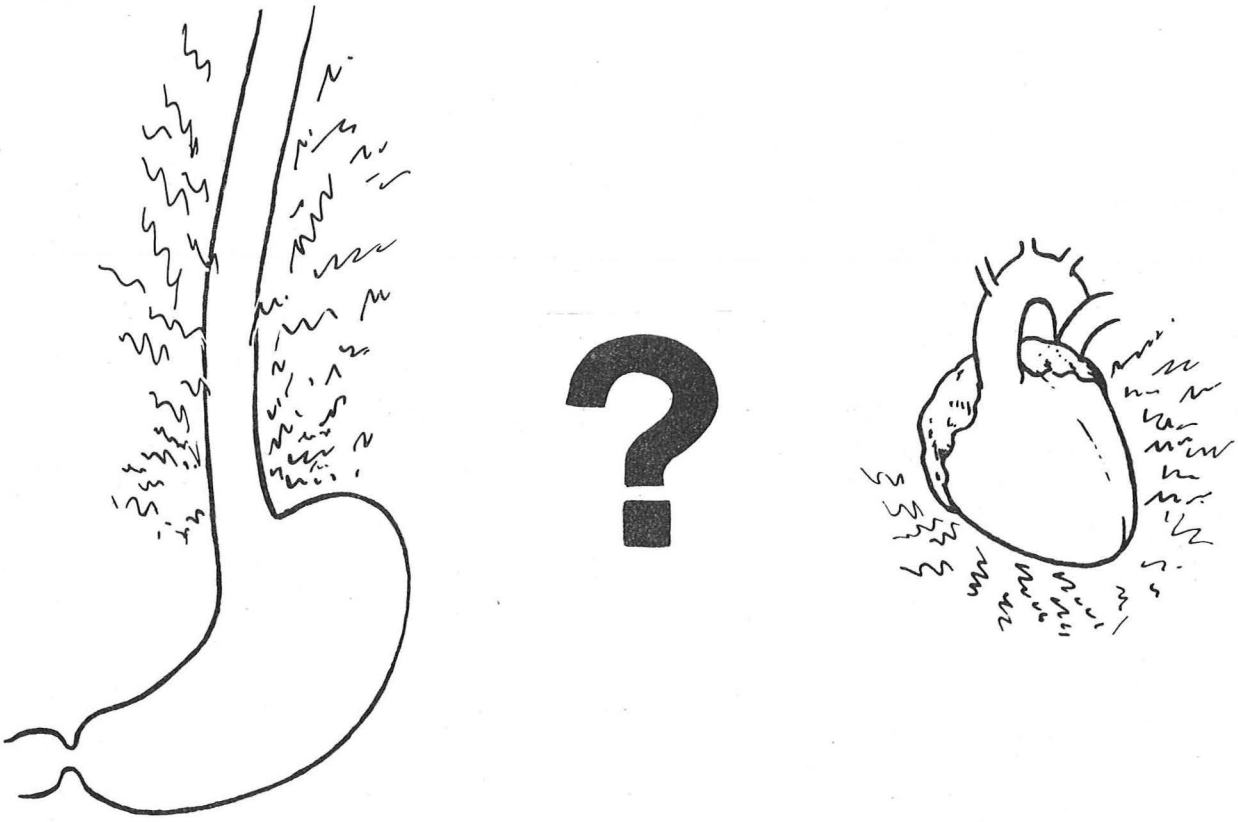
Cardiol

ANGINA



MEDICAL GRAND ROUNDS

Southwestern Medical School

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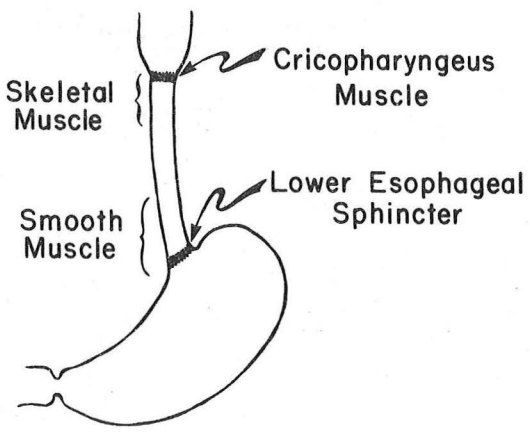
W. L. Peterson, M.D.

INTRODUCTION

Heberden's original description of angina pectoris was published in 1772. He described four features which he felt distinguished it from other causes of precordial (or central) chest pain. These included 1) a retrosternal location; 2) a strangling, suffocative quality; 3) an accompanying sense of mortal anxiety; and 4) a relationship to exertion. Since then, the word angina has become synonymous with coronary artery disease. In most instances this is appropriate. However, it has become clear that some patients with "angina" (defined in Dorland's medical dictionary as a spasmodic, choking, or suffocative pain) do not have heart disease. For example, it has been reported that 10% or more of patients referred for coronary arteriography have angiographically-normal coronary vessels. While in some instances, news of normal coronary vessels might be adequate to assuage the fears of the patient afflicted with chest pain, in other instances it is not enough. Rather, a specific alternative diagnosis is sought in order to prescribe rational therapy and to further reassure the patient that a "real disease" other than heart disease is the cause of symptoms. Attempts to find alternative causes of anginal chest pain in some instances lead to the esophagus. This discussion reviews the putative esophageal causes of chest pain and presents what data are available to support the contention that the esophagus can indeed produce "angina."

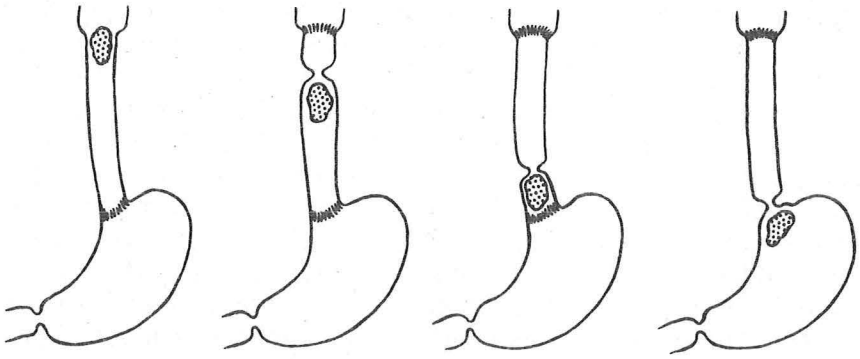
BRIEF OVERVIEW OF NORMAL ESOPHAGEAL FUNCTION

The esophagus is a muscular tube capped at either end by a sphincter (Figure 1). The tube consists of skeletal muscle in its upper third, a transition zone in the middle and smooth muscle in the lower third. Its purpose is to deliver swallowed contents from the oropharynx to the stomach.



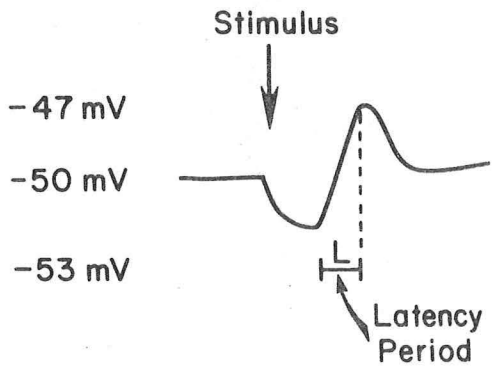
Upon swallowing, afferent impulses from the pharynx travel to the medullary "swallowing center" which then sends efferent impulses to the cricopharyngeus muscle and the esophagus. The cricopharyngeus muscle relaxes and the bolus is pushed into the upper esophagus. The esophagus then milks the bolus down to the stomach via a sequential, orderly series of contraction waves (Figure 2). In the upper esophagus,

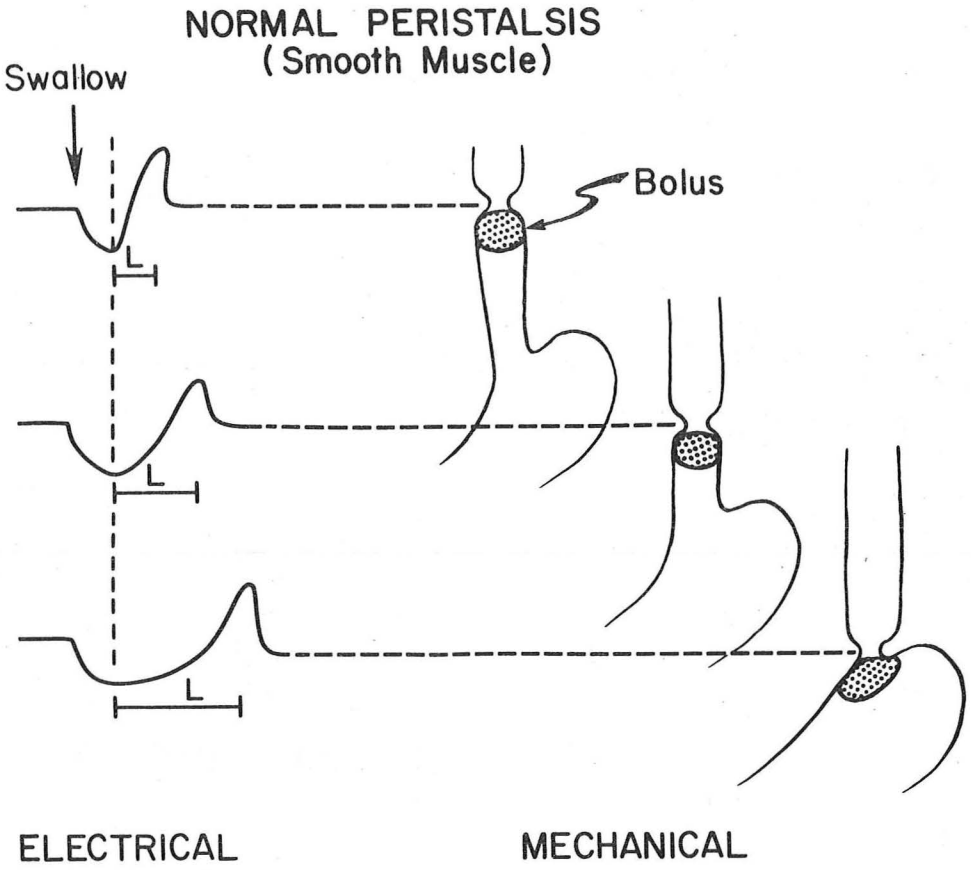
NORMAL PERISTALSIS



the sequential contractions are a result of sequentially-fired impulses (via the vagus nerve) from the swallowing center. The sequential contractions of the smooth muscle esophagus occur differently and are a result of the "off-response" and "variable latency." Upon vagal stimulation, all of the smooth muscle cells react as one, undergoing hyperpolarization (Figure 3). When the impulse turns off, the muscle cells depolarize

ESOPHAGEAL
"OFF - RESPONSE"

