# Esophageal Epithelial Response to Gastroesophageal Reflux

## A Quantitative Study

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*Exposure of the distal esophageal mucosa to acid gastric juice was quantitated by 24-hr pH monitoring in 100 individuals and was correlated with morphologic data derived from esophageal biopsies. The degree of acid exposure to the distal esophagus correlated directly with increases in both relative and absolute length of the subepithelial papillae and to relative basal zone hyperplasia. Both papillary length and basal zone hyperplasia decreased after antireflux surgery had reduced acid exposure to normal. Reflux in the recumbent position resulted in prolonged exposure of the mucosa to acid because of poor acid clearing from the esophagus. This caused longer papillae than did upright reflux, where there were more frequent reflux episodes, but with rapid acid clearance. The presence of a hiatal hernia was associated with longer papillae, lower DES pressure, increased reflux frequency, and prolonged recumbent acid clearance. Twenty-four hour pH monitoring correlated better with papillary length than did symptoms or other clinical measures of gastroesophageal reflux.*

Chronic irritation of the esophageal mucosa by noxious gastric juice has been implicated as the cause for the increased papillary length and basal zone hyperplasia observed in the esophageal epithelium of patients with gastroesophageal reflux symptoms (1-3). Distal esophageal exposure to acid gastric juice was assumed based on the presence of symptoms but was not quantitated in these studies. The purpose of the present study was to examine the relationship between esophageal mucosal exposure to acid gastric juice quantitated by 24-hr pH monitoring (4) and the associated epithelial response quantitated by morphometric data obtained from esophageal biopsy.

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## MATERIALS AND METHODS

### Population Studied

One hundred and fourteen consecutive patients referred to our esophageal function laboratory for a variety of clinical indications were interviewed and completed a questionnaire (see Table 1) modified from that described by Moran et al (5), prior to any diagnostic procedure. All patients had fiberoptic esophagoscopy with distal esophageal biopsy prior to manometry and pH testing. Fourteen patients were excluded from the study because their biopsies were improperly oriented or inadequate for evaluation. The remaining 100 patients composed the study population.

### Esophageal Motility

Esophageal motility was performed in accordance with the technique of Winans and Harris (6), using a catheter made by bonding three polyvinyl tubes (ID 0.054 in., OD



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TABLE 1. GRADED REFLUX QUESTIONNAIRE

| | |
|---|---|
| Heartburn | |
| 0 | None |
| 1 | Pyrosis present, but not primary reason for medical attention |
| 2 | Pyrosis primary reason for medical attention |
| 3 | Pyrosis severe, limiting activities of daily living |
| Regurgitation | |
| 0 | None |
| 1 | Mild, occasional sour eructation, water brash after large meal or straining |
| 2 | Moderately severe, predictable with position change |
| 3 | Severe, transadital aspiration—awaken with nocturnal cough and choking |
| Dysphagia | |
| 0 | No subjective awareness of swallowing difficulty |
| 1 | Solid food sticking a few seconds and spontaneously passing |
| 2 | Solid food sticking, liquids required to clear |
| 3 | Severe, meat impaction requiring medical attention |

0.088 in.) together, each of which had one lateral opening, 2 mm in diameter and 5 cm apart at the distal end. A Beckman pH electrode (#39042) was attached to the catheter opposite the most distal opening so that simultaneous pressure and pH measurements could be recorded. The catheter assembly was passed through an anesthetized nose and advanced into the stomach. Distal esophageal sphincter (DES) pressure was measured in millimeters of mercury from end-expiratory gastric pressure to resting end-expiratory distal esophageal sphincter pressure in the region of the respiratory inversion point during quiet respiration and on slow withdrawal of the catheter assembly from the stomach. The DES pressure used in presentation of data represents a mean value for the three orifices. Care was taken not to confuse resting DES pressure with post-deglutition contractions.

### Standard Acid Reflux Test

The standard acid reflux test (SART) was performed after manometry by introducing 300 cc of 0.1 N HCl through the distal catheter opening after gastric respiratory excursions and acid pH had assured gastric placement of the catheter. The probe was then placed 5 cm above the proximal margin of the manometrically located DES, and with the patient erect, all acid was allowed to clear the esophagus prior to testing. The patient then assumed the supine position and performed four maneuvers—deep breathing, Valsalva, Muller, and cough. These were repeated in the left lateral, right lateral, and 20-degree head-down positions, giving 16 opportunities for gastroesophageal reflux. A drop in intraesophageal pH to a value $< 4$ was considered evidence of reflux. Three or more reflux episodes out of 16 trials were considered abnormal (7, 8).

