptoms alone(10, 11). Confirmatory tests may be helpful in firmly establishing the diagnosis but are not required. Denoting "**GERD by history**" is a useful shorthand for stating that the diagnosis was made on the basis historical features alone(12). Not only can the diagnosis of GERD be made in the absence of any confirmatory tests , it can also be made when those tests were done and came back normal. For example . One-half of all patients with symptoms of GERD will have a normal endoscopic and histologic appearance of the esophagus(6, 13). If these patients are studied by ambulatory esophageal Ph monitoring, it is usually found that their episodes of heartburn did indeed correspond to an episode of GER.

Reflux esophagitis, on the other hand, does imply the presence of tissue damage(14). This means that the term reflux esophagitis should be reserved for those situations in which either a barium esophagram

or an upper endoscopy shows erosions or ulcerations or biopsies of the esophagus show the characteristic histologic changes of esophagitis(15).

PATHOPHYSIOLOGY

Twenty-five years ago, the pathogenesis of GERD was commonly assumed to be secondary to the presence of a sliding hiatal hernia(16, 17). Indeed, the usual diagnostic evaluation of patients with heartburn was a barium meal in an effort to demonstrate a hiatal hernia(18). If one was found, then the next approach was generally a surgical "repair " of the hiatal hernia.

As recently as ten years ago, the pathogenesis of GERD was thought to be a lax, hypotensive lower esophageal sphincter due to an intrinsic weakness in the sphincter muscle(19). Now however after a decade of excruciatingly tedious manometric studies of the lower esophageal sphincter(20, 21, 22, 23, 24, 25, 26, 27), a consensus has emerged that *the fundamental defect in GERD is abnormal neuromuscular control of the lower esophageal sphincter* with multiple mitigating factors including rates of acid secretion, esophageal peristalsis and gastric emptying.

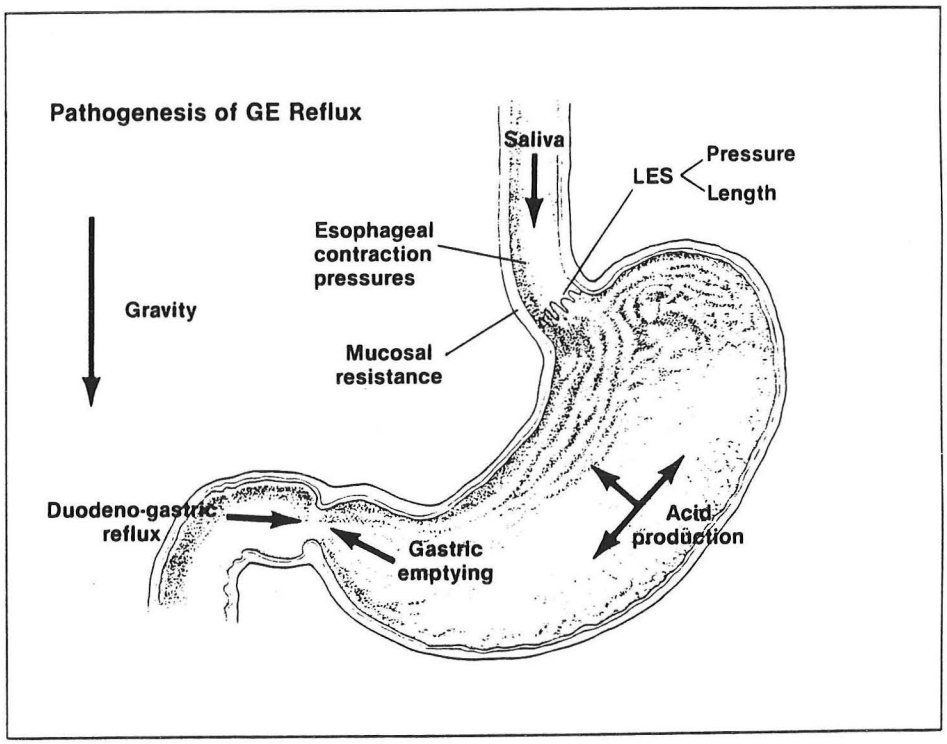
Offensive factors

GERD is part of the spectrum of acid-peptic disorders. It is a peculiarity of the field of gastroenterology that so many of the patients that we treat with gastrointestinal diseases suffer from the consequence of their own stomach's production of hydrochloric acid. If one considers the anatomical distribution of all gastrointestinal pathology occurring in the population, one is struck by the clustering of lesions immediately proximal and distal to the stomach(28). Both of these disorders (duodenal ulcer and GERD) require the presence of acid. The high prevalence of acid related diseases begs the teleological question "Why is there acid?".

Clearly, given the deleterious consequences, acid secretion must have conferred a distinct selective advantage in our past evolution. Although acid aids in the digestion of food, the absence of acid in an achlorhydric patient does not seem to result in any significant malabsorption. Probably the single most important function of gastric acidity is the partial sterilization of food and water that may be grossly contaminated with bacteria.

Whatever the reason, the parietal cells in the body and the fungus of the stomach efficiently secrete large quantities of hydrochloric acid (against a million fold concentration gradient) into the lumen of the stomach with each meal(18).

Three substances mediate the parietal cells acid secretion. First, **histamine**, secreted in a paracrine manner from nearby mast cells, binds to specific histamine receptors and plays a permissive role in acid secretion. **Acetylcholine,** released from efferent fibers in the vagus nerve, binds to muscarinic receptors on the parietal cell during the cephalic phase of acid secretion. Complete denervation of the parietal cell by means of a vagotomy reduces meal stimulated acid secretion by approximately one-third. Finally, **gastrin**, produced in the antrum and duodenum in response to the presence of fat or protein in the lumen, binds to gastrin receptors on the parietal cell and ultimately results in stimulation of the hydrogen-potassium ATP'ase (proton pump) located on the apical membrane.



The proteolytic enzyme pepsin is secreted by chief cells in the gastric mucosa in a manner that generally parallels that of the parietal cells acid secretion. Pepsin has proteolytic activity at an acid pH.

The combination of hydrochloric acid in pepsin makes gastric juice a potent substance capable of marked tissue injury(3, 6, 29, 30). However, the quantity of acid secretion is within a normal range for most patients with GERD; rather, the primary pathogenetic event is a failure of the anti-reflux barrier.

Defensive mechanisms.

Given the noxious characteristics of the acid-pepsin mixture in the stomach, the body has three mechanisms for defending the lowering esophagus against acid-peptic injury(20, 25, 31). These are the lower esophageal sphincter (LES), luminal clearance and finally epithelial resistance.

Lower esophageal sphincter

The traditional view has held that the lower esophageal sphincter is not a true sphincter in the anatomical sense, but rather a zone of tonically increased pressure in the distal esophagus that serves as a barrier to reflux. More recent studies done on fresh human cadavers have shown a distinct asymmetrical muscular thickening in the distal esophagus corresponding to an anatomical sphincter. Other investigators have emphasized the role of the crural diaphragm as an anti-reflux barrier(25). They have proposed that the diaphragmatic crura presses against the esophagus during inspiration while the lower esophageal sphincter itself provides the anti-reflux barrier during expiration. In any case, from a functional point of view, the efficiency of the barrier is dependent upon both the amplitude of the pressure applied to the esophagus and the length over which the pressure is applied. Moreover, it is essential that at least a portion of the lower esophageal sphincter be in the abdomen rather than the thorax(27, 32).