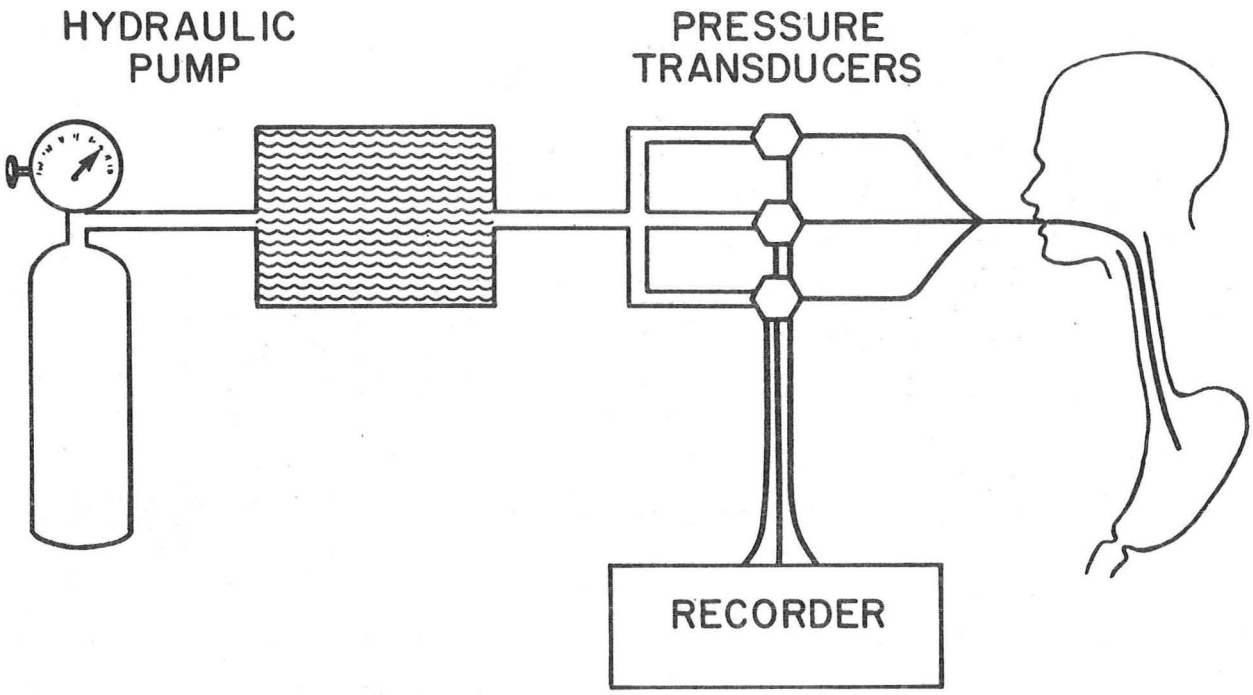


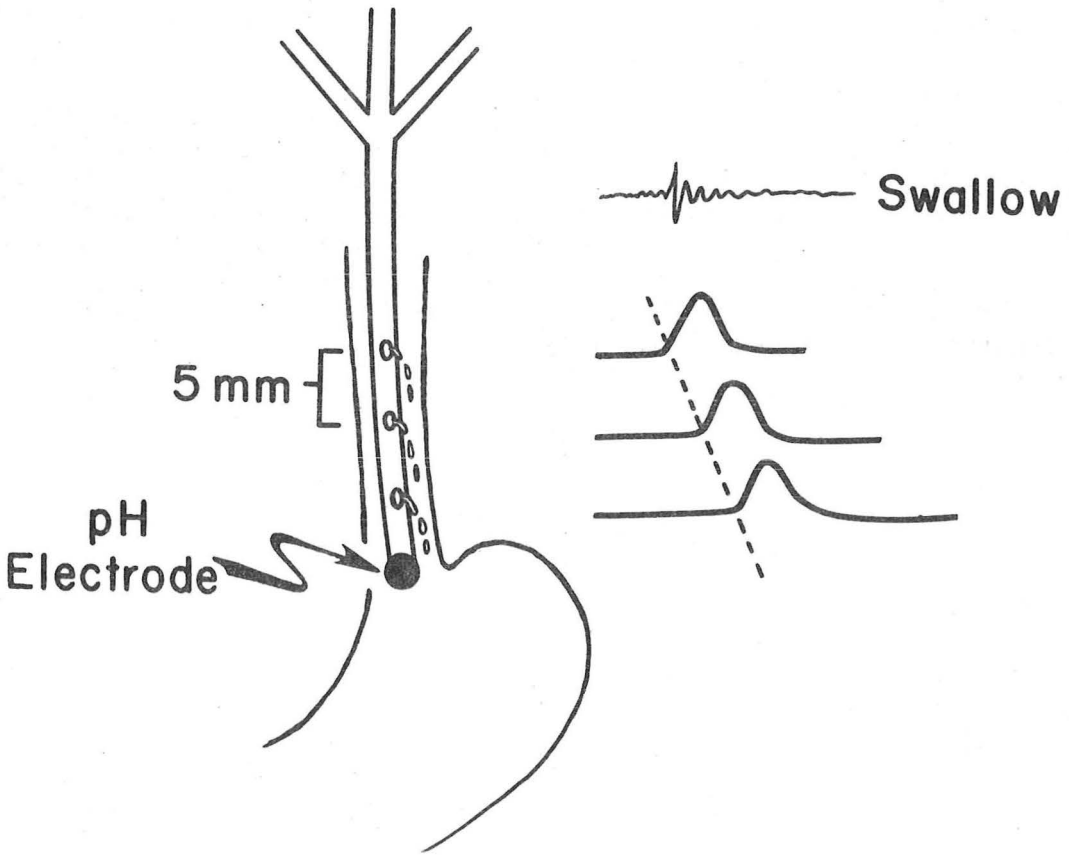


and overshoot to a peak above resting membrane potential (off-response). At this time, an esophageal contraction occurs. The time from the end of the stimulus to peak depolarization is termed the latency period. Sequential contractions occur because the latency period for smooth muscle cells increases aborally. (Figure 3A).

Measurement of esophageal movement has been carried out many ways. Standard barium x-rays (with or without cineradiography) provide only a crude assessment of motility but do measure the ability of the esophagus to transport a liquid bolus. X-ray can also detect areas of obstruction. Radionuclide scanning is a more sophisticated means of evaluating esophageal emptying, but still does not assess the motility patterns per se. Rather, a perfused catheter system (Figures 4 and 5) permits accurate assessment of esophageal motility.

ESOPHAGEAL MANOMETRY

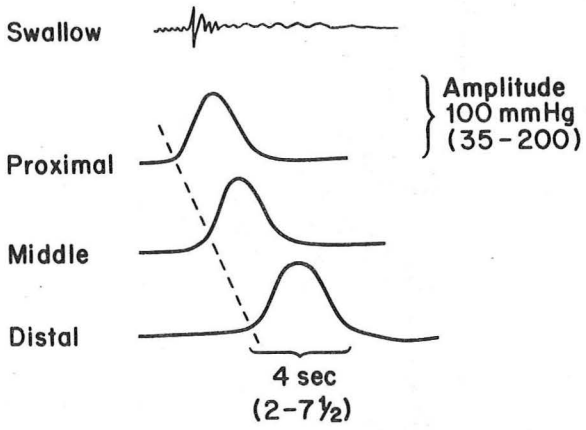




By this technique, fluid is pumped through open catheters separated by 5 cm. intervals. The pressure "seen" by these infused catheters is reflected back to pressure transducers which then display patterns on a paper recorder. Thus, as the esophagus contracts sequentially, the catheters record the sequential pressure-rises as shown in Figure 5.

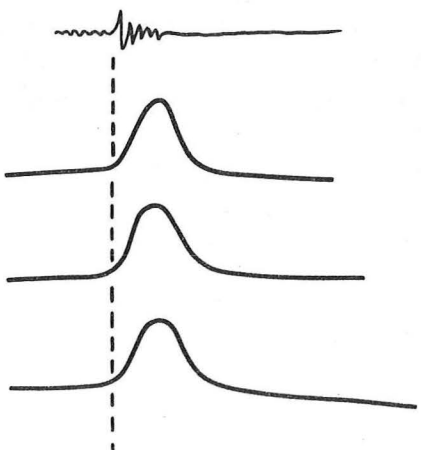
Peristalsis is the orderly, aboral progression of contraction waves. When initiated by a swallow, the peristalsis is primary (Figure 6); when initiated by esophageal distention (i.e., an incompletely delivered bolus) the peristalsis is secondary. In either case, the contractions are sequential.

PRIMARY PERISTALSIS



Normal values during primary peristalsis for contraction amplitude and duration respectively are 80-120 mmHg (nl up to 175-200 mmHg) and 4 seconds (range 2-7.5 seconds). Normal values vary somewhat from laboratory to laboratory. Simultaneous contractions, either spontaneous or in response to a swallow, are called tertiary contractions (Figure 7). Such contractions tend to be nonpropulsive and, if of very high amplitude

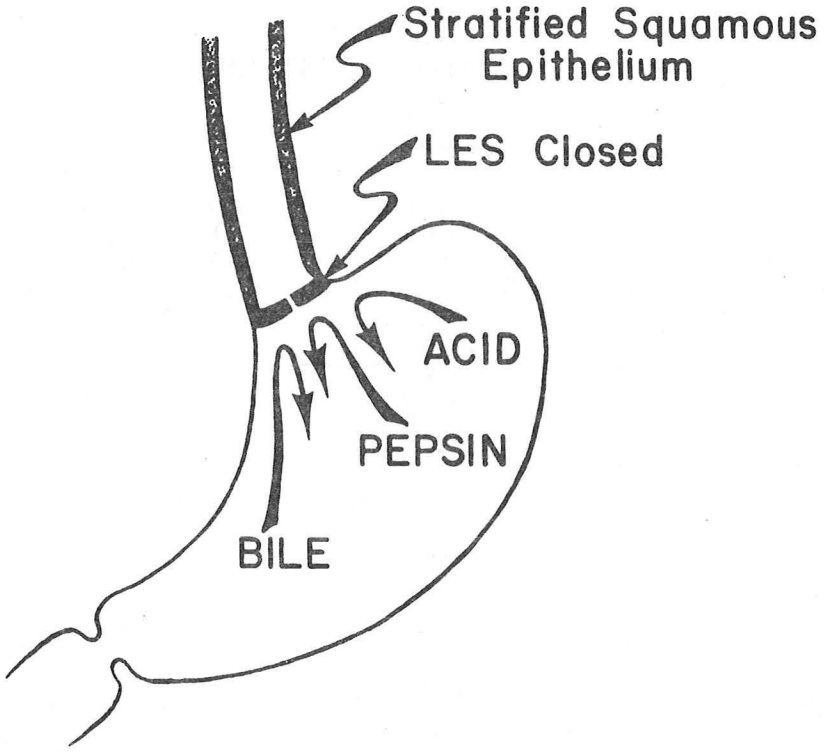
TERTIARY CONTRACTION



and long duration, may produce chest pain. Some tertiary contractions occur spontaneously in about 34%, and after swallowing in about 2%, of normal subjects, although pain is rare.

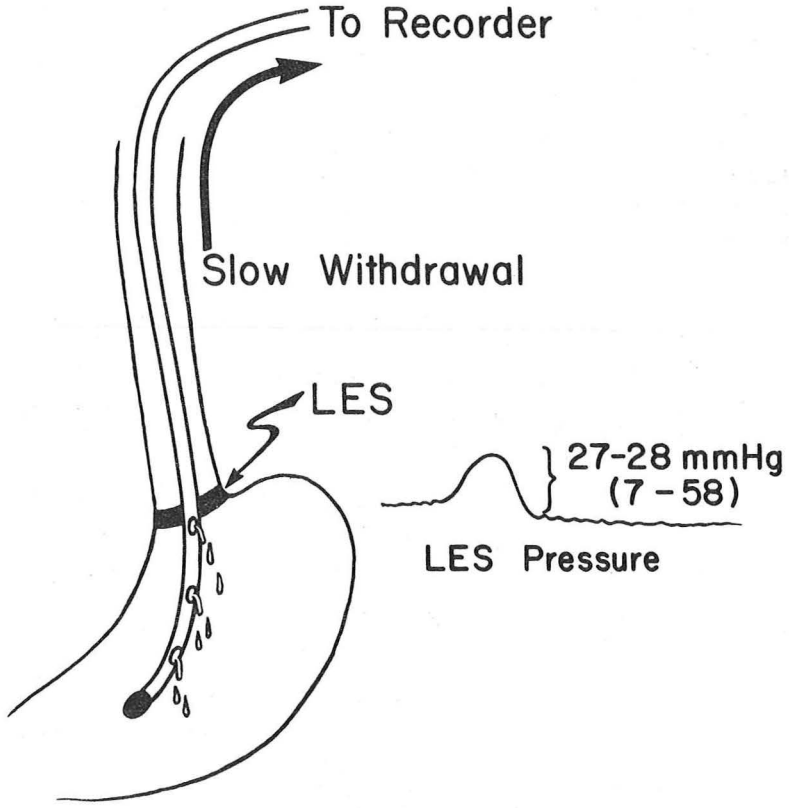
The esophagus is lined by stratified squamous epithelium. Because this mucosa responds adversely to gastric contents, and because aspiration of gastric contents creates pulmonary difficulties, it makes sense that a sphincter is present to keep such contents out of the esophagus (Figure 8).

LOWER ESOPHAGEAL SPHINCTER

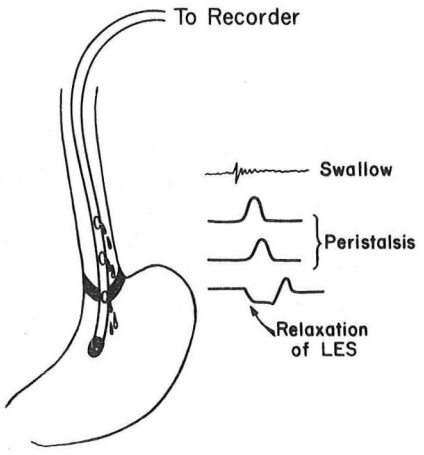


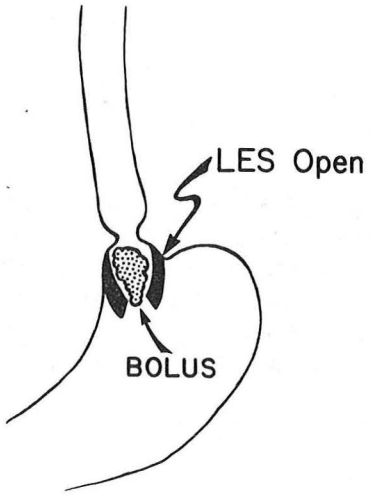
This area of high pressure is represented not by a discrete bundle of muscle, but rather by only normal-appearing esophageal muscle. It possesses special characteristics, however, which permit it to maintain a resting tone. Measurement of the tone of the lower esophageal sphincter (LES) is accomplished by the same manometry catheters used for esophageal body measurements (Figure 9). Obviously this area of high pressure must relax to allow solid and liquid boluses into the stomach (Figures 10 A & B).

