The Mode of Action of Alginic Acid Compound in the Reduction of Gastroesophageal Reflux

Leon S. Malmud, N. David Charkes, James Littlefield, John Reilley, Howard Stern, Ronald Rosenberg, and Robert S. Fisher

Temple University Medical School, Philadelphia, Pennsylvania

This study was designed to evaluate quantitatively the mode of action of alginic acid compound (AAC) in the treatment of patients with symptomatic gastroesophageal reflux. Gastroesophageal scintigraphy using an orally administered Tc-99m sulfur colloid solution was used to demonstrate that AAC decreased significantly the gastroesophageal reflux index from (9.9 ± 1.3)% to (6.5 ± 0.8)% ($p < 0.05$). No alteration of lower esophageal sphincter pressure was observed. After AAC was suitably labeled with Sr-87m, a dual-nuclide scintigraphic technique was used to show that most (>75%) of the AAC was located in the upper half of the stomach in both normal subjects and patients with gastroesophageal reflux. In those subjects in whom reflux did occur after treatment with AAC, the Sr-87m-AAC refluxed into the esophagus preferentially compared with the liquid containing Tc-99m sulfur colloid. These findings suggest that AAC diminishes gastroesophageal reflux by means of its foaming, floating, and viscous properties.

J Nucl Med 20: 1023–1028, 1979

The conventional medical treatments for symptomatic gastroesophageal reflux include agents that decrease acid-pepsin secretion (*1,2*), antacids to neutralize gastric acidity (*3*), and antirefluxants to decrease the quantity of gastroesophageal reflux. Typical antirefluxants such as bethanechol (*4*) and metoclopramide (*5,6*) probably decrease reflux by increasing lower-esophageal sphincter pressure, the major resistance factor at the gastroesophageal junction (*7*). In recent years, a therapeutic agent that combines alginic acid with a mixture of antacids (AAC) has been introduced (*8,9*). On the basis of preliminary studies performed with an in vitro model, it has been concluded that AAC decreases reflux by means of its floating, viscous properties. This hypothesis has not been tested rigorously.

A quantitative in vivo technique to evaluate the action of AAC has not been available. Recently, however, the technique of gastroesophageal scintigraphy has been used to detect and quantitate gastroesophageal reflux (*10*). The purpose of this study was twofold: first, to determine whether AAC decreased gastroesophageal reflux, and second, to investigate the mechanism of action of AAC—that is, to determine whether the material floats on the gastric contents and, if so, whether or not it refluxes preferentially to the other gastric contents.

METHODS

This study was performed following approval from the appropriate committees of Temple University Medical School. All normal subjects and patients with symptomatic gastroesophageal reflux were studied after written informed consent was obtained. The project was divided into two parts:

Part 1. Studies were performed on 15 patients with heartburn and a positive acid reflux test. These patients ranged in age between 28 and 63 yr (mean 44.6). An esophageal manometric examination and (on a different

Received Feb. 19, 1979; revision accepted May 25, 1979.

For reprints contact: Robert S. Fisher, Gastroenterology Section, Temple University Hospital, 3401 N. Broad St., Philadelphia, PA 19140.

day) serial gastroesophageal scintigraphy were performed both before and 5 min after administration of four tablets of AAC. Patients were studied in the sitting position because people with reflux are erect throughout the major portion of the day and are instructed to sleep with their heads and trunks elevated. Each AAC tablet consisted of alginic acid mixed with a combination of antacids: aluminum hydroxide, sodium bicarbonate, and magnesium trisilicate.*

Modified acid reflux test (11). A two-lumen tube assembly, consisting of two fused polyvinyl catheters, was introduced by mouth into the stomach. Intraorgan pressure was measured through a distal pressure orifice, 1.2 mm in diameter, which was infused with distilled water by a syringe pump at a constant rate of 1.1 ml/min. The pressure was transmitted through this catheter to an external transducer. The output was graphed on a multichannel recorder. Intraorgan pH was measured by a pH microelectrode, 2 mm in diameter†, which was introduced through a second polyvinyl catheter that had an end orifice 3 mm in diameter, located 5 cm proximal to the distal pressure orifice. Intraorgan pH was transmitted via a calomel electrode to a pH meter‡ and graphed on the multichannel recorder. The reference pH electrode was placed under the tongue.