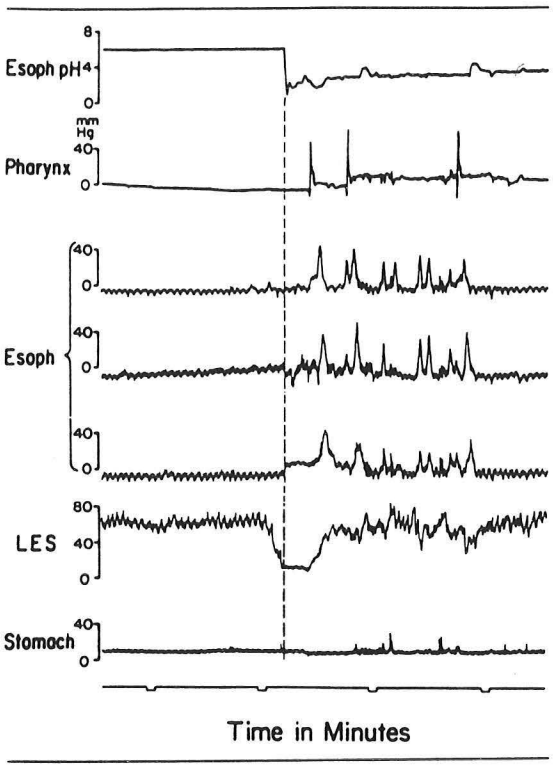
DeMeester and colleagues(27) have performed meticulous manometric studies of the lower esophageal sphincter in 50 normal subjects. From their studies, they have determined that the median pressure in normal subjects is 13 mm Hg with an overall length of 3.6 cm and an abdominal length of 2 cm. The lower limits of normal (below which a diagnosis of an incompetent LES can be made) are a pressure of 6 mm and an overall length of 2 cm and an abdominal length of 1 cm.

Table. Normal Manometric Values for LES Pressure, Overall Length, and Abdominal Length

		Percentile	
	Median	***2.5***	***97.5***
Pressure (mm Hg)	13	5.8	27.7
Overall length (cm)	3.6	2.1	5.6
Abdominal length	2	0.9	4.7

In general, most patients with complications of GERD such as Barrett, strictures or erosive esophagitis will have a manometrically demonstrable incompetent LES. However, many patients with mild or moderate symptoms of GERD will have a normal esophageal manometric study(20, 22).

The problem in trying to relate GERD symptoms to static measurements of basal LES pressure is that the pressure does not remain constant over time. Rather, even in normal subjects, the LES will transiently relax to a pressure of zero. This phenomenon, known as LES transient(23) relaxation was not appreciated until the technology became available to monitor a patients LES pressure (or distal esophageal pH) over prolonged periods of time. Shown at right is a simultaneous esophageal pH and pressure recording. The dashed line marks the onset of GER. Note that GER did not occur until the LES pressure had fallen to zero. While normal subjects display LES transient relaxation perhaps once every hour, GERD patients may demonstrate prolonged LES transient relaxations many times each hour.



Thus, the fundamental defect in most patients with GERD is not a structural abnormality in the LES leading to a "lax sphincter" but, rather a defect in the neuromuscular control of the sphincter allowing frequent, prolonged LES transient relaxations.(33, 34, 35)

Gastric emptying, though not an anti-reflux barrier per se, nonetheless aids in the prevention of reflux by removing from the stomach the noxious factors(36). In general, it has not been possible to show that gastric emptying is delayed in reflux patients as compared to normal controls.

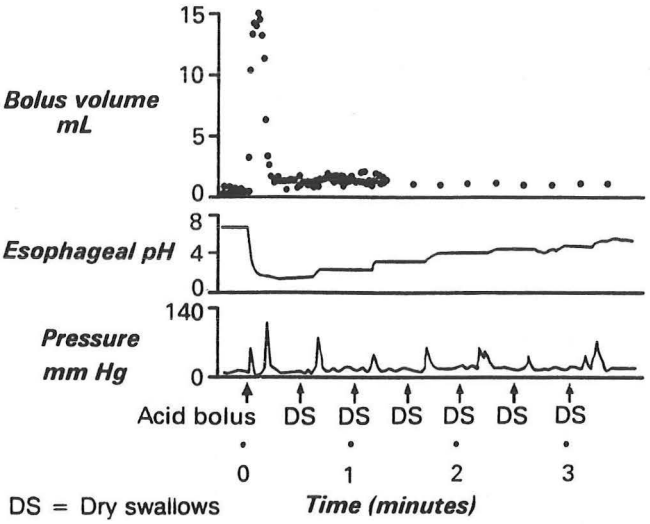
Luminal clearance

When the anti reflux barrier breaks down and gastric contents flow into the esophagus, the rate of luminal clearance determines the duration of acid exposure. Three factors may aid in clearing the esophagus of refluxed material. In the upright position, gravity assists in luminal clearance, but unfortunately, is of no help when lying in bed or on the sofa.

Peristaltic activity is the primary mechanism whereby the esophagus clears refluxed material(31). The refluxed bolus distends a segment of the esophagus which is sensed by stretch receptors in the esophagus wall. Via the myoenteric plexus of nerves within the muscular layers of the esophagus, a peristaltic wave is initiated (proximal to the distended segment) which pushes the bolus back into the stomach. It has been clearly shown that patients with GERD have an impairment in peristaltic clearance of refluxed material(37). Accordingly, the duration of exposure of the esophageal mucosa to the refluxed acid is longer in GERD patients when compared to controls. What is not known, is whether the impairment in peristaltic clearance is the cause or the result of esophagitis(23). If the latter were the case, then the development of esophagitis would lead to a downward spiral in which esophagitis leads to impaired luminal clearance which leads to more esophagitis etc.. Recent studies however, have shown that peristaltic clearance remains impaired even after the esophagitis has been healed by anti-secretory drugs(38).

Swallowed saliva is an important factor in determining the rate of esophageal clearance(39). Though the buffering capacity of saliva is only modest, studies have shown that when a small bolus of acid is infused into the distal esophagus, each dry swallow of saliva results in a small increment in the esophageal pH back toward neutrality. If the saliva is expectorated or aspirated, the esophageal pH remains low despite repetitive dry swallows(39, 40). This simple observation provides a teleological explanation of water brash.