MEASUREMENT OF LOWER ESOPHAGEAL SPHINCTER PRESSURE



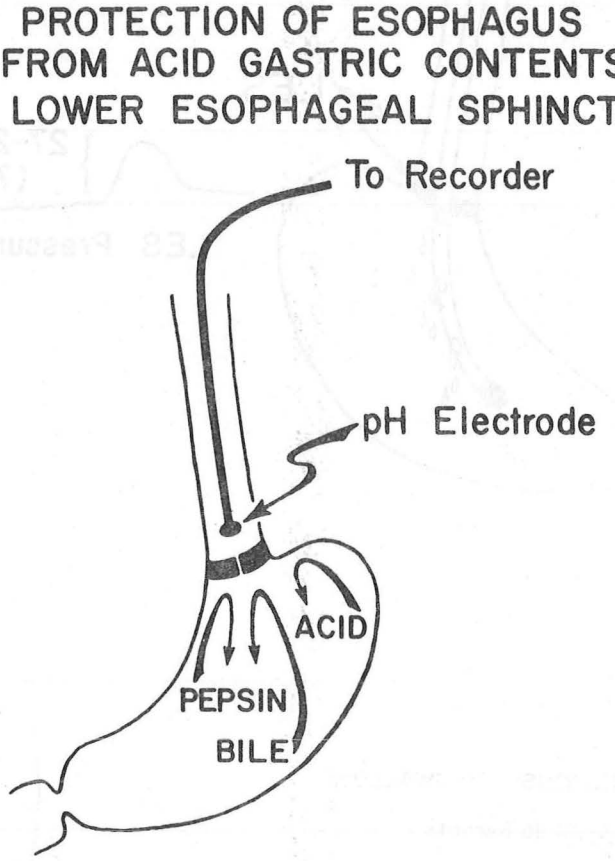
LES RESPONSE TO SWALLOW





The normal resting LES pressure is 27-28 mmHg (range 7-58). Upon swallowing it relaxes quickly to near zero pressure, ready for the bolus being pushed by the peristaltic wave above. Once the bolus has passed, the LES resumes its resting tone. The neurohumoral mechanisms of LES function are beyond the scope of this discussion. Interested individuals are referred to the chapter by Cobb and Goyal in Physiology of the Gastrointestinal Tract.

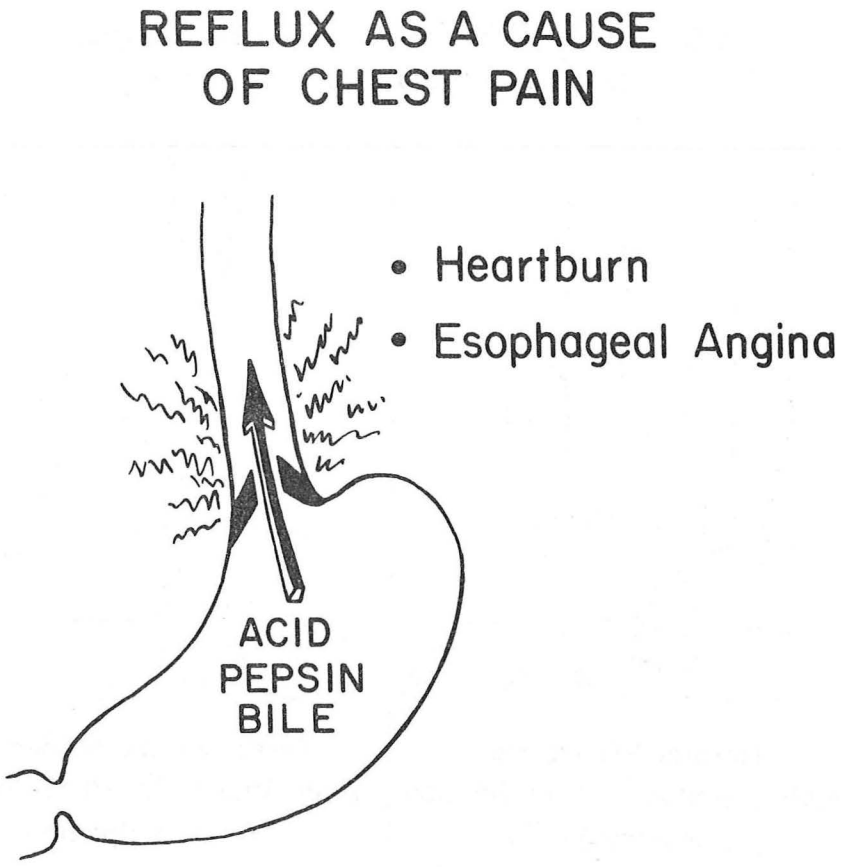
The proof of the pudding regarding LES function is how well it keeps the esophagus free of gastric contents. Since hydrochloric acid is most easily measured, monitoring the pH of the lower esophagus with an indwelling pH electrode (Figure 11) has become the standard of LES function.



Because results obtained at any one period of time may be misleading, the current vogue is to measure esophageal pH for 24 hour periods, during which subjects eat and drink normally, sleep, etc. In normal subjects, such monitoring discloses that reflux episodes (defined as periods during which the pH is <4) occur throughout the day but only infrequently and for brief periods. Any episode of reflux is quickly cleared from the

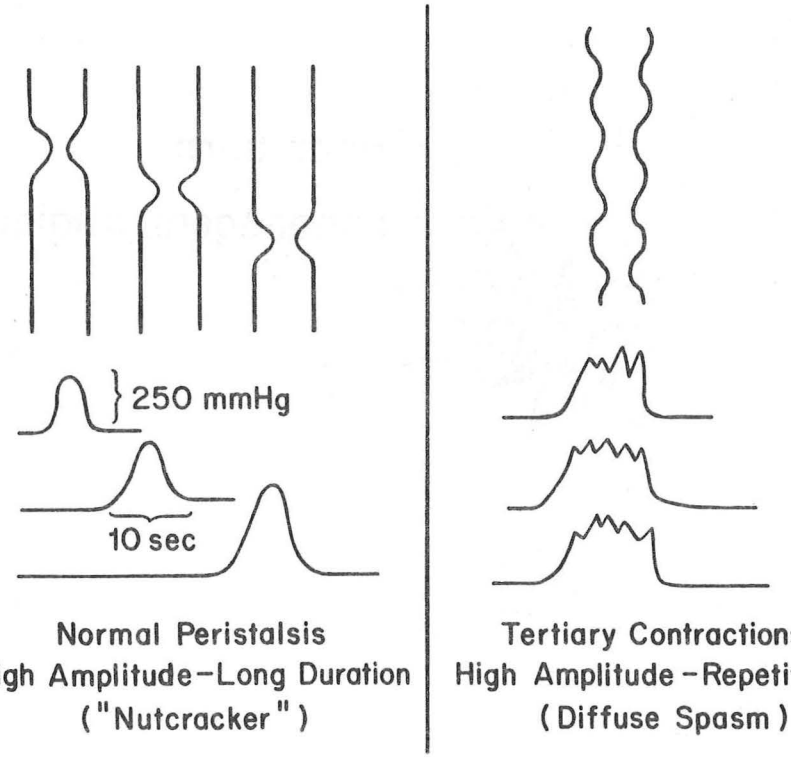
esophagus by primary peristalsis.

Several perturbations in the normal function of the tubular esophagus and/or the LES have been reported to produce chest pain. First, excessive reflux of gastric contents can produce heartburn or esophageal angina (Figure 12). In patients with reflux, heartburn is the manifestation 90% of the time, esophageal angina 10%. Second, motility disorders of the tubular esophagus and/or LES have been



reported to produce pain. Every combination of esophageal contraction abnormalities and sphincter dysfunction has been described, but the best candidates as causes of chest pain are diffuse esophageal spasm and abnormally high amplitude, peristaltic contractions ("nutcracker" esophagus) (Figure 13).

MOTILITY DISORDERS AS A CAUSE OF ESOPHAGEAL ANGINA



Normal Peristalsis
High Amplitude–Long Duration
("Nutcracker")

Tertiary Contractions
High Amplitude–Repetitive
(Diffuse Spasm)

GASTROESOPHAGEAL REFLUX

Definition and Diagnosis of the Disease

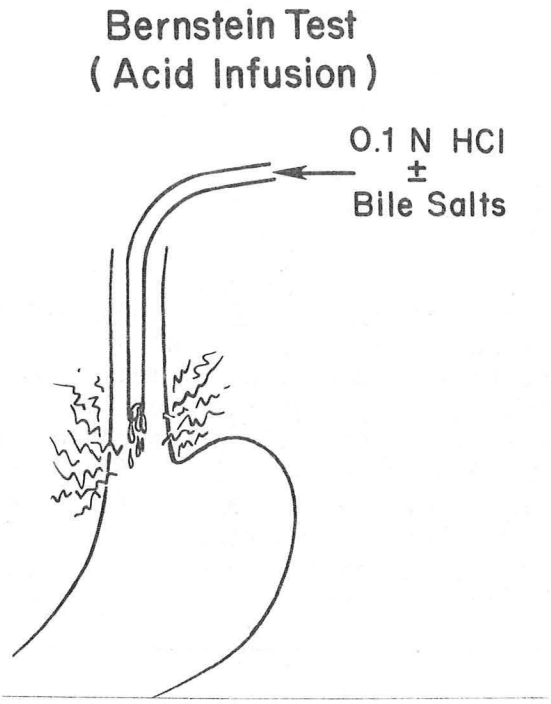
There are many ways in which gastroesophageal (GE) reflux may be defined. One may consider symptoms. Most patients with reflux who have symptoms (and not all do) tell of heartburn, a burning, substernal discomfort occurring primarily after meals, during recumbency, or while bending and lifting heavy objects. Some patients will experience esophageal angina, a dull, substernal "pressure" or "knot", occurring throughout the day and often with exercise. Of course, many patients with heartburn or angina will not have GE reflux. Tests for GE reflux may be divided into three broad categories - those that indicate the potential for reflux, those that indicate esophageal damage, and those which actually show reflux (Table 1).

Table 1. Accuracy of tests for reflux (from Richter, et al).

Test	False Negative	False Positive
1) Reflux Potential		
LES Pressure (< 10 mmHg)	40%	15%
2) Esophageal Damage		
Acid Perfusion (Bernstein)	20%	20%
Endoscopy/Biopsy	25-30%	5-10%
3) GE Reflux		
Barium X-ray	60%	15%
Scintiscanning	40%	5%
Acid Reflux Test	15%	15%
24-hr pH Monitor	10%	2%

Reflux potential - The mean LES pressure for patients with reflux is lower than in normal subjects. However, there is much overlap and only those patients with the most severe disease will have very low LES pressures.

Esophageal damage - Damage to the esophagus leads to acid sensitivity and infusion of 0.1NHCl will often reproduce a patient's symptoms (Figure 14). The addition of bile salts to the infusate is said to increase the sensitivity of the test. This test is most useful in patients with atypical symptoms. If exposure to the acid $\pm$ bile reproduces the patient's pain, it may be concluded that reflux of gastric contents is responsible for his symptoms. Endoscopy and biopsy will demonstrate histologic changes. There is, however, a broad spectrum of changes and many patients have only minimal histologic damage.



GE reflux - Barium x-rays will sometimes show spontaneous free reflux of barium from the stomach back into the esophagus, but most patients with GE reflux will not display this finding. A carefully-performed barium swallow can detect strictures and, with double-contrast technique, occasionally esophagitis and esophageal ulcers. The significance of a hiatal hernia will be discussed later. GE scinti-scanning may someday play an important role, but more data are needed.

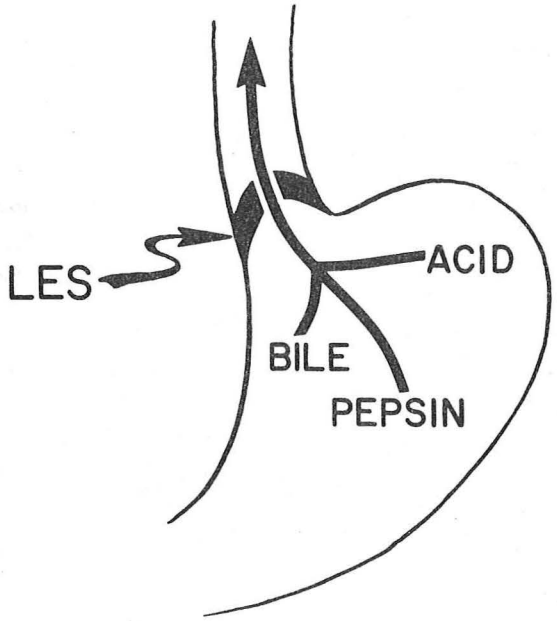
The best tests of GE reflux are those which record the actual pH in the distal esophagus. The acid reflux test is one such test. After loading the stomach with 300 ml of 0.1NHCl, one measures the pH during various maneuvers designed to elicit reflux. These include the Valsalva and Mueller maneuvers, deep breathing, and coughing. A more "physiologic" test is 24 hr pH monitoring, a variation on the standard acid reflux test. This test allows pH measurement during many periods of the day, permits correlation of reflux episodes with patient symptoms, and measures the ability of the esophagus to clear itself after a reflux episode (defined as a drop in pH below 4.0). This test has provided remarkable insight into the pathophysiology of GE reflux disease. It is now available in a portable, shoulder-carried unit, much like the Holter monitor for measurement of cardiac arrhythmias.