Following passage of this tube assembly into the stomach, 30 ml of 0.1 *N* hydrochloric acid were introduced into the stomach through the distal pressure orifice. The tube assembly was withdrawn slowly until the distal pressure orifice was located in the midportion of the lower esophageal sphincter. The pH microelectode was introduced through the second catheter and fixed 4 cm proximal to the pressure orifice, and basal intraesophageal pH was recorded. The gastroesophageal pressure gradient was increased in increments by inflating an abdominal binder. Intraesophageal pH was measured as the gastroesophageal pressure gradient was increased from 10 to 35 mm Hg in increments of 5 mm Hg. A drop of intraesophageal pH below 4 was regarded as a positive test. Each patient studied had a positive acid-reflux test before AAC.

Esophageal manometry (12,13). A three-lumen tube assembly was used to measure pressure in the lower esophageal sphincter. Three water-filled catheters with side orifices, measuring 1.2 mm in diameter and spaced at 5-cm intervals, transmitted intraesophageal pressures to external transducers‖. Pressures were recorded on a rectilinear polygraph. Each pressure catheter was infused with distilled water by a syringe pump at a rate of 1.1 ml/min. Pressure at the lower esophageal sphincter was measured at the midrespiratory excursion point, and the intragastric pressure was used as a zero reference. Gastric and esophageal pressures were expressed relative to atmospheric.

The three-tube assembly was introduced via the nose into the stomach of a fasting patient. After stable baseline recordings were obtained, the tube assembly was withdrawn in increments of 1 cm from the stomach across the lower esophageal sphincter into the distal esophagus. Pressures were measured for 1 min at each site. Belt pneumographs were placed around the chest and over the larynx to monitor respiration and swallowing. The mean pressure of the lower esophageal sphincter (mean of the three pressure orifices) was recorded during two pull-through maneuvers on each patient, before and 5 min after administration of AAC. The mean value of the six measurements was recorded.

Gastroesophageal scintigraphy (10). The equipment and techniques employed to detect and quantitate gastroesophageal reflux directly have been described previously. Following an overnight fast, each patient was placed in a sitting position in front of a gamma camera fitted with a diverging medium-energy collimator. Data from the camera were stored in and processed by a data analyzer. The radiopharmaceutical (150 μCi), drawn from the daily sterile and pyrogen-free preparation of Tc-99m sulfur colloid, was diluted in 300 ml of water and ingested by the patient. The gastroesophageal pressure gradient was increased in 5-mm increments from 10 to 35 mm Hg by inflating an abdominal binder. A scintiphoto was obtained during a 30-sec timed exposure at each pressure gradient. A "gastroesophageal reflux index" was computed by the formula, $RI = E - E_B/G_o \times 100$, in which RI represents the gastroesophageal reflux index; E = esophageal counts; E_B = esophageal background counts; and G_o = maximal gastric counts. Gastric background counts were negligible compared with gastric counts. The amounts of radioactivity in the esophagus and stomach were compared by counting the activities within esophageal and gastric areas of interest prescribed with a light pen on the face of the computer's oscilloscope. Serial gastroesophageal scintigraphy was performed before, and 5 min after, administration of AAC.

All data were analyzed by L.S.M., who had no knowledge of whether or not AAC had been administered. The Student's t-test was used in the statistical analysis of the paired data (*14*).