### Twenty-Four Hour pH Monitoring

Distal esophageal pH monitoring was performed by passing a Beckman pH probe (#39042) through the nose and placing it 5 cm above the proximal margin of the manometrically located DES (4). A reference lead (Beckman #40249) was placed on the forearm, in a manner that assured good skin contact. Both the pH probe and the reference lead were connected to a Beckman Zeromatic SS3 pH meter and a 10-in. potentimetric strip-chart recorder running at 6 in./hour. Cigarette smoking (9, 10) and coffee drinking (11) were prohibited during the monitoring period because of their effects on gastroesophageal reflux. All individuals had an intragastric pH of $< 4$. The 24-hr examination was divided into two periods: upright and recumbent. During the upright period, all individuals maintained a sitting or standing position and ate three meals in which the pH of the food and beverage was five or more to avoid simulating a reflux episode. During the recumbent period all individuals slept horizontally with no restrictions as to prone, supine, or lateral position. Reflux was defined as a drop in pH to a value less than 4. The number of reflux episodes and the time required to return the intraesophageal pH to 4 after each episode (acid clearance time) were recorded. Esophageal mucosal exposure to acid gastric juice during the 24 hours was expressed both as cumulative time (minutes at pH $< 4$); and as percent (number of minutes at pH $< 4$/ $1440 \times 100$) time the pH was $< 4$. A previously reported scoring system that incorporated six components from the record (percent acid exposure for periods: 24 hr, upright and recumbent; and reflux episodes: total number, those equal to or greater than 5 min and longest) was used to define each patient's reflux status by a composite score. A score that exceeded two standard deviations above the mean observed in 15 asymptomatic control volunteers reported elsewhere (4) was considered abnormal and used to divide the population of this study into those with normal and abnormal 24-hr pH scores. In those with abnormal scores, three patterns of reflux were noted: (1) Upright refluxers had abnormal upright acid exposure (ie, $> 6.3\%$) (4) but normal recumbent acid exposure (ie, $< 1.2\%$) (4). (2) Recumbent refluxers had abnormal recumbent acid exposure (ie, $> 1.2\%$) (4), but normal upright acid exposure (ie, $< 6.3\%$) (4). (3) Bipositional refluxers had abnormal acid exposure in both the upright and recumbent positions. All groups spent comparable time in both positions. Both the upright and recumbent reflux frequencies (number of episodes/hour) were determined by dividing the number of episodes by the hours spent in the respective postures. The mean acid clearance time was determined by dividing the total duration of acid exposure, either upright or recumbent, by the number of reflux episodes.

### Esophagoscopy and Biopsy

Esophagoscopy was performed with the ACMI polydirectional panendoscope (F.O. #7089P) after a 1% dyclonine hydrochloride gargle and premedication with intravenous meperidine hydrochloride and diazapam. A hiatal hernia was diagnosed when gastric mucosa was fixed or prolapsed 2 or more cm above the diaphragmatic hiatus during quiet respiration without excessive air insufflation. All biopsies were obtained 2–3 cm above the esophagogastric junction using the ACMI Martin biopsy forceps. Endoscopic biopsies were adequate for evaluation when they were meticulously mounted on gel foam to assist

with perpendicular sectioning and then fixed in 10% neutral buffered formalin. The use of low-power magnification was necessary to obtain adequate orientation of the biopsies early in the study, but was not necessary as experience increased. One to three biopsies were obtained from each patient (48 patients had one biopsy, 47 had two, and 5 had three biopsies).

### Radiographic Examination

The presence of a hiatal hernia was determined from the "working" upper-gastrointestinal series obtained prior to esophagoscopy and esophageal function studies. Patients were examined by several radiologists who used the prone oblique position with Valsalva maneuver to examine for a hernia. A hernia was diagnosed by standard radiographic criteria, such as the presence of a B ring, 4 or more folds traversing the esophagogastric (EG) junction, a junction 2 cm or more in diameter, and a supradiaphragmatic pouch 3 cm or more in diameter.