Mechanisms of Reflux

Reflux of gastric contents into the esophagus occurs in two settings (Figure 15). First, reflux can occur during episodes of inappropriate, spontaneous, complete relaxation of the LES. These episodes occur

primarily during the postprandial period and often follow by 10-15 seconds a normal, swallow-induced relaxation. Reflux occurs during spontaneous relaxations but usually not during swallow-induced relaxations, which are accompanied by a peristaltic sweep which keeps gastric contents from entering. The second mechanism of reflux occurs when gastric pressure overwhelms the resting LES pressure. Thus, the more periods of time during the day the LES pressure is low or absent, the more likely reflux will occur.

CIRCUMSTANCES BY WHICH GASTRIC CONTENTS REFLUX INTO THE ESOPHAGUS

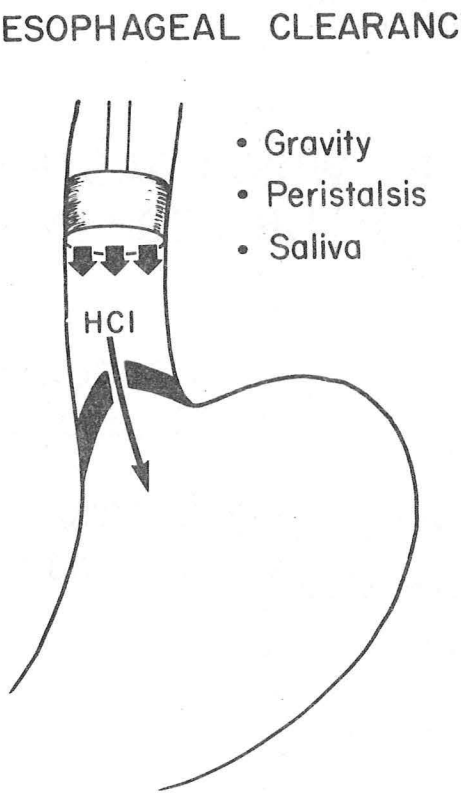


- Inappropriate, Complete Relaxation of LES
- Gastric Pressure Overwhelms Resting LES Pressure

Mechanisms of Normal Esophageal Clearance

Once gastric contents are in the esophagus, they must be cleared (Figure 16). Gravity and primary peristalsis are the most important clearance factors. Peristalsis begins 20 to 60 seconds after a reflux episode and after one or two peristaltic sweeps, a 15 ml bolus of acid will be reduced to less than 1 ml in volume. The pH does not change,

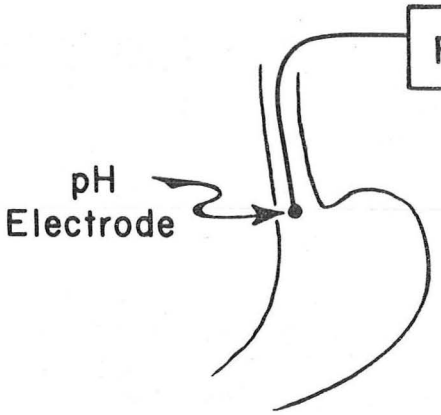
however, and it is postulated that saliva finishes the job of normal acid clearance by neutralizing the small remaining volume of acid. A saliva flow of 1.2 ml/min will produce in 5 minutes enough bicarbonate-rich saliva to titrate 1 ml of 0.1NHCl from pH 1.2 to pH 4.0.



Reflux in Normal Subjects

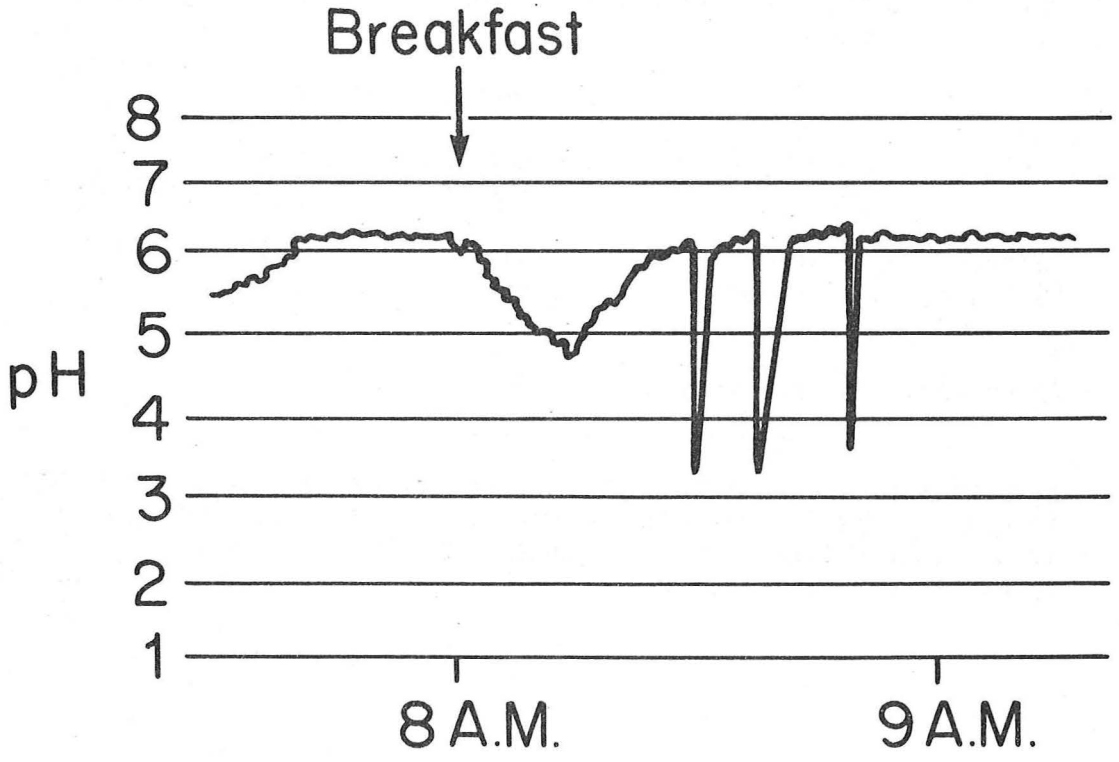
In interpreting 24 hr pH patterns in health and disease, we must keep in mind the fact that the total time of each day during which esophageal pH is below 4.0 is proportional to the number of individual reflux episodes X the duration of the reflux episodes. We shall see that the duration of individual reflux episodes is more important in terms of disease than the total number of reflux episodes. During the day, normal subjects reflux frequently but because of excellent esophageal clearance mechanisms, (gravity, peristalsis) reflux is present only 2% of the total time of upright posture (Figure 17). These episodes occur primarily during the three hours after a meal (Figure 18) and are almost all related to transient (5-30 seconds), inappropriate, complete

24 HOUR pH MEASUREMENT IN NORMAL SUBJECTS AND PATIENTS WITH REFLUX



	pH < 4	
	UPRIGHT	SUPINE
NORMAL	2%	0.3%
REFLUX	10%	8%

REFLUX IN NORMAL SUBJECT



relaxation of the LES. At night, while in the supine position, normal subjects reflux rarely, 0.3% of the time. These episodes occur during transient arousals from sleep or when fully awake and, like the episodes occurring in the upright position, are cleared by primary peristalsis. The efficient clearing mechanisms and the rarity of supine reflux result in reflux episodes of short duration. Only 12% of reflux episodes in normal subjects persist for more than five minutes, only 1% for 20 minutes or more.

Of all reflux episodes in normal subjects, 94% occur during inappropriate relaxation of a normal-pressure LES. In 5% of the reflux episodes, the resting LES pressure wanders down to pressures <10 mmHg and is overcome (or "blown open") by an increase in gastric pressure, so called "stress reflux". Finally, 1% of the reflux episodes occur when resting LES pressure disappears, permitting "free reflux".

Reflux in Patients

As shown in Figure 17, patients with GE reflux disease experience reflux 10% of the time while upright and 8% of the time while supine. Two factors account for the fact that esophageal pH is less than 4.0 for a greater percentage of the day in patients than in control subjects. First, patients have more reflux episodes, especially while upright, and second, patients experience longer durations of reflux episodes, especially while supine.

Reflux frequency - As shown in Table 2, patients with endoscopic esophagitis experience four times as many total reflux episodes during a 12 hr period when compared to controls. This is due to an absolute, and

Table 2. Reflux episodes and mechanisms responsible in 10 patients with reflux esophagitis and 10 normal control subjects (from Dodds, 1982).*

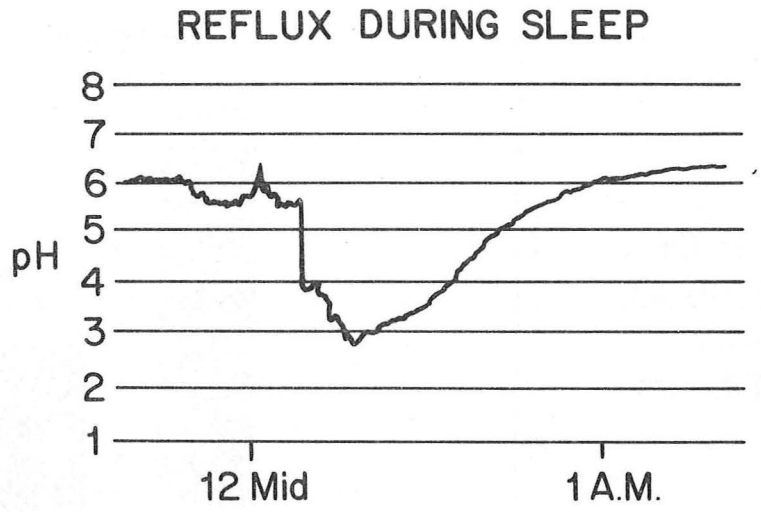
		Reflux episodes due to:		
	Total Reflux Episodes	Transient LES Relaxation	Stress Reflux	Free Reflux
Control	89(100%)	84(94%)	4(5%)	1(1%)
Patients	352(100%)	229(65%)	60(17%)	63(18%)

*
(% of total in parenthesis)

significant, increase in the frequency of reflux due to each mechanism. Not only do reflux patients have more episodes due to transient LES relaxation, they reflux more often under the stress of increased abdominal pressure. Free reflux accounts for almost 20% of the total reflux episodes.

The fact that patients with reflux esophagitis have more episodes of "stress" and "free" reflux is explained by the tendency of many such patients to have low resting LES pressures.

Reflux duration - The duration of reflux episodes in the upright position is very brief since gravity clears fluid from the esophagus quite rapidly. At night, when subjects are supine, gravity is ineffective and primary peristalsis is essential to clear the esophagus. Unfortunately, the frequency of swallowing drops from 72/hour during the awake, upright state to 7 or less per hour during sleep. This is not harmful for normal subjects who reflux infrequently at night, but is devastating for the patient who experiences reflux episodes during sleep. (Figure 19).



Adequate esophageal clearance demands arousal from sleep and initiation of primary peristalsis. Not only are reflux patients less sensitive to gastric contents (and therefore do not awaken as quickly during reflux as normal subjects) but once they do awaken, their peristaltic waves are less effective than those of normal controls. The end results are periods of sustained reflux in the supine position.