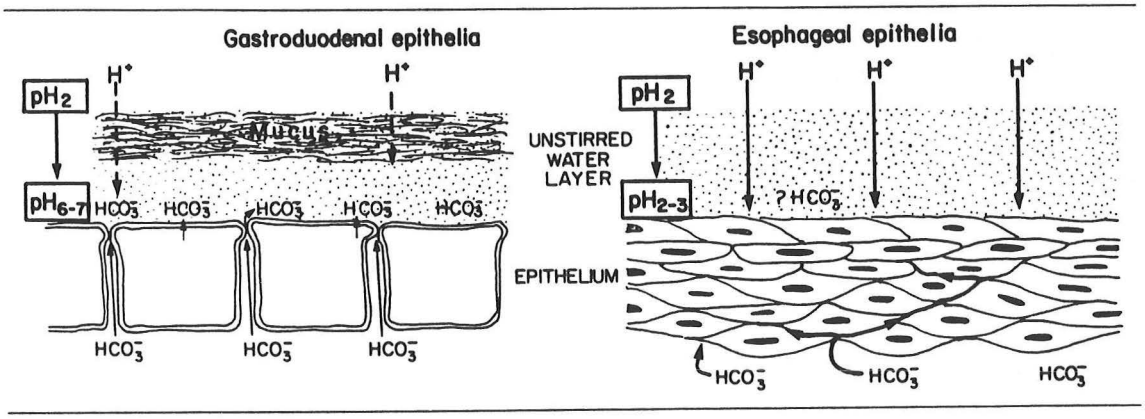
Effect of Peristalsis and Saliva on Esophageal Acid Clearance and Emptying of Fluid Volume



(Reprinted with permission from Helm et al.[3])

Epithelial resistance

Though much is known regarding mucosal defense mechanisms against acid-peptic injury in the gastric and duodenum mucosa, surprisingly little is known about similar mechanisms at work in the distal esophagus. It would appear that mucosal defenses in the esophagus are rather primitive when compared to those in the stomach and duodenum.



First and foremost, there is no mucous layer protecting the esophagus(39). The only physical barrier is an unstirred layer of water through which protons may freely diffuse up to the epithelial cell. Whereas in the stomach and duodenum, the epithelial secretion of bicarbonate buffers surface acid and produces a gradual pH gradient between the lumen and the epithelial surface, in the esophagus, the pH at the mucosal surface is essentially the same as it is in the lumen. Tight junctions between the squamous epithelial cells serve as a partial barrier to the diffusion of protons, however, the tight junctions are not totally impermeable and if the concentration gradient is great enough (i.e., the pH is low enough) then penetration occurs(39). In animals studies, tight junctions may remain relatively impermeable to protons at a pH at 2.0, but become freely permeable when the pH is lowered to 1.0.

Once hydrogen ions have penetrated into the mucosa, bicarbonate derived from the blood appears to be the major buffer. Accordingly the mucosal blood flow may be an important determent of the degree of tissue injury(39).

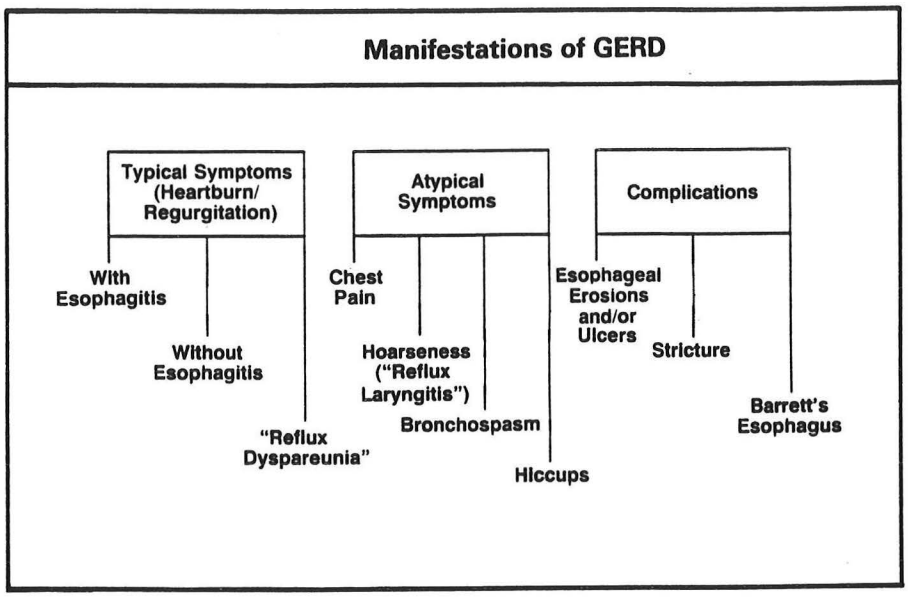
It is not known whether those patients with esophagitis have it because they have an intrinsic defect in mucosal defenses or simply because the mucosal defenses were overwhelmed by the intensity and duration of acid exposure.

CLINICAL MANIFESTATIONS

The clinical manifestations of GERD are protean. They range from trivial heartburn to a lingering death from adenocarcinoma of the esophagus. A useful way to classify the clinical spectrum is to divide the patients into those with typical symptoms, those with atypical symptoms, and those with complications of GERD(6).

Typical symptoms:.

Heartburn is by far the most common symptom associated with GERD, occurring in half of all patients. Effortless regurgitation and water brash are also common symptoms. Dysphagia, particularly if it is progressive, suggests a complication of GERD such as a peptic stricture or carcinoma. Odynophagia is rare in uncomplicated GERD and suggests the possibility of an infectious esophagitis such as candidiasis or herpes simplex.



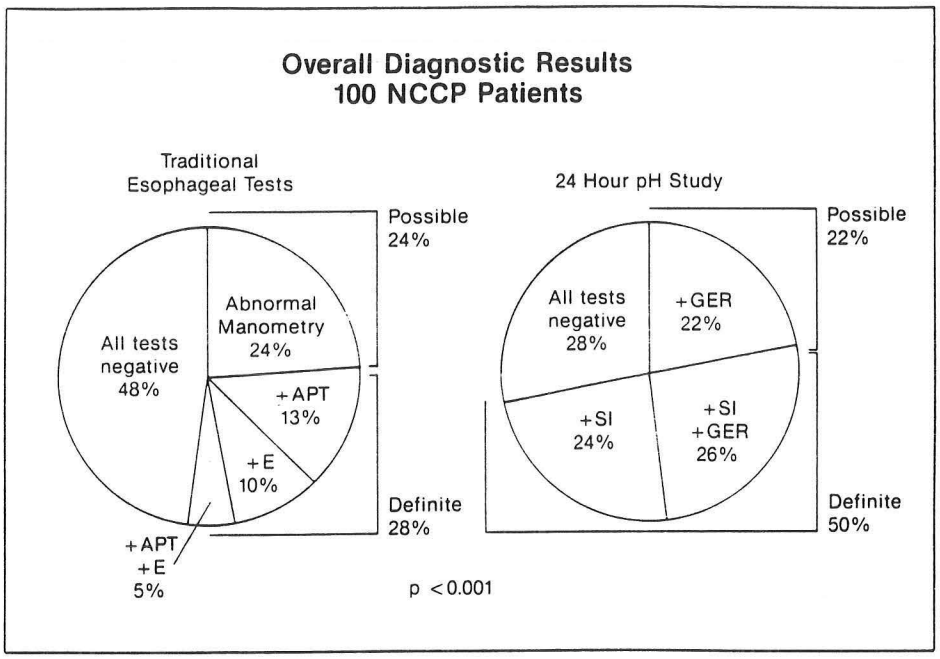
It should be emphasized that all of these typical symptoms may occur in the presence or absence of actual esophagitis. It is impossible to predict on the basis of the severity of symptoms whether esophagitis is present. Depending on the population being examined, up to half of the patients with classic GERD symptoms will not have endoscopic or histologic evidence of esophagitis(18, 41).

Reflux dyspareunia is a recently recognized symptom of GERD(42). The definition of reflux dyspareunia is typical heartburn occurring during sexual intercourse. In one prospective study, 77 of 100 women with known GERD reported reflux type symptoms during intercourse. Conservative measures (avoidance of the missionary position) produced improvement in 61 of the 77 women(42).