Part 2. Ten normal subjects, ages ranging from 23 to 37 yr (mean, 28.9) were studied, along with ten patients with heartburn and a positive gastroesophageal scintiscan, ages ranging from 29 to 67 yr (mean, 48.0). Gastroesophageal scintigraphy was regarded as positive when the esophagus became visible to the scan reader basally or as the pressure gradient was increased. The mean gastroesophageal reflux indices were (2.1 ± 0.4) % and (12.0 ± 2.8) % in normal subjects and reflux patients, respectively. Normal subjects and the patients with gastroesophageal reflux were studied before and after administration of AAC labeled with strontium-87m (Sr-87m-AAC).

Labeling of AAC with Sr-87m. Alginic acid was

supplied as a dry powder.§ A 0.2% alginic acid solution (w/v) was made by dissolving the powder in sterile water. Fifteen milligrams of strontium nitrate carrier were added to 2 mCi of Sr-87m nitrate; 10 ml of the 0.2% alginic acid solution were added, and the mixture rotated in a test tube at room temperature for 30 min. The resultant gel was centrifuged for 10 min and the supernatant carefully removed. Twice the precipitated gel was washed with 10 ml of absolute ethanol, centrifuged, and the supernatant removed. Following the final wash, the gel was spread along the inner surface of the tube and the tube placed in an 80°C water bath under vacuum for 20–30 min to dry the strontium alginate.

All fractions or aliquots of the fractions were counted in a scintillation spectrometer to determine the percentage recovery, the percentage binding, and the specific activity. The radiolabeled alginic acid was then added to unlabeled alginic acid to a total weight of 200 mg, and the total added to the antacids (dried aluminum hydroxide gel, 80 mg; sodium bicarbonate, 70 mg; and magnesium trisilicate, 20 mg), binders and other inert ingredients that constitute an AAC tablet*. This powder was pressed into a tablet the standard size of an AAC tablet, in a 5000-psi tablet press.

Dual nuclide scintigraphy. Three hundred milliliters of water mixed with 150 μCi of Tc-99m sulfur colloid (TcSc) were ingested by a fasting subject. The patient was positioned in front of a gamma camera and serial gastroesophageal scintigrams were obtained (see Gastroesophageal Scintigraphy, Part 1). Two tablets of Sr-87m AAC, formulated with ~500 μCi Sr-87m, were administered to each subject. The scanning procedure outlined previously was repeated, but now with both tracers. Tc-99m activity was counted using a 140-keV ± 20% window on a gamma camera and Sr-87m activity using a 360-keV ± 35% window. Sr-87m scatter into the Tc-99m window was corrected for by using calculations derived from two pure sources of known activity (phantoms). Data processing consisted of seven steps, as follows:

1. The list-mode data were used to generate two frame-mode images, one for the Tc-99m window counts and the other for the Sr-87m window counts. This was performed at each pressure for a total of 12 images.

2. Using a light pen, regions of interest were defined within these frames, corresponding to the upper and lower stomach. In some patients, an additional area of interest for the esophagus was also defined. If necessary, the regions were adjusted for each pressure in order to account for cephalad movement of the abdominal contents as pressure was increased and the stomach moved slightly cephalad. A number of points in the upper and lower stomach were made as close to equal as the irregular shape of the stomach permitted.

3. The total counts from each region for each frame were calculated and printed out.

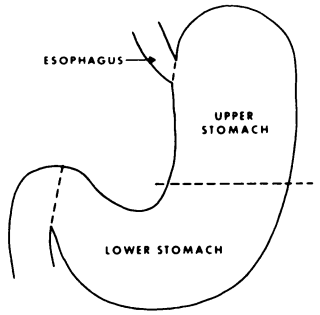

FIG. 1. Sketch to show areas of interest in esophagus and stomach. Total activity in esophagus and stomach was defined as 100%.

4. In each region of the six frames corresponding to data collected from the Tc window, the counts were corrected for Sr-87m scatter by subtracting 22% of corresponding counts for that region from the appropriate strontium image. This percentage was determined empirically from the observed scatter in the Tc window in several patients who had been given only Sr-87m but no technetium.