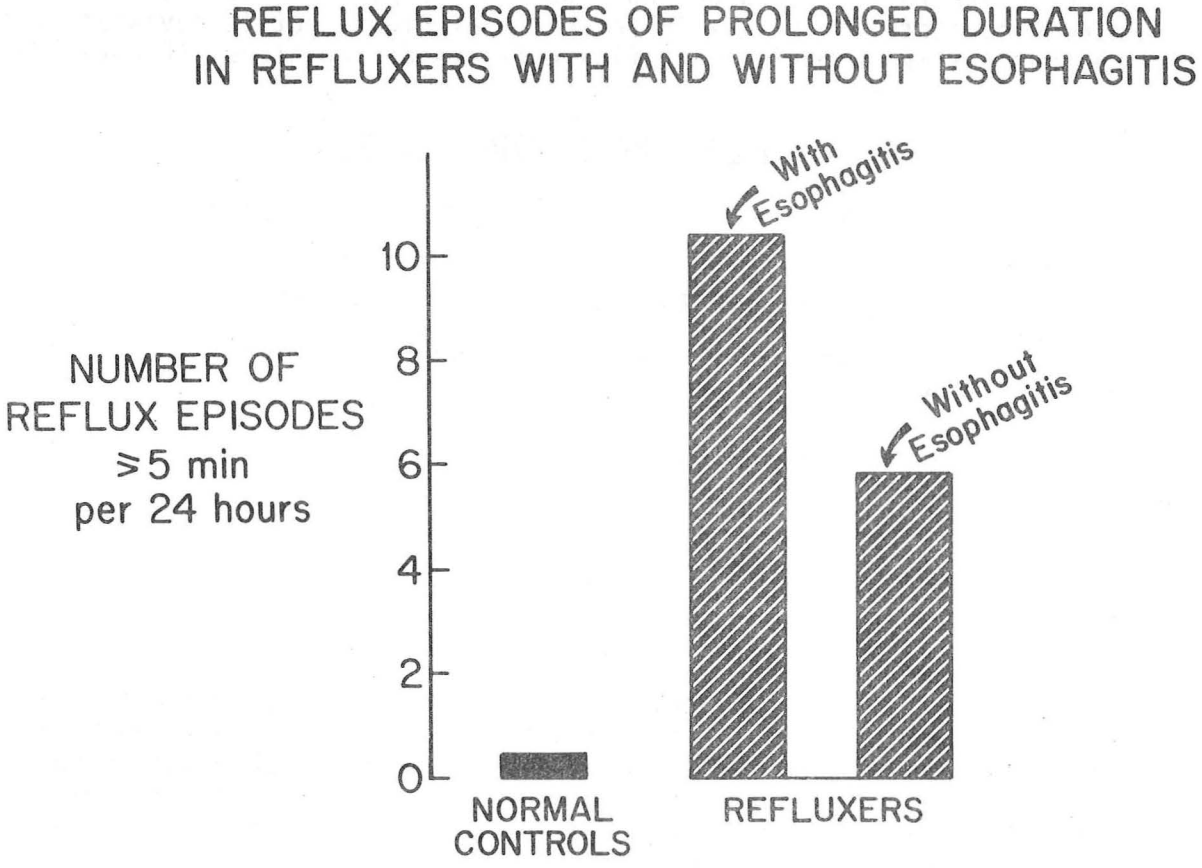
In summary, the total time of exposure to gastric contents in reflux patients, while upright, is related primarily to an increased number of "physiologic" reflux episodes during the postprandial period (i.e., during transient, complete LES relaxation). Periods of "stress" reflux also occur during periods of increased abdominal pressure (i.e., coughing, bending, etc.) and perhaps some episodes of free reflux occur also. Gravity clears all of these reflux episodes promptly so duration is brief. While supine, reflux patients have far fewer numbers of reflux episodes than when upright, but those that occur are of very long duration.

Spectrum of Disease

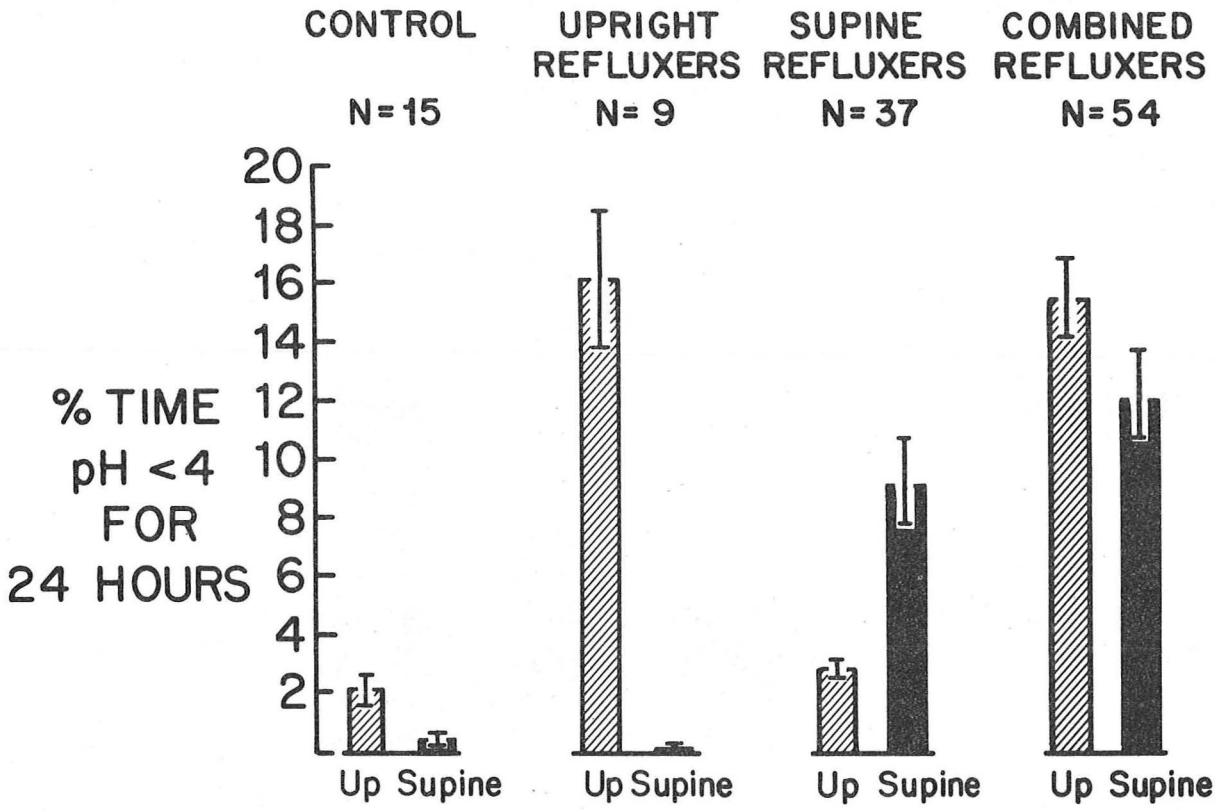
The pathophysiologic considerations above describe reflux patients in general. While most all experience some form of chest pain, there is a marked variation in the mucosal response to reflux of gastric contents. Some patients with reflux have pain and only microscopic histologic

evidence of esophagitis, others have macroscopic esophagitis, and still others develop severe mucosal injury (i.e., bleeding, stricture, Barrett's esophagus). While this discussion deals with pain from GE reflux, a few comments are in order explaining why some patients have more marked mucosal damage than others.

The best data suggest that patients with gross (macroscopic) esophagitis have a greater number per day of reflux episodes lasting 5 minutes or longer (Figure 20). It has already been discussed that reflux episodes

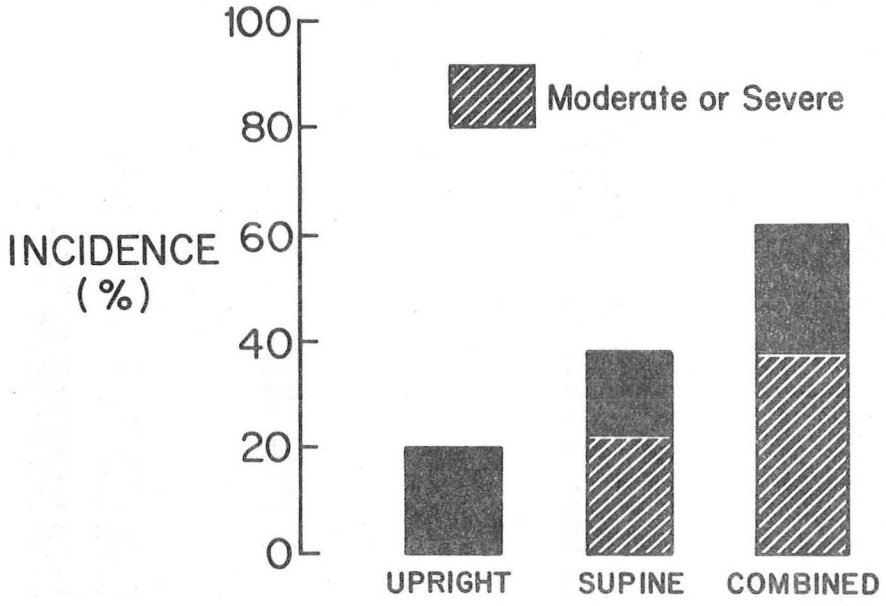


of long duration occur primarily during the hours of sleep. Thus, one would predict that patients who reflux primarily while upright would be less likely to have macroscopic esophagitis. Johnson and DeMeester have characterized such patients (Figure 21).



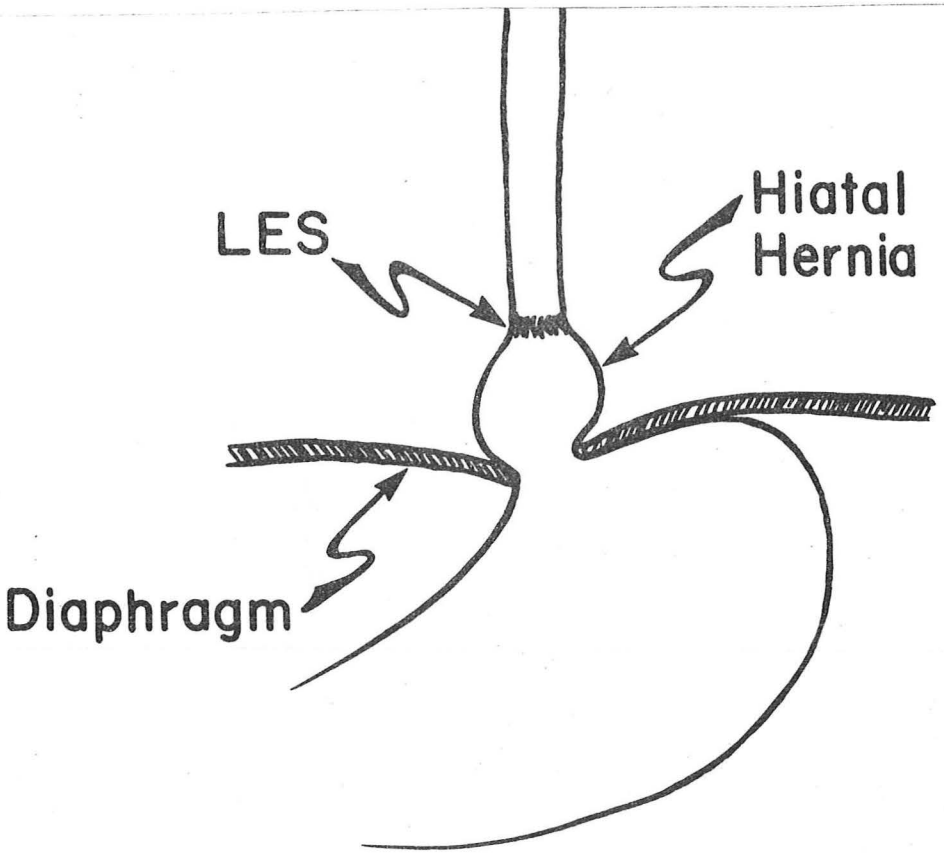
Of 100 patients with excessive reflux documented by 24 hr pH monitoring, they found 9 who refluxed only in the upright position. These patients, while experiencing pain, have a relatively low incidence of endoscopic esophagitis (Figure 22). Patients who reflux primarily while supine (n = 37) or while both upright and supine (n = 54) have an increased incidence of endoscopic esophagitis, including moderate or severe damage. What is it that predisposes patients to supine reflux and within this group, what factors contribute to prolonged duration of reflux?

INCIDENCE AND SEVERITY OF ENDOSCOPIC ESOPHAGITIS IN PATIENTS WITH UPRIGHT, SUPINE, OR COMBINED REFLUX



LES pressure - In general, the lower the LES pressure, the more severe the histologic changes. While patients with higher LES pressures can certainly reflux via inappropriate relaxation of the sphincter, they are less prone to stress reflux or free reflux. On the other hand, patients with very low LES pressure have more episodes of stress or free reflux. While they are upright this is not such a problem, but when they are supine this leads to prolonged episodes of reflux. It should be pointed out that some investigators believe that severe esophagitis (perhaps mediated by prostaglandins - see Eastwood) leads to low LES pressures rather than the other way around. The question of which comes first, reflux or esophagitis, remains to be settled.