### Histologic Examination

All esophageal biopsy specimens were routinely processed and stained with hematoxylin and eosin. A pathologist (RCH) who had no knowledge of the clinical data evaluated subserial sections at three or more levels of each biopsy block until perpendicular cuts were obtained. This resulted in 18–54 sections from one biopsy. All sections were scanned to determine which one was the best oriented, and measurements were obtained from this section. Each papilla that contained a central core was measured. Biopsies with less than two perpendicularly oriented papillae were considered inadequate for evaluation. The measurements from each papillae (range 2–7) were averaged so that a single set of values was derived from each biopsy. Measurements of the basal zone were taken adjacent to measured papillae. When more than one biopsy was obtained, the values for the individual biopsies were averaged to yield a single set of data. If marked differences in the degree of papillary extension and basal zone hyperplasia occurred in two or more biopsies from the same patient, then the more abnormal biopsy was used to calculate the data. This variability occurred in only six patients; the remaining patients had either single biopsies or multiple biopsies with comparable histologic changes.

The Martin biopsy forceps was able to obtain biopsies of adequate depth as evidenced by the fact that four contained muscularis mucosae, 35 included portions of lamina propria, and 53 had the epithelial basal lamina with intact overlying epithelium. The eight remaining biopsies did not contain basal lamina, but were considered adequate for evaluation because the lowermost portion of the biopsy clearly included most of the basal layer as indicated by its morphology.

All biopsy measurements were made at 100×, using an eyepiece micrometer (American Optical #405) and expressed in arbitrary units having the following conversion factor: one micrometer unit equals 0.01 mm, or 10 $\mu$m. Epithelial measurements were expressed in millimeters.

Figure 1 shows a satisfactory biopsy and defines the measurements made: (1) total thickness of epithelium (T) as measured from basal lamina (BL) to luminal surface; (2) thickness of basal zone (BZ) as measured from basal lamina to point at which nuclei were separated by distance equal to their diameter; (3) papillary length (P) as measured from basal lamina to basal lamina at apex of papilla; and (4) suprapapillary epithelium (E) as measured from basal lamina at tip of papilla to luminal surface. Percent papillary length and basal zone hyperplasia were calculated by the formula: $P$ or $BZ$ (mm)/$T \times 100$.

### Statistical Evaluation of Data

Data were expressed in mean values with 1 SE of the mean stated or shown on bar graphs. The correlations of papillary extension and/or basal zone hyperplasia with 24-hr pH monitoring, DES pressure, standard acid reflux test, and reflux questionnaire were examined for statistical significance by regression analysis. The difference between epithelial changes and acid reflux as measured before and after surgery was compared by the paired $t$ test. The difference in reflux frequency and acid clearance time after changes in posture was statistically examined by the paired $t$ test. Students' $t$ test for unpaired values was used to determine the significance for differences in epithelial dimensions, reflux frequency, and acid clearance times.

## RESULTS

### Esophageal Histology and 24-Hr pH Monitoring

There was a direct correlation between percent papillary length (Figure 2) and both the 24-hr pH composite score and the percent of time that the pH was $< 4$ for the total monitored period. A similar direct correlation could be made with absolute papillary length (Figure 3). There was also a direct correlation between percent basal zone hyperplasia and the percent of time that the pH was $< 4$ (Figure 4).

When the study population was divided into two groups based on 24-hr pH composite scores, 69 patients with an abnormal score had greater percent papillary extension, longer absolute papillary length, and thinner suprapapillary epithelium than 31 patients with a normal score (Table 2). The epithelial thickness, however, remained comparable in the two groups. The basal zone tended to be thicker in those with abnormal 24-hr pH composite scores.

Five patients from our surgical antireflux experience reported elsewhere (12, 13) had 24-hr pH monitoring and esophageal biopsies both before and after antireflux surgery (mean 31 weeks) to determine if papillary extension and basal hyperplasia would diminish after reduction of acid reflux. After surgery the 24-hr pH composite score and the percent time the pH was $< 4$ returned to normal, and