Atypical symptoms:

Noncardiac chest pain (NCCP): Each year, approximately 600,000 Americans undergo coronary angiography and it is estimated that between 10 and 30 percent of these are found to have no significant coronary disease(5, 43, 44). Typically the patients are diagnosed as having noncardiac chest pain and are reassured that nothing serious is amiss. However, the symptoms generally continue and the patients continue to seek medical care. In the past, the next diagnostic evaluation was often an esophageal manometry study in an effort to document the presence of diffuse esophageal spasm or a nutcracker esophagus as an explanation for the chest pain. However, these studies were often equivocal or nonspecific. The recent application of ambulatory esophageal pH monitoring to these patients has shown that in approximately 50 percent of these patients, the symptoms of chest pain definitely correlates with an episode of GER.

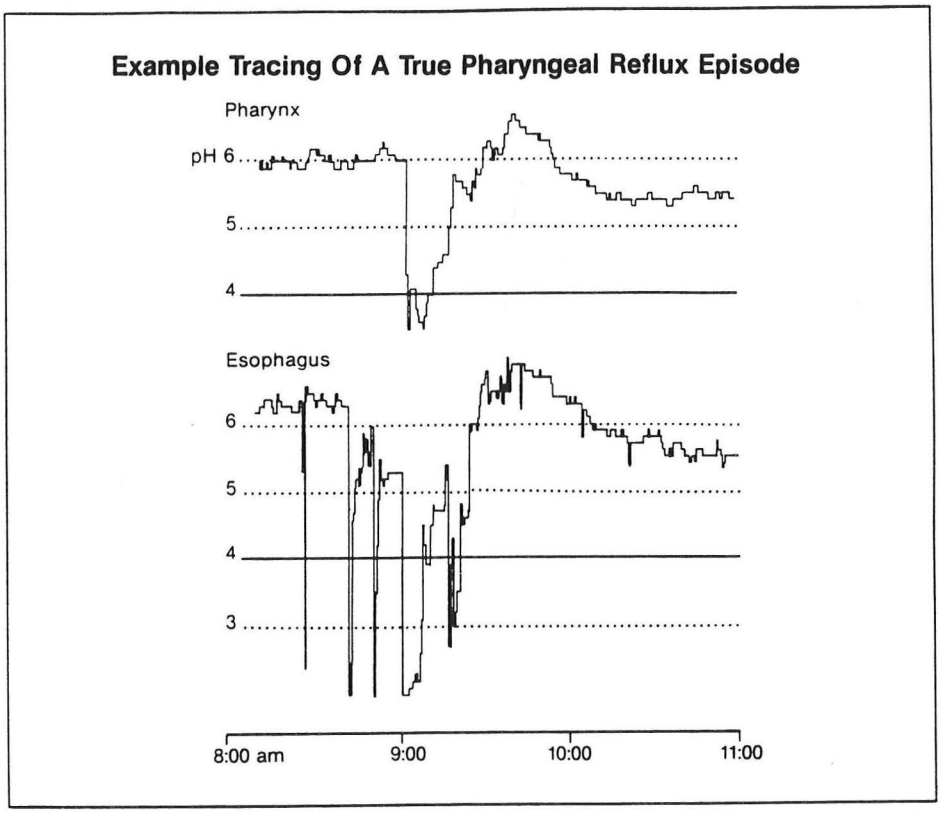
In a study by Richter(44) of 100 consecutive patients referred (after cardiac catheterization) for evaluation of non-cardiac chest pain, all patients underwent traditional testing of esophageal manometry, acid perfusion test (APT) and provocative testing with edrophonium (E) as well as a 24 hour pH study. A definite diagnosis was made only if the chest pain was replicated by provocative testing or was associated temporally with an episode of GER (symptom index, SI +). As shown at the right, an ambulatory pH study was far superior at establishing a diagnosis of GER as the cause of the NCCP.



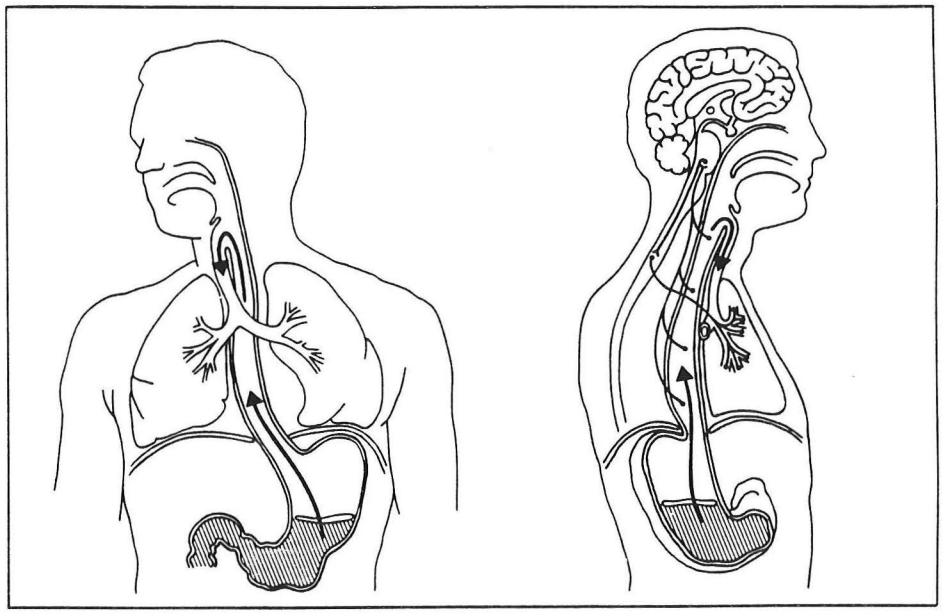
The primary utility of ambulatory pH monitoring is that the technique allows a symptom that may occur only sporadically to be correlated with a measurable physiologic event, namely acid reflux. Interestingly, in half the patients, the frequency and duration of the episodes of acid reflux were not severe enough to be called abnormal. Nonetheless, the chest pain clearly occurred only during episodes of acid reflux. Thus, some patients with noncardiac chest pain may be hypersensitive to physiologic episodes of GER(5, 44).

Laryngeal symptoms: Hoarseness and habitual throat clearing have been related to GER in some patients(45, 46, 47). The frequency in which these symptoms are actually due to the GER is not known. The mechanism is thought to be not GER but rather gastropharyngeal reflux with direct acid irritation of the larynx or trachea.

Actual demonstration of gastropharyngeal reflux by placement of pH probe above the upper esophageal sphincter(5) in these patients have been difficult to demonstrate, bringing into question the relationship between the symptoms and GER. Nonetheless, a subset of these patients will respond to drugs directed at inhibiting acid secretion. An example of gastropharyngeal reflux is shown at right(5). Some investigators have proposed that laryngeal carcinoma may be a consequence of chronic acid injury(47).



Pulmonary symptoms: The relationship between asthma and GER has been extensively studied over the past several years(48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58). When carefully looked for by ambulatory pH monitoring, from 30 percent to 80 percent of asthmatic patients have been found to have an excessively high frequency and duration of acid reflux(58).