5. The corrected Tc-99m counts for each region at each pressure were then printed out.

6. The percentage of the corrected technetium counts in each region was determined for each pressure and printed out.

7. The percentage of Sr-87m counts in each region was determined for each pressure and printed out.

Specific areas of interest in the esophagus and in the upper and lower sections of the stomach were designated (Fig. 1). The sum of activity in the esophagus and the two parts of the stomach was defined as 100%.

RESULTS

Part 1. Serial gastroesophageal scintiphotos obtained on a patient before and after administration of AAC are shown in Fig. 2. Before AAC, reflux was seen at all gastroesophageal pressure gradients. Five minutes after administration of AAC, reflux was observed only at the highest pressure gradient, 35 mm Hg. In the patients with gastroesophageal reflux, AAC did not alter the lower esophageal sphincter pressure, which measured 12.1 ± 0.9 mm Hg before and 12.7 ± 0.8 mm Hg ($p > 0.05$) after AAC administration (Fig. 3). In contrast, the gastroesophageal reflux index decreased significantly from (9.9 ± 1.3)% before to (6.5 ± 0.8)% ($p < 0.05$) after ingestion of AAC (Fig. 3).

Part 2. Dual-tracer scintiphotos from a normal subject without reflux are shown in Fig. 4. Images are illustrated using the technetium, strontium, and combined windows. No gastroesophageal reflux of Tc-99m or Sr-87m was

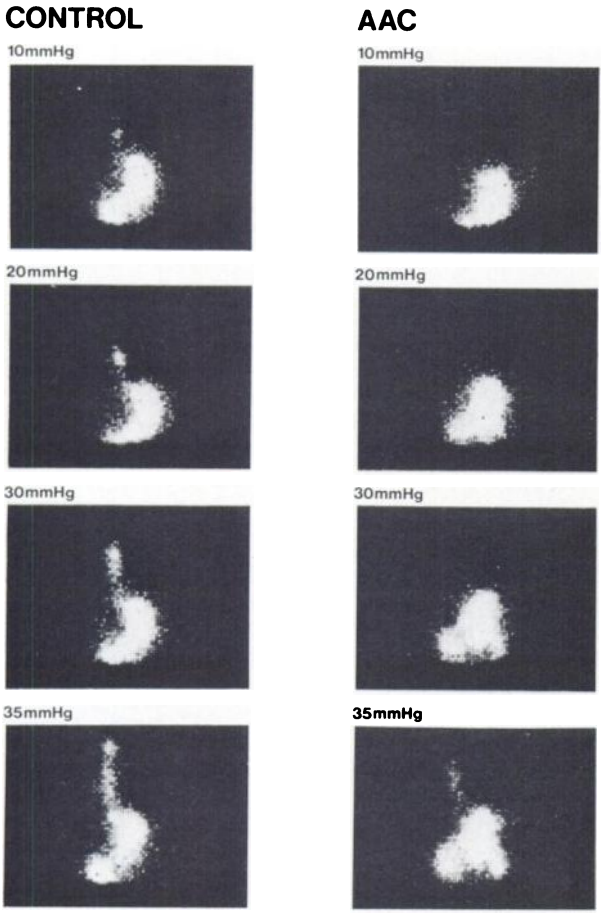

FIG. 2. Serial gastroesophageal scintigrams in patient with reflux, before and after treatment with alginic acid compound (AAC). Before treatment, reflux occurred spontaneously at rest (pressure gradient = 10 mm Hg) and increased progressively as the gradient was increased. After treatment with AAC, reflux did not occur until pressure gradient reached 35 mm Hg.

seen basally at gastroesophageal pressure gradients of either 10 mm Hg or (maximal) 35 mm Hg. The technetium activity was distributed equally between the two halves of the stomach, but the Sr-87m AAC activity was located primarily in the upper half. The composite results of studies performed on all ten normal subjects are shown in Table 1. Before Sr-87m AAC was administered, Tc-99m activity was minimal in the esophagus and was distributed equally throughout the upper and lower halves of the stomach. The Tc distribution was unchanged by Sr-87m AAC. However, approximately 85% of the Sr-87m activity was located in the upper half of the stomach.