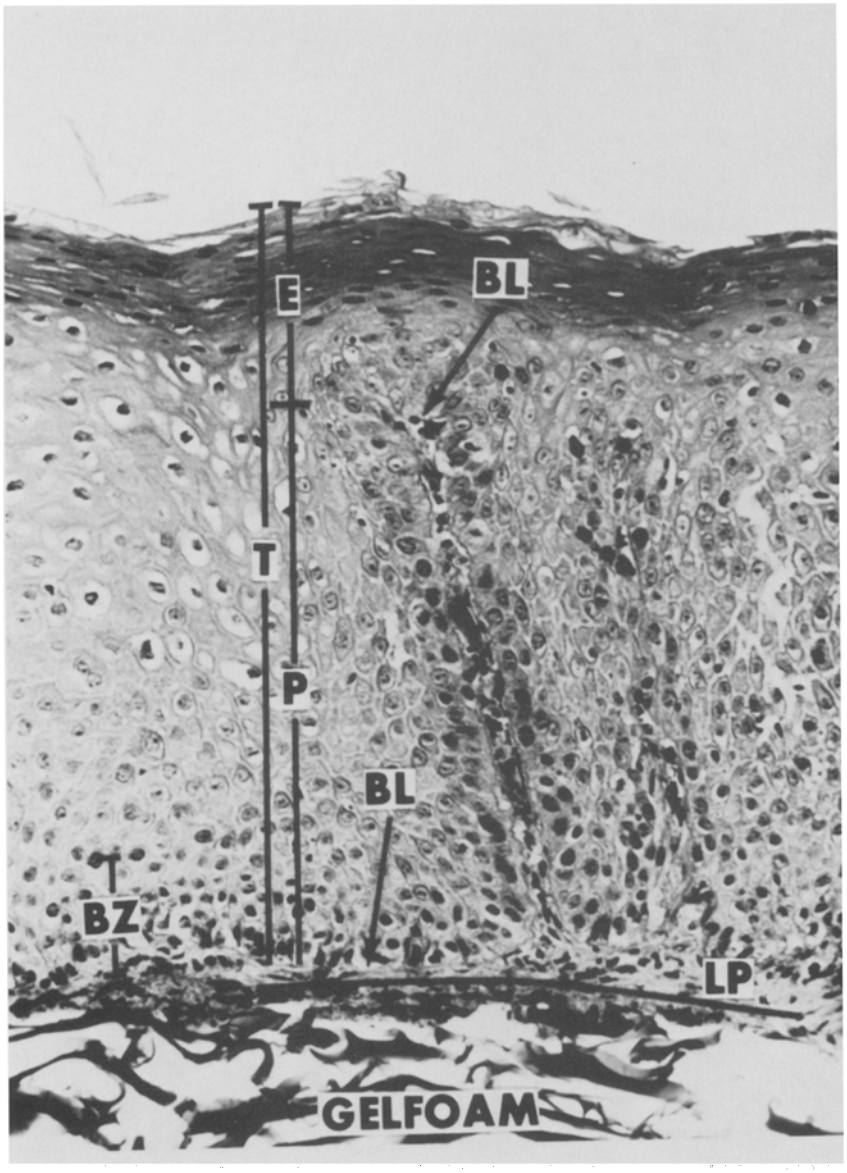


**Fig 1.** Perpendicular mounted esophageal biopsy on gel foam showing all measured components. (See text for explanation.)

both absolute and relative (%) papillary length decreased (Table 3). Absolute papillary length experienced the larger change. Percent basal zone hyperplasia also tended to diminish.

### Influence of Reflux Pattern on Papillary Length

The mean papillary extension exceeded 60% (long papillae) only in those groups with a large recumbent acid exposure (Figure 5B, shaded portion of bars, recumbent and bipositional refluxers) as a result of both increased recumbent reflux episodes (Figure 5C) and prolonged recumbent acid clearance times (Figure 5D). In contrast, mean papillary extension was < 60% (short papillae) in those groups with minimal recumbent acid exposure due to few recumbent reflux episodes and rapid recumbent acid clearance, (Figure 5A–D, normal and upright refluxers).