Esophageal clearance - There are two aspects of esophageal clearance which may predispose some patients to greater mucosal damage than others. First, older patients appear to respond to reflux with less salivary output than younger patients. While not proven, this may explain why the severe complications of reflux tend to occur in older patients. Second, there is now evidence that our old friend, the hiatal hernia, (Figure 23), also plays a role. DeMeester and his colleagues studied 102 patients with



symptoms of reflux. Of these, 53 had a hiatal hernia at endoscopy and 49 did not. Of those with a hiatal hernia, 44/53 (83%) had evidence of excessive reflux by 24 hr pH monitoring compared to 21/49 (43%) without a hiatal hernia ($p < 0.001$). Although as a group, patients with a hiatal hernia had a lower mean LES pressure, when patients with and without reflux were considered, the presence of a hiatal hernia had no significant influence on LES pressure (Figure 24). However, as shown in

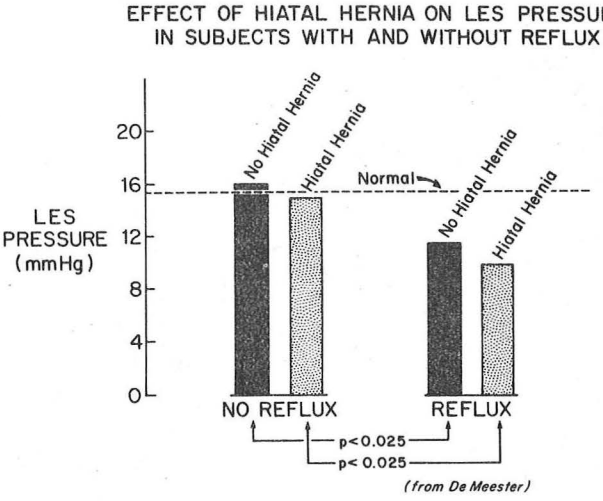
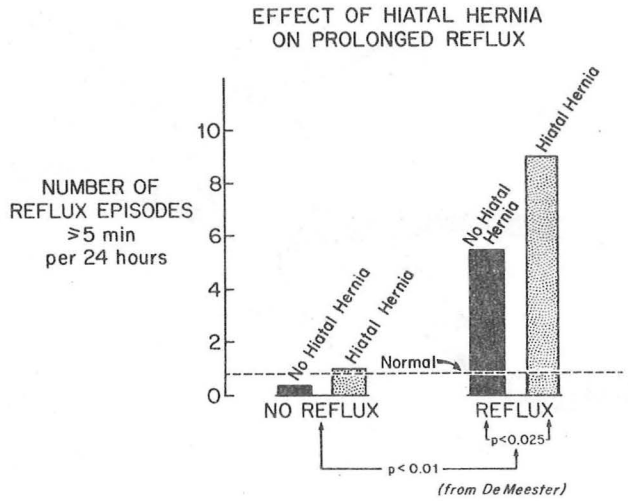
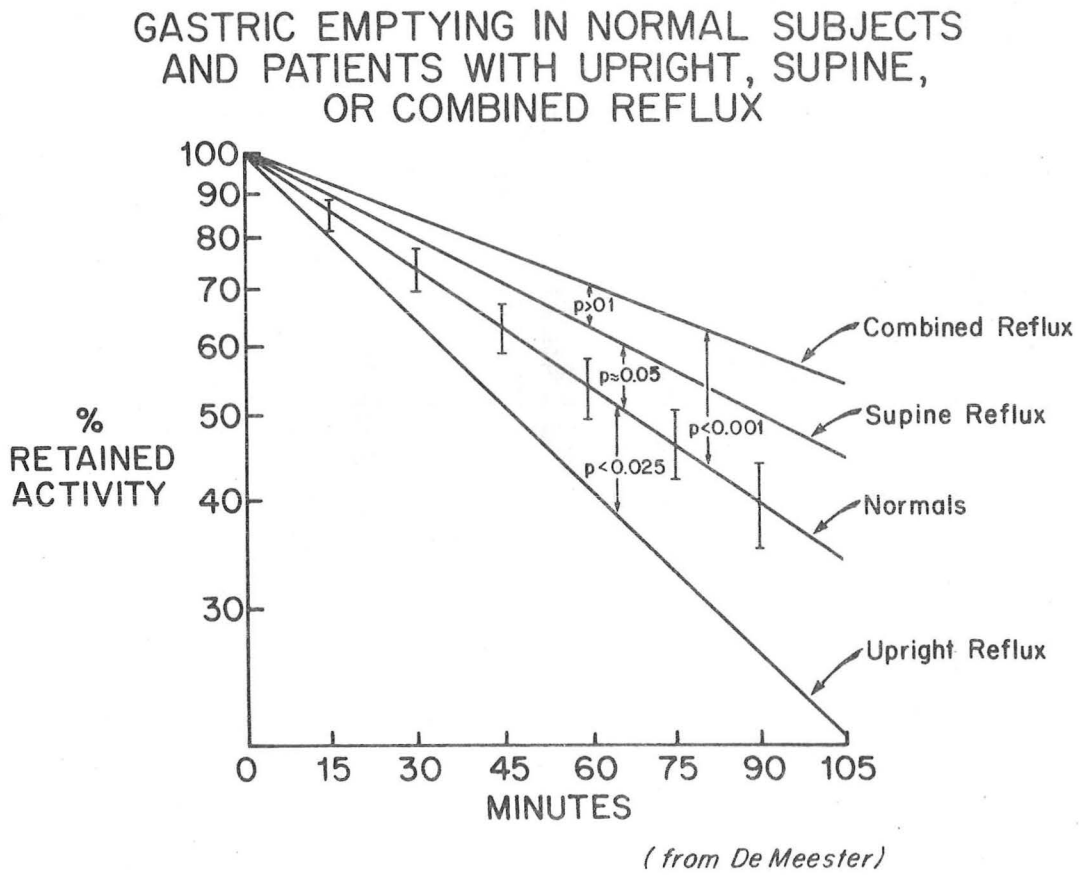


Figure 25, reflux patients with hiatal hernia has significantly more episodes > 5 minutes' duration than reflux patients without a hiatal hernia. Scintigraphic studies of esophageal emptying suggest that the presence of a hiatal hernia results in delayed esophageal emptying when patients are in the supine position.



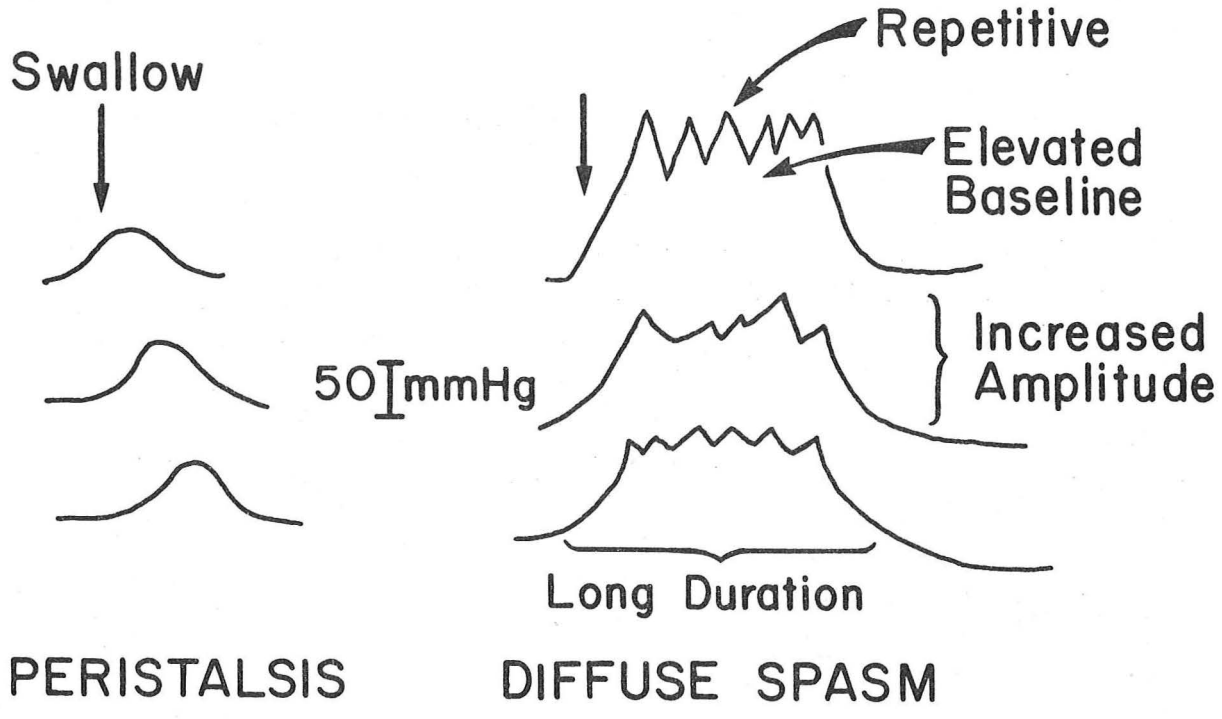
Gastric emptying - Patients with supine or combined reflux have significantly delayed gastric emptying of a radionuclide-labeled meal (Figure 26). It is of interest that patients with upright reflux have enhanced gastric emptying.



PAINFUL PRIMARY ESOPHAGEAL MOTOR DISORDERS

Moersch and Camp described in 1934 eight patients with "diffuse spasm of the lower part of the esophagus." Of note, two of the eight had "angina-like" chest pain. During the ensuing 20 years, others described patients believed not to have cardiac disease who experienced anginal chest pain. Many of these patients were found to have abnormal radiographs of the esophagus showing disordered motility. Evans termed the condition esophageal arrhythmia.

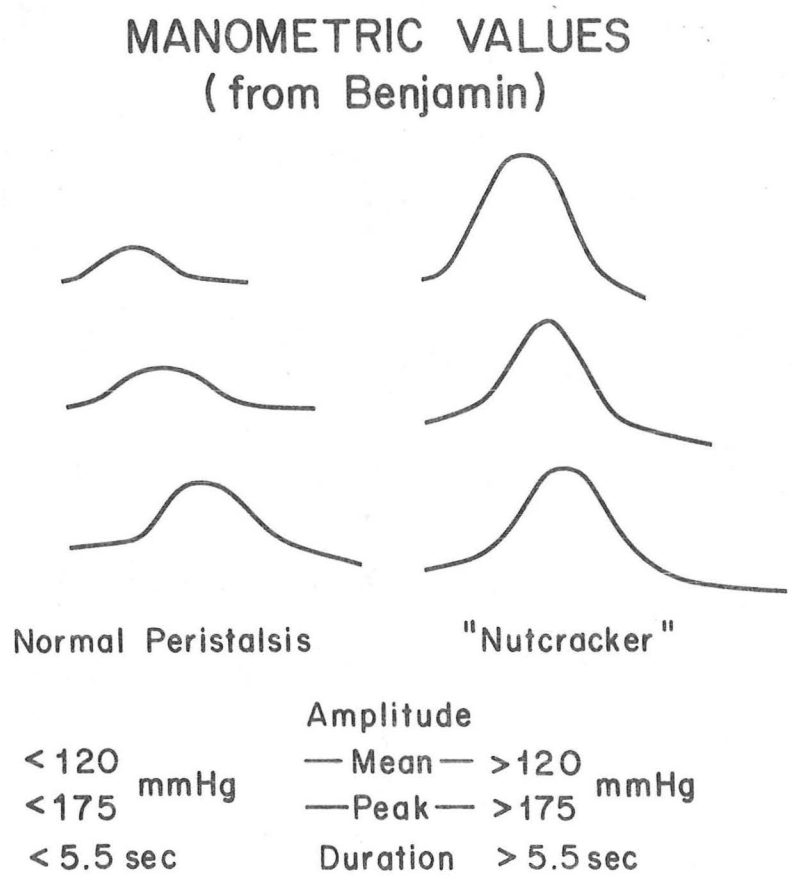
During the 1950's esophageal manometry entered its early stages and the pattern of motility found in diffuse esophageal spasm (DES) was described. Distal esophageal contractions were often tertiary (i.e., repetitive, non-peristaltic, beginning simultaneously), and often with elevated baseline pressures. It was later noted that the duration of the contractions was prolonged and the amplitude increased (Figure 27).



Clinically these patients experienced intermittent chest pain, often associated with dysphagia. The pain was at times exercise-induced and relieved with nitroglycerin. The clinical course was not progressive.

As more patients with the clinical syndrome were studied manometrically, a variant was noted in which contractions were often of abnormal duration and amplitude but peristaltic. During the 1970's, esophageal manometry equipment improved and more accurate tracings could be obtained. The Seattle group reported in 1977 thirteen patients whom they felt had esophageal motility disorders as a cause of anginal chest pain. Ten of these had peristaltic contractions of increased amplitude (9) or duration (1) and only three had DES. Pope called these patients "super-squeezers". In 1979 the Bethesda group made very careful manometric measurements in asymptomatic subjects to define "normal". They found, using low-compliance manometric systems, that normal subjects rarely had repetitive, simultaneous contractions; that mean contraction amplitude was <120 mm Hg; that contraction amplitude never exceeded 175 mm of Hg; and that mean contraction duration was less than 5.5 seconds.

This group next studied 290 patients with chest pain and/or dysphagia. Thirty-eight had "abnormal" motility studies - 10 achalasia, 5 scleroderma, 3 DES, and 20 "nonspecific". From the latter 20, seven were found with high amplitude peristaltic contractions (Figure 28).