Two mechanisms have been proposed to explain the connection between reflux and asthma(5). Bronchospasm may occur from direct reflux of gastric contents into the airway (left) or as a reflex response to the stimulation of esophageal receptors by refluxed acid(right). Despite the application of sensitive techniques such as proximal esophageal pH probes and radionuclide scanning, it has been extremely difficult to document gastropulmonary reflux in most cases. A second possible mechanism postulates the existence of a reflex pathway involving signals from acid receptors in the esophagus being carried via afferent vagal fibers to the vagal nuclei in the brainstem which then stimulates a reflex bronchospasm mediated by vagal efferents to the lungs. Such a reflex could have a protective effect by initiating pulmonary defenses against GER before aspiration occurred(48, 59). An alternative explanation of this so called esophagobronchial reflex is that it is not a reflex at all but rather a classic Pavlovian conditioned behavioral response to GER. In this case, the stimulus is recurrent bouts of microaspiration that eventually conditions the patient to cough in response to any sensation of GER. Clearly, there are several plausible explanations for the connection between GER and asthma or

coughing(48). Those asthmatics most likely to have GER as a component of their disease include a) adult onset asthma (particularly in the absence of antecedent allergic symptoms) or b) asthma that worsens postprandial or at night(5).

Hiccups: refractory, unrelenting hiccups in otherwise healthy individuals may be due to unrecognized GERD(60).

Unfortunately, for most of the above atypical manifestations of GERD, the response to therapy with potent antisecretory drugs has not been nearly effective as when the same drugs are used to treat typical symptoms of GERD.

Complications:

Erosions and Ulcerations: Severe erosive esophagitis is considered a complication of GERD, usually presenting with daily pyrosis. Frank gastrointestinal bleeding and iron deficiency are uncommon manifestations. Deep esophageal ulcers are less common than erosions and may present with continuous epigastric pain that mimics PUD of the stomach or duodenum. Additionally, odynophagia, which is uncommon in uncomplicated GERD is frequently present in patients with esophageal ulcers(61). A deep ulceration in the mid-esophagus suggests the presence of Barrett metaplasia and always warrants biopsy to exclude adenocarcinoma.

Patients with GERD complicated by severe erosions or ulcerations are extremely difficult to treat and will almost invariably require potent anti-secretory medication. Even then, the relapse rate exceeds 80% within six months.

Strictures: A subset of patients with GERD complicated by ulceration have a propensity to heal the ulcer with excess fibrous tissue leading to the insidious onset of solid food dysphagia. The progression is usually over a period of months or even years and, in contrast to malignant strictures, is usually not associated with significant weight loss(61). Treatment is vigorous antisecretory medication (usually omeprazole) along with dilation of the stricture. Relapse is the rule unless medical therapy is continued.

Barrett esophagus: Barrett esophagus is a acquired lesion resulting from long standing acid reflux in which the squamous mucosa lining the distal esophagus undergoes a metaplasia into columnar mucosa that resembles the mucosa in the stomach or small intestine(61). Histochemical stains clearly show that Barrett esophagus is a true metaplasia and not the simple encroachment of gastric mucosa into the esophagus. The diagnosis is made endoscopically by observing displacement of the squamo-columnar junction more than 2 cm proximal to the esophagogastric junction and must be confirmed by endoscopic biopsy.

The exact prevalence of Barrett metaplasia is not known, but approximately five to ten per cent of patients undergoing endoscopy for GERD will be found to have the lesion.

There is considerable controversy as to the natural history of the lesion. Some initial studies suggested that the risk of developing adenocarcinoma was up to 50% in Barrett esophagus(62), but that figure is undoubtedly a gross overestimate as many of the patients had been referred for evaluation of dysphagia and an adenocarcinoma was discovered at the same time that the diagnosis of Barrett esophagus was made. While knowing the lifetime prevalence of adenocarcinoma in Barrett's may be interesting from an epidemiologic point of view, in caring for individual patients with Barrett's, it would be more useful to know the annual incidence of adenocarcinoma in those individuals who do not have carcinoma at the time the diagnosis of Barrett's was made.

By combining data from six different studies done since 1984, the annual incidence of adenocarcinoma is approximately 500 cases per 100,000 patients at risk per year(61). *Thus, a Barrett's patient with a life expectancy of 20 years has a life time risk of approximately 10%. of developing adenocarcinoma.*

At the present time, it is not known whether medical therapy directed at healing esophagitis will reduce the risk of subsequent adenocarcinoma(63). Surveillance endoscopy in Barrett's is a controversial strategy based on the premise of detecting either early carcinomas or dysplastic epithelium with a high probability of subsequent carcinoma and intervening with an esophagectomy. The controversy revolves around the twin issues of the low cost-effectiveness of surveillance and the high risk-benefit ratio of surgery. In my opinion, surveillance should be considered only in patients who are good surgical risks and who would consent to an esophagectomy if persistent, severe dysplasia is present.

DIAGNOSTIC TESTS

In patients with typical symptoms, and no suspicion of any complications (dysphagia, weight loss, blood loss) a diagnosis of GERD can be made on the basis of history alone. Empiric treatment can be initiated and expensive diagnostic testing can be reserved for those patients who have failed a trial of medical therapy or in whom a complication is suspected. A barium swallow, upper endoscopy and ambulatory pH monitoring are the three best tests available to confirm the diagnosis.

Radiography: A standard barium esophagram, usually done in conjunction with a full UGI series is a quick and inexpensive way to delineate the anatomy of the esophagus and the stomach. Hiatal hernias are readily seen as are most strictures of the esophagus. Peptic ulcer disease distal to the esophagus can be excluded with reasonable certainty at the same time. Additionally, unsuspected lesions such as esophageal diverticula or paraesophageal hernias can also be detected.

The main disadvantage to a barium esophagram is that it is frequently normal in the setting of GERD, even if the distal esophagus is inflamed. The sensitivity of a barium esophagram, even using double contrast, is very poor at detecting mucosal lesions such as esophagitis or Barrett metaplasia(32, 64, 65). Deep ulcerations in the esophagus may be detected but shallow erosions are often missed.

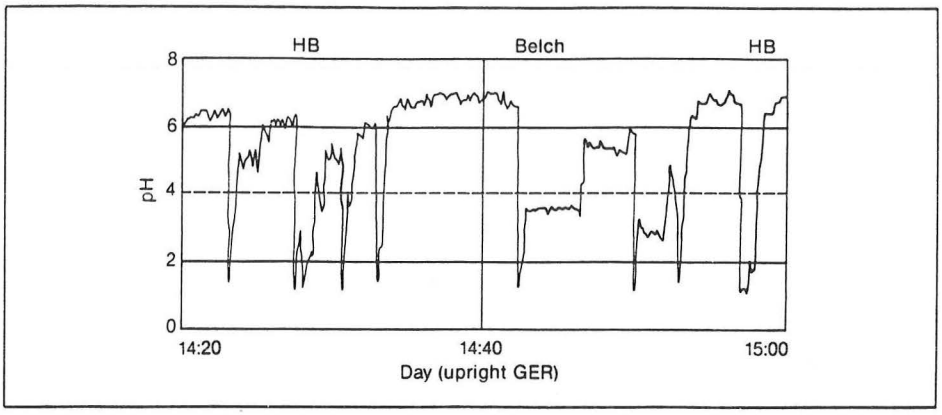
EGD: Esophagoscopy is by far the most sensitive test for detecting mucosal lesions. Mild grades of esophagitis can be readily detected and the diagnosis confirmed by endoscopic biopsies. In cases where infectious causes of esophagitis (such as herpes simplex virus or Candida) may be mimicking the symptoms of GERD, then endoscopy allows for identification (by culture or tissue stains) of the specific etiologic agent. If strictures or other are lesions are present, biopsies can be obtained and the lesion dilated if necessary, all at the same setting. Finally, like a barium swallow/UGI series, an upper endoscopy can exclude other upper gastrointestinal tract pathology.