Recumbent and bipositional refluxers with long

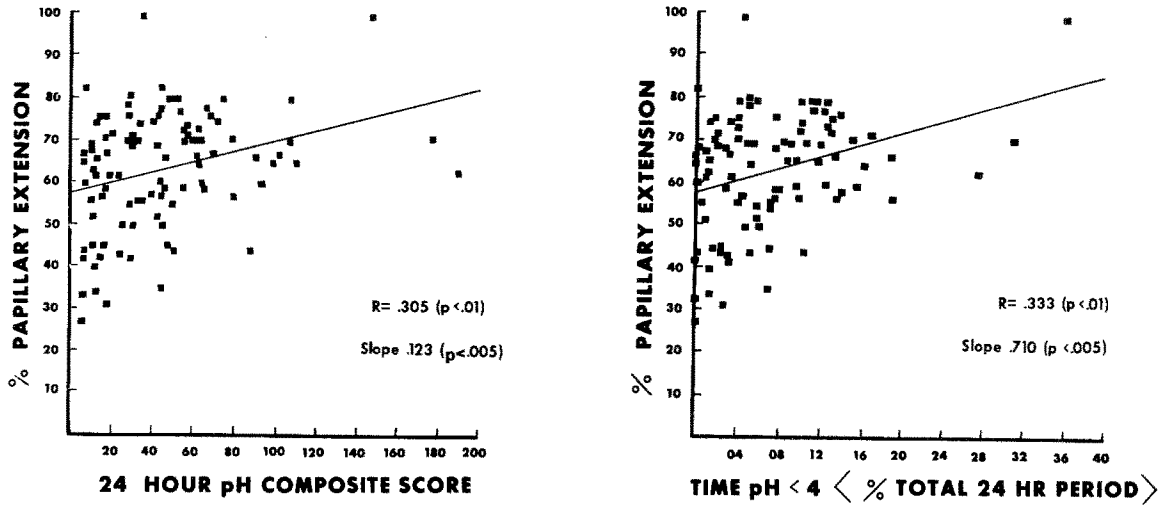


**Fig 2.** Direct correlation of percent papillary extension with 24-hr pH composite score, and percent time pH < 4 for total 24-hr period.

papillae experienced a significant increase in acid clearance times after assuming recumbency (Figure 5D). This was in contrast to those groups with short papillae whose acid clearance either improved after they assumed recumbency (upright refluxers) or was rapid in both positions (normal 24-hr pH).

The frequency of upright reflux episode (Figure 5C) significantly exceeded recumbent episodes in all groups, but this upright acid exposure (Figure 5B, unshaded portion of bars) had less effect on percent papillary extension (Figure 5A) because of rapid upright acid clearance from the esophagus (Figure 5D).

Total acid exposure alone did not have a strong influence on papillary extension, (Figure 5B vs Figure 5A). Upright refluxers had percent papillary extension similar to patients with a normal 24-hr pH score, despite an eight-fold difference in total acid exposure, a level of exposure comparable to that seen in bipositional refluxers.

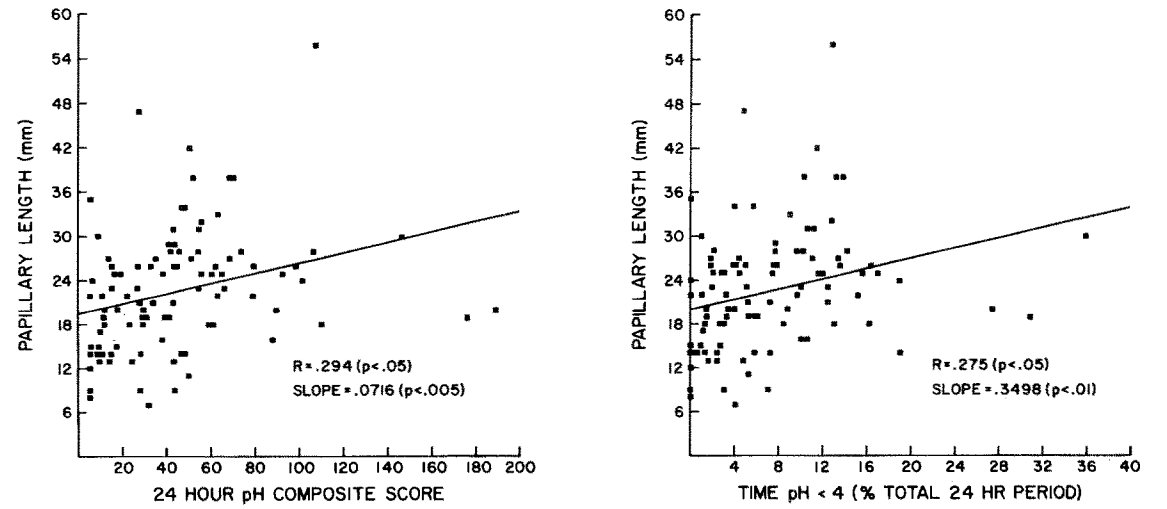


**Fig 3.** A direct correlation of absolute papillary length with 24-hr pH composite score and percent time pH < 4 for total 24-hr period.