Contraction duration was also prolonged in five of the seven. What Pope called "supersqueezer esophagus", they called "nutcracker esophagus" (NCE). Following acid perfusion of the distal esophagus, one of the patients developed anginal chest pain accompanied by the manometric pattern of DES. This suggests first that there is an overlap between the two motility disorders, and second that some patients with central chest pain may have reflux-induced motility disorders.

Clinically, patients with DES and nutcracker esophagus cannot be distinguished. Both abnormalities appear to be associated with pain and/or dysphagia and both are intermittent. Both are diseases of the distal esophagus. Radiographically, DES produces abnormalities ranging from mild serrations (tertiary contractions) to striking abnormalities given such names as curling, beading, corkscrew esophagus, rosary bead esophagus, and others. It should be pointed out that such x-ray findings usually are not accompanied by chest pain and can occur in asymptomatic patients. The barium x-ray will be normal in 65% of patients with manometrically-diagnosed nutcracker esophagus. In the other 35%, there will be radiographic findings comparable to those seen in patients with DES. Benjamin has listed what he considers the manometric criteria for each syndrome:

DES	NCE
1. Simultaneous, non-peristaltic contractions which are repetitive (>3) and of increased duration (>5.5 sec)	1. Peristaltic contractions of increased amplitude (mean of 10 swallows >120 mmHg or any >175 mmHg)
2. Contractions occur spontaneously or after swallow	2. Mean duration of contractions often prolonged (>5.5 sec)
3. Normal peristalsis often seen	
4. Contractions often of increased amplitude	

Additionally, patients with each of these syndromes have been found to have abnormalities of the LES (hypertension and/or incomplete relaxation), further attesting to the manometric incest of motility disorders. Several patients have been documented to progress from DES to achalasia.

WHAT DOES ALL THIS MEAN?

Unquestionably, there are many people in this world who have "abnormal" esophageal motility or "abnormal" amounts of reflux. But just as being shorter or taller than "normal" does not imply disease, abnormal esophageal function does not prove the esophagus is a cause of anginal pain, much less an important one.

ANGINA: CARDIAC VERSUS ESOPHAGEAL

Can Esophageal Pain Mimic Cardiac Angina?

Patients with cardiac angina classically have exercise-induced, gripping chest pain radiating to the neck and arms. It is not dif-

ficult to differentiate these patients from those with reflux when the latter present with burning pain, brought on by food or stooping, and relieved promptly with antacids. However, Bennett and Henderson, in separate series, reported that 25% of patients with reflux had exercise-induced pain, 20% had pain radiating to the arms, and 15% experienced pain to the jaw. More convincing evidence that GE reflux can produce angina-like pain comes from DeMeester who found that 13/50 patients with angina, but no evidence of cardiac disease, experienced their typical symptoms at the time pH monitoring disclosed GE reflux. Thus, reflux can mimic cardiac angina.

Distention of the esophagus produces angina-like pain. Kramer distended the esophagus with a balloon in 19 patients with well-documented angina. In seven, the pain produced was identical to their angina. While it is possible that balloon distention triggered cardiac angina, Kramer felt this was unlikely for three reasons. First, the pain disappeared immediately as the balloon was decompressed. Second, the electrocardigram did not change during distention, while changes had been noted during exercise-induced angina. Third, normal volunteers also noted distressing chest pain attendant to balloon distention.

Alban-Davies compared symptoms in patients with well-documented coronary artery disease or esophageal spasm. His results are summarized in Table 3.

Table 3. Prevalence of each symptom in patients with esophageal spasm or coronary artery disease (from Alban-Davies).

	Esophageal Spasm (N=22)	Coronary Artery Disease (N=15)
Exercise-induced Pain	82%	93%
Pain Relieved with NTG	95%	93%
Heartburn	50%	53%
Dysphagia (any)	50%	40%
Long episodes of pain	82% (P <0.05)	33%
Pain radiates to stomach	32% (P <0.05)	0%

Clearly, it can be difficult to differentiate by clinical symptoms alone those patients with esophageal motility disturbances from those with cardiac angina.

What Proportion of Patients with Anginal Chest Pain Have An Esophageal Cause?

This is a difficult question to answer. Most series present data from selected patients referred after a cardiac evaluation has been unrewarding. Bennett prospectively evaluated 124 patients presenting to an emergency room with central chest pain. Of these, 75 (70%) had

a provisional diagnosis of ischemic heart disease on clinical grounds. A final diagnosis of ischemic heart disease was made in 57/75 and of "esophagitis" in 9/75 (12%).

Alban-Davies noted that 77/100 patients presenting emergently with anterior chest pain had pain of an anginal character. Careful evaluation suggested that about 70% had ischemic heart disease, 10% "definite" esophageal disease [60:40, reflux:motility disorder] and another 10% "probable" esophageal disease [all motility disorders]. Other diseases producing angina-like pain included pneumonia, pericarditis, and gastric ulcer.

In summary, perhaps 10 to 20% of patients with anginal chest pain will have an esophageal origin. While this is substantial, the clear message is that coronary artery disease is the cause in the vast majority of such patients and should always be considered first.

In What Proportion of Patients with Non-Cardiac Angina can the Esophagus be Proven to be the Source?

DeMeester believes three conditions must be met before concluding that the esophagus is the source of anginal chest pain. First, there must be no evidence of a cardiac cause. Second, the pain must occur during evaluative studies of the esophagus. Third, the pain must disappear when the esophageal abnormality is treated or corrected.

Gastroesophageal Reflux - Studies listed in Table 4 excluded cardiac disease by different criteria, but most patients underwent coronary arteriography in addition to other tests of cardiac disease. Each of the studies required reproduction of pain (spontaneous or acid-induced) during esophageal evaluation but in only two was therapy noted to be successful during long-term follow-up.

Table 4. GE reflux as a cause of anginal chest pain in patients without evidence of coronary artery disease.

Author	Pain Noted During	No. Studied	No. With Pain	Follow-up ?
Brand	pH monitoring	160	14 (9%)	
DeMeester	pH monitoring	50	12 (24%)	Yes
Alban-Davies	acid infusion	26	5 (19%)	
Areskog	acid infusion	55	15 (27%)	
Chalbanian	acid infusion	33	4 (12%)	
Ferguson	acid infusion	31	4 (13%)	
Kline	acid infusion	14	3 (21%)	Yes
Wu	acid infusion	12	0 (0%)	
		381	57 (15%)	

The best of these studies is that of DeMeester who performed 24 hr pH monitoring in 50 consecutive patients who had clinically-suspected

coronary artery disease, negative coronary arteriography, and negative ergotamine provocation (no pain, no arterial spasm). Nine patients had severe ST segment depression on a resting electrocardiogram but 41 others underwent exercise tolerance tests. Of these, 20 experienced pain during the test (6 with EKG changes), 5 developed ST depression without pain, 13 stopped when fatiqued, and 3 had normal tests.

Twenty-three (46%) patients had excessive reflux as defined by 24 hr monitoring. Of these, 12 experienced their chest pain coincident with episodes of GE reflux. All 12 patients with reflux and chest pain responded to therapy, 8 by surgery and 4 by medical therapy. Five of the other 11 "refluxers" also experienced pain relief with therapy. Thus, of 50 patients with non-caridac angina, almost half had evidence of GE reflux, a third responded to therapy for GE reflux, and a quarter experienced pain coincident with reflux episodes. Differences among DeMeester's results and those of other investigators probably reflect different patient selection and different testing techniques.

Primary Esophageal Motility Disorders - Results of esophageal manometry in patients with non-cardiac angina are shown for several studies in Table 5.

Table 5. Results of esophageal manometry in patients with "non-cardiac" angina.

Author	No.	Abnormal Motility Noted With Pain	Abnormal Motility Noted Total	Type of Abnormality* NCE	DES	NSEMD
Alban-Davies	26	1 (4%)	11 (42%)	? +	?	?
Brand	145	14 (10%)	57 (39%)	32	10	15
DeMeester	50	0 (0%)	14 (28%)	?	1	?
Chalbanian	39	?	28 (72%)	17	2	9
Wu	23	?	9 (39%)	5	-	4
	283		119 (42%)			

*NCE=Nutcracker, DES=Diffuse esophageal spasm, NSEMD=nonspecific esophageal motility disorder. Other abnormalities such as achalasia, scleroderma are not listed.
+?=data not given or uninterpretable.

Several points can be made from these data:

1. There is a high prevalence (42%) of abnormal esophageal motility in patients with non-cardiac angina.

2. In three studies where it was carefully looked for, NC esophagus is the most common abnormality with DES occurring much less often.

3. Only 15 of 221 evaluable patients were noted to have chest pain concordant with a period of abnormal motility, and 14 of these came from one study. Thus, if abnormal motility is indeed a cause of

chest pain, documenting it by a random manometric study is almost futile. Twenty-four hour manometry (comparable to DeMeester's 24 hr pH measurements) might increase the yield. Such studies are not yet available. Another approach is to provoke a period of abnormal motility with a pharmacologic agent and hope the patient experiences pain.

Provocative Tests of Abnormal Esophageal Motility

Pentagastrin - Noting that the LES in patients with achalasia is super-sensitive to gastrin, and noting the overlap between achalasia and DES, Eckardt and Weigand administered pentagastrin to a patient with DES. The body of the esophagus responded with increased contractile activity which was abolished either by nitroglycerine or atropine. They and others have since studied additional patients with DES or nutcracker esophagus (NCE) with the following conclusions:

1. Pentagastrin in pharmacologic doses increases the amplitude of contractions, baseline esophageal pressure, and repetitive wave activity in patients with DES or NCE.

2. Simultaneous chest pain does not often occur.

3. Administration of pentagastrin to patients with a clinically-suspected motility disorder, but normal or only non-specifically abnormal esophageal motility, is of little use.

Bethanechol - It has been suggested that DES, like achalasia, is a disease of vagal denervation and perhaps, therefore, supersensitive to a cholinergic agonist. When bethanechol is given to patients with DES, there is an increase in contraction amplitude and duration. In one study (Mellow) three of six patients experienced pain which correlated directly with contraction duration. Administration to patients with NCE or non-specific motility disorders produces enhanced motility disturbance but rarely with concomitant chest pain.

Tensilon - Edrophonium, a cholinesterase-inhibitor given in doses of 80-120 µg/kg intravenously, will increase contraction amplitude and duration in patients with DES. Mellow noted that six of eight patients experienced concomitant chest pain. Patients with NCE may also develop chest pain with enhanced motility disturbances. Benjamin noted this occurrence in three of ten patients and London in 10/10. The special aspect of London's study was that all 10 patients had already undergone coronary arteriography during which ergonovine produced chest pain without coronary artery spasm.

Ergonovine - Ergonovine is an alpha-adrenergic stimulant of smooth muscle contraction. It has gained importance in cardiology by its ability to elicit coronary artery spasm in patients with variant angina. Alban-Davies studied 42 patients with chest pain and normal coronary arteries. Twenty-four (60%) of the patients developed chest pain and concomitant motility disturbances, primarily DES, after intravenous doses of ergonovine (0.5-1.0 mg). Of note, six additional

patients with known coronary artery disease were exercised until angina ensued. None displayed abnormal esophageal motility. Results in 64 patients with angina and negative coronary arteriography (including no arterial spasm with ergonovine) are shown from three studies in Table 6. Gravino, Koch, and London studied a total of 19 patients with ergonovine-induced chest pain and normal coronary

Table 6. Chest pain and abnormal motility in patients with completely normal coronary arteries.

Author	No. Studied	No. With Pain and Abnormal Motility
Dalal	27	13 (48%)
Eastwood	14	5 (36%)
Koch	23	10 (43%)
	64	28 (44%)

arteriography. Seventeen (89%) developed abnormal esophageal motility tracings during the pain. Of particular note, the patient studied by Gravino experienced complete relief of pain and improvement in esophageal motility with administration of atropine. As mentioned previously all ten of London's patients also responded to Tensilon. He made the point that adrenergic denervation in animals leads to supersensitivity both to alpha adrenergic and cholinergic agents.

Ergonovine was given to 21 normal subjects in the above studies. Two (given up to 1.0 mg) developed chest pain. All other subjects received doses from 0.1 to 0.4 mg. Eastwood commented that even at these doses, his subjects all developed uncomfortable side effects. It should also be remembered that several deaths from irreversible coronary artery spasm have been reported. Ergonovine should probably never be used in patients with suspected esophageal angina until a negative response of the coronary arteries has been documented. Even then, it should be used with extreme caution.

In summary, tensilon is probably the provocative agent of choice in patients with suspected esophageal angina. Ergonovine should be used only in very special circumstances.

What Is the Mechanism by Which the Esophagus Produces Angina?