The procedure is extremely safe with a serious complication rate of less than 1 per 1000. The main disadvantage to an upper endoscopy is that it is an invasive and expensive procedure.

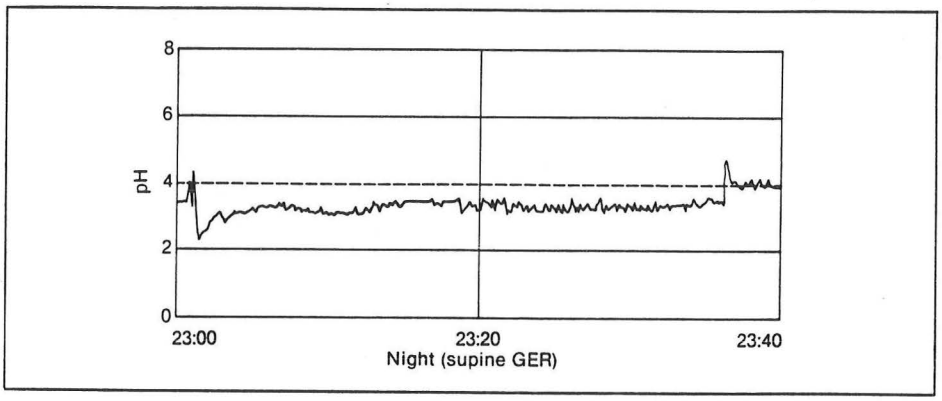
Ambulatory pH monitoring: In this test(66), a small catheter is placed through the nose and into the esophagus. Using manometry, the lower esophageal sphincter is identified and the pH probe is carefully positioned between 3 and 5 centimeters proximal to the LES. The tube is then taped into place at the nose and attached to a small pH recording device that is fastened to the patient's belt. The pH in the patients distal esophagus is then recorded four times each second for the next 24 hours.

The patient is advised to go about their daily activities and in fact encouraged to engage in any activities that ordinarily produce the symptom in question. Whenever symptoms do occur, be it heartburn, chest pain, etc.., the patient presses a button on the recording device and keeps a diary of what the symptoms were and how long it lasted. After 24 hours, the patient returns to the hospital to have the tube removed and the data from the recorder down loaded on to a micro-computer. The pH is displayed as a function of time and events are correlated (or not correlated) with episodes of GER.

Two typical tracings are shown at right(5). In the upper panel, a daytime refluxer is shown with with multiple episodes of GER that are rapidly cleared. Note that the symptom of heartburn coincides with a pH < 4.0.



In the lower panel, a nighttime reflux pattern is shown characterized by long periods of acid reflux owing to the supine position and lack of peristalsis during sleep.



In addition to correlating symptoms with pH, an overall assessment as to the severity of GER can be made by calculating the fraction of the total time that the pH was less than 4.0. This is calculated for the intervals that the patient was asleep, postprandial, etc.. thereby giving an indication as to whether the patient is predominantly a daytime or night time refluxer.

Despite the capability of quantifying the severity of acid reflux, the primary utility of ambulatory pH monitoring is in the evaluation of atypical symptoms to see if they correlate with episodes of GER.

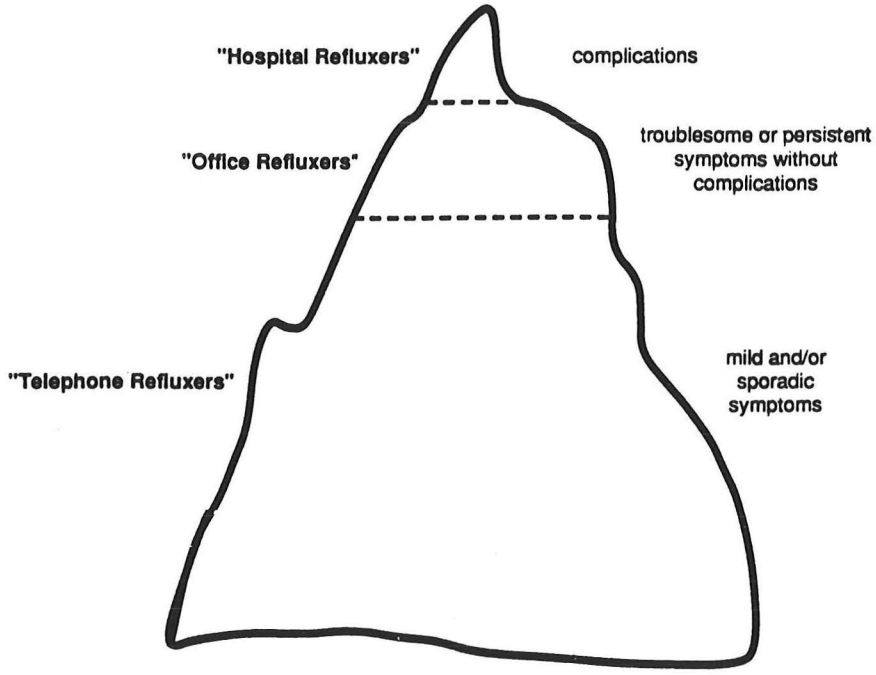
TREATMENT:

Lifestyle changes: Before the advent of effective antisecretory drugs, patients were often given advice to alter their lifestyle in such a way as to minimize the frequency and duration of acid reflux episodes(67, 68, 69). Elevating the head of the bed by at least six inches serves to pool nocturnal acid secretion in the body and the antrum of the stomach thereby minimizing acid reflux. The object of elevating the head of the bed is to keep the thorax at all times higher than the abdomen. Sleeping on several pillows only serves to keep the head and shoulders higher than the chest and is completely ineffective at reducing GER. Most patients find that placing blocks under the head of their bed is totally impractical. An alternative is a foam rubber wedge 40 inches in length and 10 inches high on one side. These devices can be purchased in the width of a single bed allowing for a noneffected sleeping partner to remain horizontal.

The patient should be instructed not to eat any food within 2 hours of going to bed. This is to minimize nocturnal acid secretion when the esophagus is most vulnerable to prolonged episodes of acid reflux. Specific foods that the patient has noted to cause heartburn should be avoided. On the other hand, it is not useful to give a long list of foods that <u>may</u> cause heartburn as the patient, when faced with such restrictions may give up on any dietary restraint at all. They should be encouraged to lose weight if they are over weight and advised to stop cigarette smoking at all cost(70, 71). The initiation of treatment for long standing heartburn is an excellent opportunity to begin a smoking cessation program.

While all the above measures are rational and prudent, by themselves, they are not likely to be effective for moderate or severely symptomatic GERD.

Antacids: Antacids provide immediate but temporary relief from heartburn. For many people with mild symptoms of occasional heartburn, antacids taken for symptomatic relief is all that is needed. Clinical trials comparing antacids with placebo have shown equivocal results with some trials showing no difference and others giving advantage to the antacid(72, 73). In any case, antacids are widely consumed in the general population (generally without consulting physicians) so patients must think that they work. Moreover, the easy availability of an inexpensive safe placebo that works one-third of the time is a useful therapy in itself.