Dual-tracer scintiphotos from a patient with gastroesophageal reflux are shown in Fig. 5. Before treatment, a significant part of the gastric contents, labeled with TcSc, refluxed into the esophagus. In contrast, treatment with Sr-87m AAC markedly diminished the quantity of Tc-99m reflux. Although only minimal reflux of Tc-99m was present after treatment, Sr-87m AAC refluxed preferentially into the esophagus. The composite results of studies performed on ten patients with symptomatic gastroesophageal reflux are shown in Table 2. Before treatment, (12.0 ± 2.6)% of the Tc activity refluxed into the esophagus. The remainder was distributed equally throughout the stomach. After administration of Sr-87m AAC, the reflux of Tc decreased significantly to (7.8 ± 1.8)% ($p < 0.05$). In contrast, (14.8 ± 2.2)% of the Sr-87m AAC was in the esophagus. Of interest, (62.3 ± 4.0)% of the Sr-87m AAC was located in the upper half of the stomach.

DISCUSSION

A new product, which combines alginic acid and a mixture of several antacids (AAC), has been postulated to relieve the symptoms of gastroesophageal reflux both by decreasing the quantity of reflux and by neutralizing the esophageal acid (*8*). It has been suggested that an AAC tablet, after it is chewed, forms a viscous foam that floats on top of the liquid surface within the stomach and acts as a barrier to reflux. The antacids are suspended within the foam.

The present study demonstrated that administration of AAC to patients with symptomatic reflux was associated with a decreased amount of gastroesophageal reflux. Lower esophageal sphincter pressure was unchanged. Since patients were evaluated in the same position before and after treatment with AAC, gravitational effects do not provide an explanation. Based on observations in Part 1, we conclude that AAC blocked

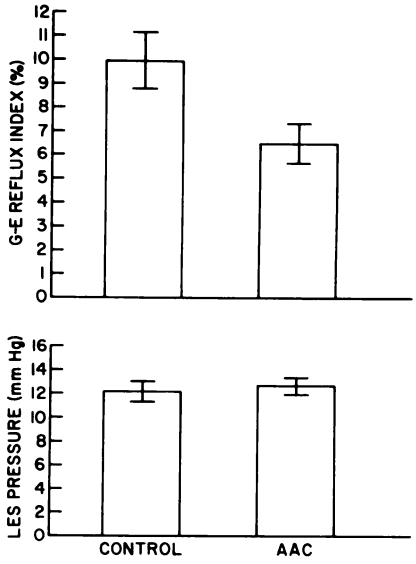

FIG. 3. Measurements of lower esophageal sphincter (LES) pressure and gastroesophageal (GE) reflux index in 15 patients with gastroesophageal reflux before and after administration of alginic acid compound (AAC). Each bar represents mean ± s.e.m. LES pressure was not changed by AAC but GE reflux indices were decreased significantly.