It is not known how DES or NCE actually produce anginal pain. Distention of the esophagus can elicit pain, but it is unclear whether either DES or NCE produces esophageal distention. Other possibilities include stimulation of tension receptors in esophageal muscle, production of muscle metabolites as a result of prolonged contraction of smooth muscle, or perhaps the development of ischemia during prolonged tetanic contraction.

Reflux of gastric contents may produce chest pain via stimulation of pain fibers in damaged esophageal mucosa or perhaps via acid-induced motility disorders. While acid infusion occasionally induces abnormal esophageal motility, most experts believe this is the mechanism of chest pain in only a few patients. Simultaneous 24 hr pH measurement and esophageal manometry may provide answers here.

CONCLUSIONS

1. Abnormalities of esophageal function can produce anginal pain.

2. Most patients with angina will have ischemic heart disease. The proportion of patients having esophageal disease is at most 20%, while 10% or lower is probably a more realistic estimate.

3. Gastroesophageal reflux may be a cause of anginal chest pain in 25-50% of patients in whom ischemic heart disease has been fully excluded. Twenty-four hour pH monitoring is a valuable tool in such patients.

4. Esophageal motility disorders may account for another 40-50% of patients in whom ischemic heart disease has been fully excluded. However, provocative tests are required to correlate abnormal motility with chest pain. A random esophageal manometry study is of very low yield.

SUGGESTIONS FOR EVALUATING PATIENTS WITH CHEST PAIN

In general, patients with angina should be assumed to have ischemic heart disease until proven otherwise. Although each patient must be managed individually, several general comments can be made regarding the tests of esophageal function:

Acid Infusion (Bernstein) Test - This test is simple, cheap, relatively non-invasive, and with the addition of bile salts to the acid infusion, very sensitive. I would have a low threshold for using this test, especially if symptoms are brought on by stooping, etc. False positive results do occur.

24 Hour pH Monitoring - This test is not so simple but is still relatively non-invasive. It will probably become available in most large hospitals within the next several years and may be of value in selected patients. It will probably be an expensive test.

Esophageal Manometry - The procedure is widely available and can detect esophageal motility disorders. Unfortunately, it rarely provides proof that abnormal motility is the cause of chest pain. An acid reflux test can be performed during routine esophageal manometry. The presence of acid reflux may prompt a trial of anti-reflux therapy, especially if pain is noted concomitant with periods of reflux.

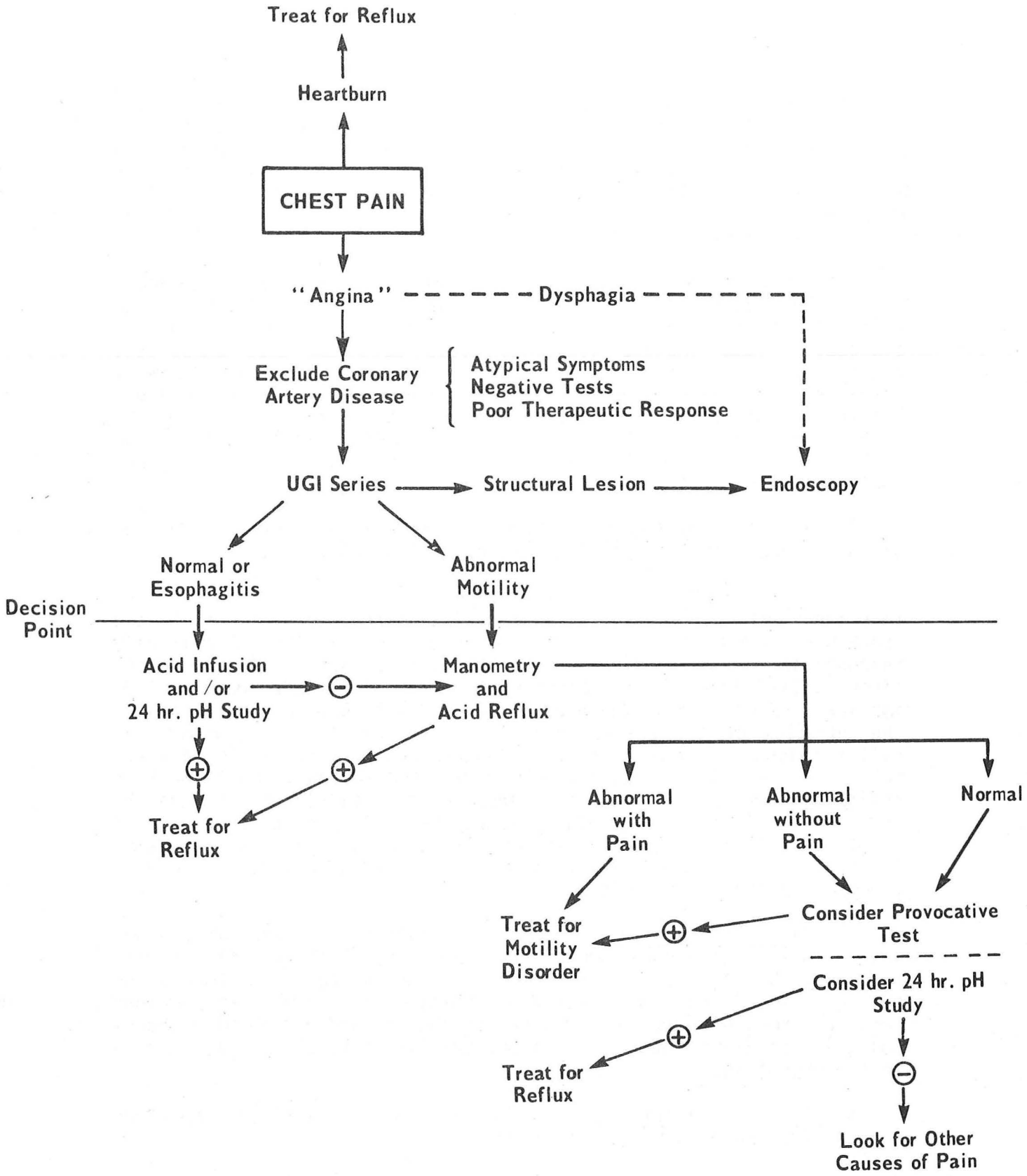
Provocative Tests of Esophageal Motility - Most experts feel that Ergonovine, while perhaps effective in eliciting abnormal motility with chest pain, is potentially dangerous and should be used only after negative coronary angiography. Even then, it should be used with caution. Tensilon is probably the best of the other drugs available, although its real value remains to be determined.

One algorithm of management is displayed in Figure 29. Patients who present with central chest pain can be divided into those with heartburn, those with angina, and of course those with other causes such as pleurisy, pericarditis, costochondritis, etc. Those with heartburn can be treated for reflux. Those with angina should have coronary artery disease excluded. How this is accomplished will vary from patient to patient. In some, the presence of atypical symptoms and a negative exercise test may be adequate. In others, a poor response to therapy or a negative cardiac catheterization may be required.

Once coronary artery disease in an individual patient has been excluded to the physician's satisfaction, (remembering that one may still return to such a diagnosis at some later date), an UGI series is a reasonable first test, primarily to exclude structural lesions of the esophagus, stomach, and duodenum. If any is found, or if the patient has dysphagia, endoscopy should be performed. Having excluded structural lesions, the physician is now at a decision point. Is it necessary to proceed with further diagnostic tests? How severe are the patient's symptoms? Is an empiric trial of anti-reflux therapy warranted? [In my opinion, it would be unwise at this point to institute an empiric course of therapy with nitrates or calcium channel blockers (see below) without attempts at making a specific diagnosis]. If a decision is made to go for a diagnosis, one begins with an acid infusion test, a 24 hr pH study, or esophageal manometry with an acid reflux test and proceeds from there (Figure 29).

TREATMENT OF ESOPHAGEAL CAUSES OF CHEST PAIN

It is beyond the scope of this discussion to discuss therapy in depth. Such will be the topic of a future presentation. However, some general comments are in order.


Treat for Reflux
Heartburn
CHEST PAIN
"Angina"
Dysphagia
Exclude Coronary Artery Disease
Atypical Symptoms
Negative Tests
Poor Therapeutic Response
UGI Series
Structural Lesion
Endoscopy
Normal or Esophagitis
Abnormal Motility
Decision Point
Acid Infusion and/or 24 hr. pH Study
Manometry and Acid Reflux
Treat for Reflux
Abnormal with Pain
Abnormal without Pain
Normal
Treat for Motility Disorder
Consider Provocative Test
Consider 24 hr. pH Study
Treat for Reflux
Look for Other Causes of Pain

Treatment of Gastroesophageal Reflux

Medical - Certain foods, such as citrus juices, tomato products, coffee, and some spices, are notorious for irritating the distal esophagus and should be avoided in those patients experiencing discomfort. Beyond these measures, the overall goal of therapy in patients with GE reflux is to reduce the time the esophageal pH is acid. Ways to accomplish this goal are to reduce the number of reflux episodes, to reduce the acidity of gastric contents, and to improve esophageal clearance.

1. Reduction of reflux episodes - Patients should avoid between-meal snacks which stimulate gastric acid and promote inappropriate relaxation of the LES. Substances which lower LES pressure should be avoided. These include nicotine, foods such as fats, chocolate, alcohol, and carminatives (peppermint, spearmint) and drugs such as nitrates, anti-cholinergics, theophylline, and calcium channel blockers. Finally, drug therapy may reduce reflux episodes by strengthening the LES (bethanecol and metoclopramide) or promoting gastric emptying (metoclopramide). Gaviscon (foam barrier) is probably not an effective way to reduce reflux episodes.

2. Reduction of Gastric Acidity - Antacids or cimetidine can be given to reduce the "aggressiveness" of gastric contents.

3. Improvement of Esophageal Clearance - This is probably the most important approach to reduce the time gastric contents are in the esophagus, since it is poor clearance at night which is primarily responsible for severe disease. Nighttime sedatives should be avoided since arousal from sleep (necessary to clear the esophagus) would be impaired. Elevation of the head of the bed with 6 inch blocks reduces the duration of individual reflux episodes by 70%. The number of reflux episodes is not affected. Bethanecol, a cholinergic agonist, not only strengthens resting LES tone (thereby reducing nighttime reflux episodes by 25%), but also enhances peristaltic effort (thereby reducing the duration of reflux episodes by 50%). These effects occur at night, but not during the day when most reflux episodes are due to inappropriate complete relaxation of the LES and when gravity promotes prompt esophageal clearance.

4. Overall Approach - Patients should be advised about drugs which lower LES pressure, should be given a few dietary instructions, and should be advised to stop smoking. Antacids are prescribed during the day and the head of the bed is elevated at night. If symptoms persist, cimetidine may be added during the day and a dose of bethanecol given at night. Where metoclopramide fits into the scheme remains to be determined.

Surgical - Patients who fail to respond to medical therapy often benefit from surgical fundoplication.

Treatment of Esophageal Motility Disorders

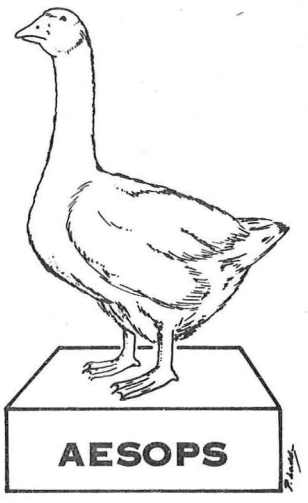
Bougienage - Passage of large-diameter mercury bougies has been a traditional form of therapy for esophageal motility disorders. While anecdotal reports suggest transient effectiveness in some patients, the rationale for its use escapes me and proof that it actually works is unavailable. A "placebo-controlled" trial (Winters) suggests that bougienage is not effective.

Smooth Muscle Relaxants - Because DES and NCE are diseases primarily of smooth muscle contraction, and because esophageal ischemia is one putative mechanism of esophageal pain, it is not surprising that smooth muscle relaxants/vasodilators have been tried. Although these drugs are contraindicated in patients with GE reflux, nitroglycerin and long acting nitrates have been reported to be effective in small numbers of patients with esophageal motility disorders. Hydralazine has been shown by Mellow to blunt the provocative effect of bethanecol in five patients with DES or NCE, and in four patients, long-term therapy with hydralazine (75-200 mg/day) produced marked symptomatic improvement.

Calcium channel blockers have been used to decrease LES pressure in patients with achalasia with some success. However, the effect of these drugs on esophageal contraction amplitude and duration in animals and normal human subjects have been conflicting. Their role in patients with DES or NCE, therefore, remains to be determined.

Anticholinergic Drugs - These drugs have been tried empirically with questionable success. A recent report suggests the combination of an anticholinergic agent with a calcium channel blocking agent might prove most effective in reducing contraction amplitude (Hongo).

Surgery - A long myotomy is recommended for patients with well-documented DES who fail medical therapy. Results are usually reported as excellent, although I would offer two comments. First, GE reflux should be excluded so that an inappropriate operation is not performed. Second, esophageal surgery should not be done without ruling out coronary artery disease.



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