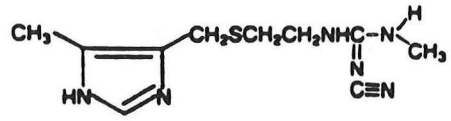


Alginates: Alginic acid containing products are a novel means of protecting the lower esophagus from acid reflux. Alginic acid is a naturally occurring carbohydrate extracted from certain species of algae that has the property of forming a viscus to semisolid gel when placed in water. Typically the alginic acid preparations taken for relief of heartburn (e.g. Gaviscon) contain potassium bicarbonate which, upon contact with gastric acid releases carbon dioxide gas which is entrapped in the alginic acid gel. A semisolid gas-filled raft floats to the fundus of the stomach thereby providing a physical barrier separating the distal esophagus from the hydrochloric acid in the stomach. Alginate preparations are effective only in the upright position. Thus, their main utility is found in the treatment of daytime heartburn(74). Anecdotally, they work well as prophylaxis against "joggers heartburn". Additionally, they may be a useful adjunct in the treatment of breakthrough daytime heartburn in patients being maintained on H2 blockers(74). Clinical studies have shown that alginate preparations relieve symptoms, reduce the frequency and duration of GER but by themselves do not heal esophagitis.

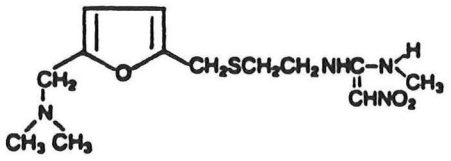
H2 receptor antagonists: As shown at the right(75), four drugs in this class are available in the United States. Except for differences in potency of acid suppression and duration of action, there are few significant differences between the four drugs. As a class, the H2 receptor antagonist have an almost unparalleled safety record(75).

Cimetidine, the first H2 receptor antagonist to become available, was developed for the treatment of peptic ulcer disease. Clinical trials established the minimum dose necessary to heal duodenal ulcers and similar doses were established for the other H2 receptors antagonist as they came on the market. Unfortunately, when clinical trials were set up to test the efficacy of H2 receptor antagonist for the treatment of reflux esophagitis, the same dose was used as was needed to treat peptic ulcer disease.

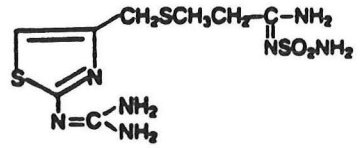
Cimetidine



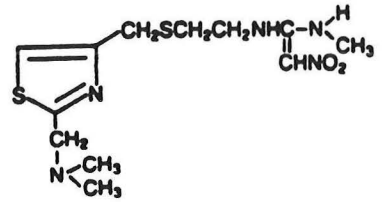
Ranitidine

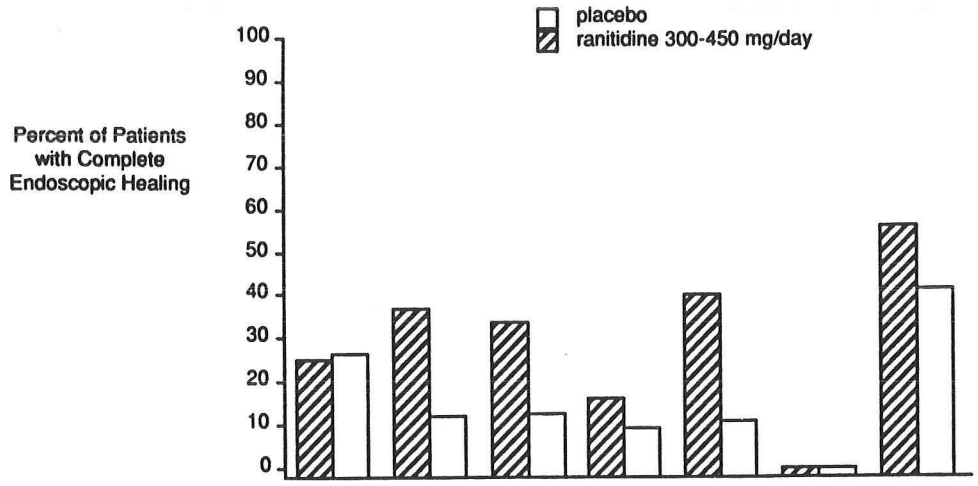


Famotidine



Nizatidine





The results of early trials on patients with proven reflux esophagitis treated by ranitidine or placebo are shown above(75). The dose of ranitidine varied among the studies from 300 to 450 mg per day and was given for 6 to 8 weeks. In five of the seven studies, the ranitidine healing rate was 2 to 3 times greater than the placebo healing rate. In the largest study, although 56 % of ranitidine treated patients healed, 41% of placebo treated patients also healed. These studies and others underscore the disappointing rates of complete healing achieved with standard doses of H2 blockers At standard doses, H2 receptor antagonist were only able to heal esophagitis in approximately 50% of the cases. When the dose of the H2 blocker was doubled, healing rates at 8 weeks went up to only the 60 to 70% range(75).

Proton pump inhibitors: Omeprazole, the only drug of its class currently available, is a potent inhibitor of the hydrogen-potassium ATP'ase located in the canalicular membrane of the parietal cell(28, 76, 77, 78). The drug is completely inactivated in the presence of acid and therefore must be given in an enteric coated capsule. No parenteral form of the drug is available.

The drug is readily absorbed in the pH neutral environment of the small intestine and has a very brief serum half life. However, the drug irreversibly binds to and permanently inhibits the hydrogen potassium ATP'ase. Accordingly, though the serum half life is very short, the pharmacological half life of the drug is 36 hours (not coincidentally the half life of the parietal cell). While H2 receptor antagonist given in standard doses will reduce acid output by about 60 to 70%, omeprazole given in the standard daily dose of 20 mg reduces acid output by 95%.

Efficacy: In every single study that has been done, comparing omeprazole to any other treatment of esophagitis, omeprazole has proven to be the superior agent.

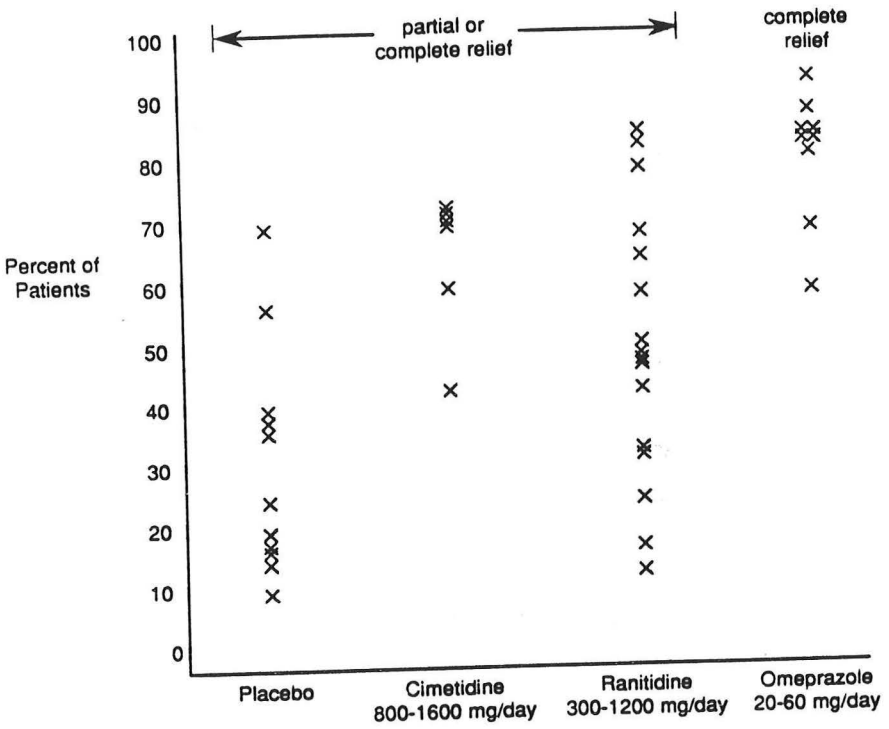
A compilation of more than 30 separate clinical trials assembled by Sontag(75) clearly shows that omeprazole is superior both at relieving reflux symptoms and in healing esophagitis at 6 to 8 weeks.