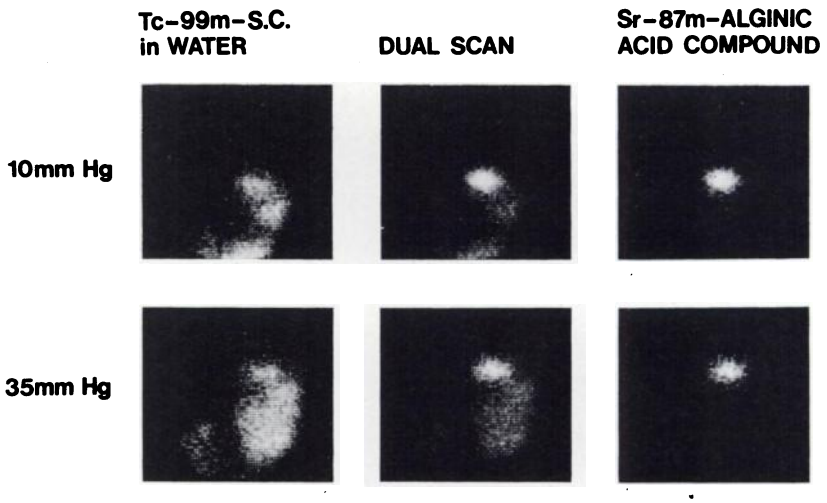

FIG. 4. Dual-tracer gastroesophageal scintigrams in normal subject at gastroesophageal pressure gradients of 10 and 35 mm Hg. Tc-99m sulfur colloid was used to label a water meal and Sr-87m labeled alginic acid compound. With Tc-99m window (left), Tc activity is seen distributed evenly throughout stomach, without reflux. With Sr-87m window (right), AAC was found predominantly in upper half of stomach.

reflux by a nongravitional mechanism independent of the lower esophageal sphincter.

In Part 2, studies with Sr-87m AAC demonstrated that, indeed, the majority of the administered AAC floated atop the liquid surface within the stomach. This was in contrast to TcSc in water, which was distributed rather homogeneously throughout the two halves of the stomach. Furthermore, in patients with symptomatic gastroesophageal reflux, the total amount of reflux was decreased by AAC, and the AAC appeared to reflux into the esophagus preferentially compared with the other gastric contents.

One might reasonably ask how AAC, even if it floats, deters gastroesophageal reflux. Previous studies have demonstrated that AAC foam is more viscous than the normal gastric contents (unpublished data). We suspect, therefore, that AAC reduces reflux by its floating, foaming, and viscous properties.

This study was possible due to several technological advances. Included are esophageal manometry using infused, open-tipped catheters that provide a sensitive and accurate method for measuring gastrointestinal sphincter pressures (*12,13*); the modified acid reflux test, which provides qualitative detection of gastroesophageal reflux (*11*); and gastroesophageal scintigraphy, which allows both detection and quantitation of reflux (*10*). In addition, by labeling alginic acid with Sr-87m, a dual-tracer technique was developed that provides identification and location of Sr-87m AAC and Tc-99m sulfur colloid in water within the field of interest. This application of a dual-tracer method to study the action of AAC in vivo suggests that other gastrointestinal therapeutic agents might be studied similarly using tracer quantities of appropriate gamma emitters to label the agent in question.

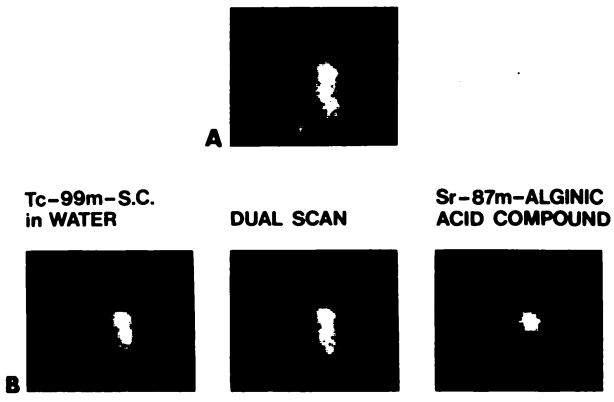

FIG. 5. A single-tracer gastroesophageal scintiphoto before (A) and dual-tracer images after (B) treatment of single reflux patient with Sr-87m-labeled alginic acid compound. Before treatment (A), appreciable gastroesophageal reflux of Tc-99m activity was present. After treatment with alginic acid compound, reflux of Tc-99m decreased markedly (B, left). In contrast Sr-87m-labeled alginic acid compound refluxed preferentially (B, right); most of alginic acid compound was in esophagus and upper half of stomach.

TABLE 1. QUANTITATIVE DUAL-TRACER GE SCAN DATA. PERCENTAGES OF Tc AND Sr ACTIVITY IN NORMAL SUBJECTS

	Before AAC	After AAC	
	(Tc window)	(Tc window)	(Sr window)
Esophagus	2.1 ± 0.4	1.9 ± 0.4	2.6 ± 0.4
Stomach: upper	52.7 ± 3.4	54.7 ± 2.9	85.0 ± 2.0
Stomach: lower	45.2 ± 3.8	43.4 ± 3.2	12.4 ± 2.2

TABLE 2. QUANTITATIVE DUAL-TRACER GE SCAN DATA. PERCENTAGES OF Tc AND Sr ACTIVITY IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE

	Before AAC	After AAC	
	(Tc window)	(Tc window)	(Sr window)
Esophagus	12.0 ± 2.6	7.8 ± 1.8	14.8 ± 2.2
Stomach: upper	46.7 ± 3.0	49.7 ± 2.1	62.3 ± 4.0
Stomach: lower	41.3 ± 2.5	42.5 ± 1.6	22.9 ± 4.1

FOOTNOTES

* Gaviscon, Marion Laboratories, Inc., Kansas City, MO.
† Microelectrodes, Inc., Londonderry, NH.
‡ Beckman Instruments, Palo Alto, CA.
‖ Statham P23BB,
§ Marion Laboratories, Inc., Kansas City, MO.

ACKNOWLEDGMENT

The authors thank N. David Charkes, for his suggestions concerning the use of an isotope of strontium to label alginic acid.

REFERENCES

1. BEHAR J, BRAND DL, BROWN FC, et al: Cimetidine in the treatment of symptomatic gastroesophageal reflux. A double blind controlled trial. *Gastroenterology* 74: 441-448, 1978
2. WESDORP E, BARTELSMAN J, PAPE K, et al: Oral cimetidine in reflux esophagitis: a double blind controlled trial. *Gastroenterology* 74: 821-824, 1978
3. CASTELL DO, LEVINE SM: Lower esophageal sphincter response to gastric alkalinization. A new mechanism for treatment of heartburn with antacids. *Ann Int Med* 74: 223-227, 1971
4. FARRELL RL, ROLING GT, CASTELL DO: Cholinergic therapy of chronic heartburn. A controlled trial. *Ann Int Med* 80: 573-576, 1974
5. DILAWARI JB, MISIEWICZ JJ: Action of oral metoclopramide on the gastroesophageal junction in man. *Gut* 14: 380-382, 1973
6. BEHAR J, BIANCANI P: Effect of oral metoclopramide on gastroesophageal reflux in the post-cibal state. *Gastroenterology* 70: 331-335, 1976
7. FISHER RS, MALMUD LS, ROBERTS GS, et al: The lower esophageal sphincter as a barrier to gastroesophageal reflux. *Gastroenterology* 72: 19-22, 1977
8. STANCIU D, BENNETT JR: Alginate/antacid in the reduction of gastroesophageal reflux. *Lancet* 1: 109-111, 1974
9. FISHER RS, ROBERT GS, LOBIS IF, et al: Use of gastroesophageal scintiscan to evaluate anti-reflux maneuvers. *Gastroenterology* 68: 893, 1975
10. FISHER RS, MALMUD LS, ROBERTS GS, et al: Gastroesophageal (GE) scintiscanning to detect and quantitate GE reflux. *Gastroenterology* 70: 301-308, 1976
11. TUTTLE SG, GROSSMAN MI: Detection of gastroesophageal reflux by simultaneous measurement of intraluminal pressure and pH. *Proc Soc Exp Biol Med* 98: 225-227, 1958
12. WINANS CS, HARRIS LD: Quantitation of lower esophageal sphincter competence. *Gastroenterology* 52: 773-778, 1967
13. POPE CE: A dynamic test of sphincter strength: its application to the lower esophageal sphincter. *Gastroenterology* 52: 779-786, 1967
14. SNEDECOR GW, COCHRAN WC: *Statistical Methods.* Sixth edition. Ames, Iowa, Iowa State University Press, 1967