Clearly, the healing of esophagitis requires a much greater degree of acid suppression than does the healing of peptic ulcers. Although omeprazole is an expensive drug (averaging over $3.00 per tablet), the large doses of H2 receptor antagonist needed to achieve a comparable degree of acid suppression are substantially more expensive than omeprazole.

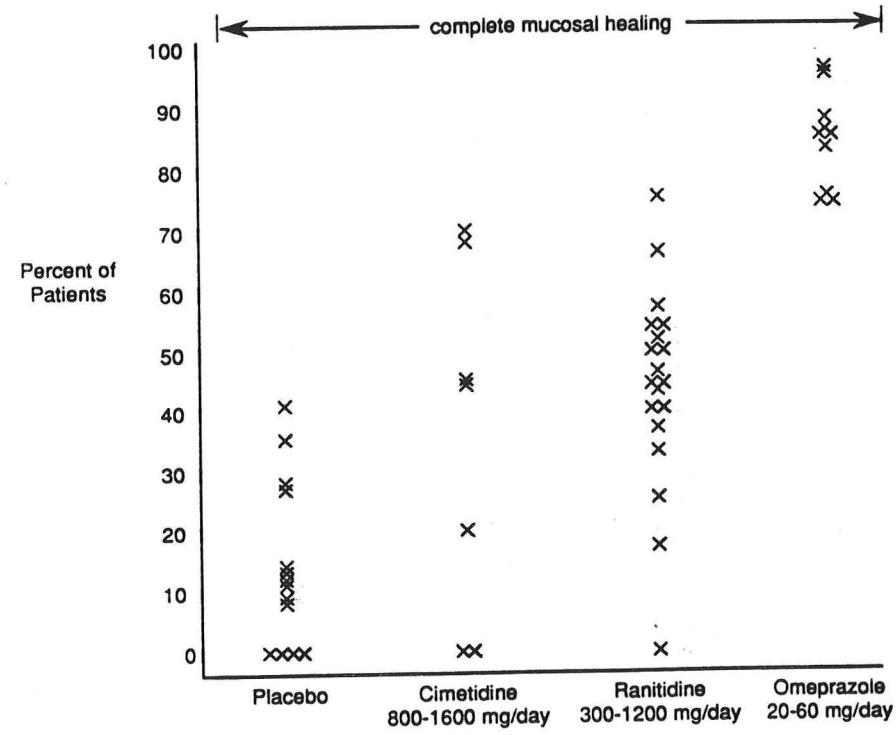
Safety: Though the short term safety of omeprazole is firmly established(79, 80, 81, 82, 83), the long term safety has been a matter of lingering doubt. The degree of acid suppression achieved with omeprazole frequently results in a moderate (and sometimes extreme) hypergastrinemia(84, 85). In rats, the hypergastrinemia brought about extremely high doses of omeprazole given life long resulted in hypertrophy of gastric mucosal enterochromaffin-like cells and an occasional gastric carcinoid(86). Because of the concern about potential gastric carcinoids in humans, the Food and Drug Administration has approved omeprazole for short term use only (up to 8 to 12 weeks).

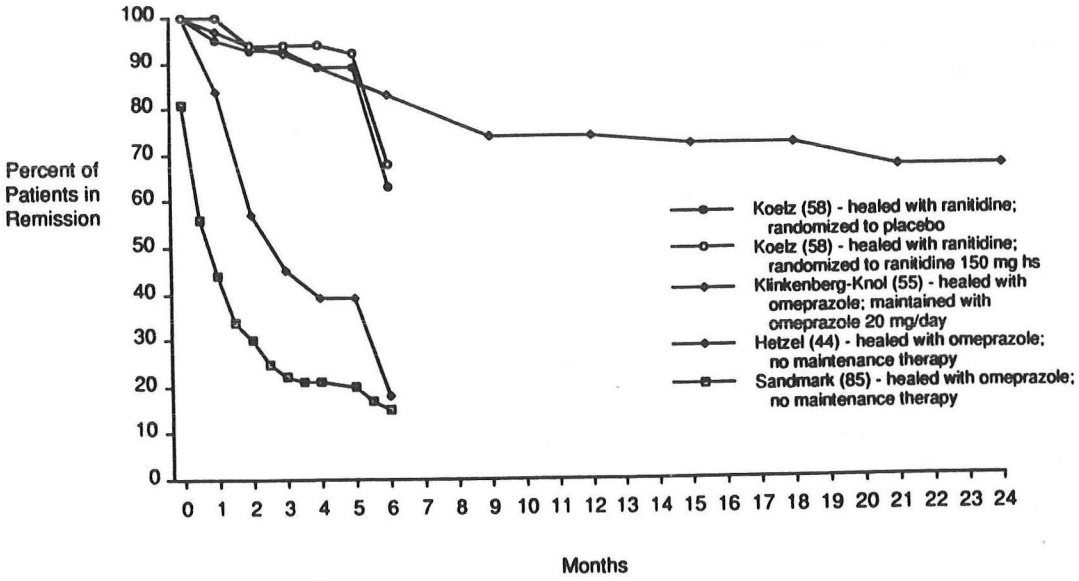
However, in studies done abroad(79) where the drug has been used for extended periods of time up to 6 years no human carcinoid has been reported.

Reflux Symptoms at 6-8 Weeks



Endoscopic Esophagitis at 6-8 Weeks





Relapse: Though omeprazole has been a major therapeutic breakthrough by consistently healing esophagitis, the relapse rate after cessation of drug therapy remains extremely high. Of those patients who achieved a complete healing of reflux esophagitis with omeprazole, 80% will relapse within six months (above). Moreover, maintenance therapy with low or standard doses of H2 receptor antagonist are ineffective at preventing relapse(75).

In general, the same dose of antisecretory drug is necessary to prevent relapse as was necessary to achieve healing of esophagitis in the first place.

Since omeprazole is not currently approved for long term use, the clinician has the problem of having to convince their patient to stop taking omeprazole after 12 weeks while at the same time knowing full well that relapse is all but inevitable. At the present time, maintenance therapy with standard or high dose H2 blockers is worthwhile, but the physician should anticipate a high rate of relapse. Until the long term safety of omeprazole is established, the best that the clinician and their patient can hope for is a sustained remission on maintenance H2 blockers.

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