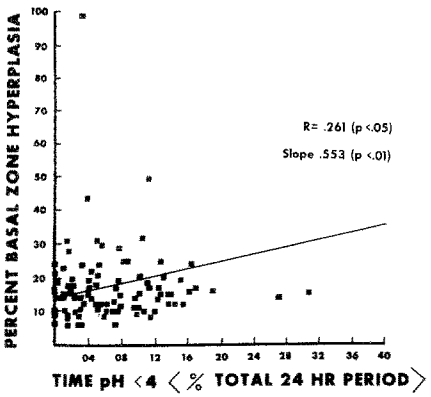


**Fig 4.** A direct correlation of percent basal zone hyperplasia with percent time pH < 4 for total 24-hr period.

### Influence of Hiatal Hernia on Reflux Pattern

Patients with a hiatal hernia, present both radiographically and endoscopically, had longer percent papillary extension, lower DES pressure, and more frequent upright and recumbent reflux episodes than those with no hernia (Figure 6A–C). The frequency of reflux diminished in recumbency, regardless of the presence or absence of a hiatal hernia (Figure 6C). Patients with a hiatal hernia experienced a significant increase in acid clearance time after assuming recumbency and also had a longer recumbent clearance time than those with no hernia (Figure 6D). Acid clearance times were less affected by a hiatal hernia in the upright posture (Figure 6D). Patients with a hiatal hernia diagnosed only endoscopically tended to have longer papillae, lower DES pressure, more frequent upright and recumbent reflux episodes, and longer recumbent acid clearance time than those with a hernia diagnosed only radiographically (Figure 6A–D).

### Other Measures of Reflux Correlated to Papillary Length

The numbers obtained from the scoring system of the dysphagia section of the reflux questionnaire showed a direct correlation to percent papillary extension ($r = 0.250$; $P < 0.05$) even though only 8% of all individuals had an esophageal stricture demonstrated radiographically or endoscopically. The numerical scoring obtained from the regurgitation and heartburn section of the questionnaire, as well as the composite score, did not show a statistically significant correlation with percent papillary extension. Also, DES pressure and the standard acid reflux test both failed to show a statistically significant correlation with percent papillary extension.

## DISCUSSION

Esophageal epithelial hyperplasia as evidenced by papillary elongation and basal zone hyperplasia in patients with severe gastroesophageal reflux symptoms has been attributed to chronic irritation by noxious gastric juice (2). If refluxed gastric juice was responsible for these changes, one would expect quantitative measures of distal esophageal acid exposure to correlate with lengthened papillae and basal zone hyperplasia. Our studies support this hypothesis in that papillary length and basal zone hyperplasia were shown to correlate directly with exposure of the esophagus to acid. In fact, the mean values for a normal 24-hr pH composite score (11) and the total acid exposure time (2%) observed in asymptomatic control volunteers reported elsewhere (4), when plotted on the $x$ axis of the regression analysis, intercepted the $y$ axis for percents papillary length and basal zone hyperplasia at values approximately 60 and 15, respectively. These

TABLE 2. COMPARISON OF EPITHELIAL MEASURES IN PATIENTS WITH ABNORMAL AND NORMAL 24-HR COMPOSITE SCORES

| *24-hr pH composite score* | *Abnormal (N = 69)* | *Normal (N = 31)* |
|---|---|---|
| Suprapapillary "protective" epithelium (E) (mm)* | 0.11 ± 0.005 | 0.15 ± 0.01 |
| Papillary length (P) (mm)* | 0.24 ± 0.01 | 0.19 ± 0.01 |
| Basal zone (BZ) (mm) | 0.069 ± 0.006 | 0.049 ± 0.004 |
| Epithelial thickness (T) (mm) | 0.36 ± 0.01 | 0.34 ± 0.01 |
| Papillary extension (%)† | 67 ± 1.5 | 56 ± 3 |
| Basal zone (%) | 19 ± 2 | 15 ± 1 |

*$P < 0.01$ between abnormal and normal.
†$P < 0.001$ between abnormal and normal.

TABLE 3. EFFECT OF ANTIREFLUX SURGERY ON DISTAL ESOPHAGEAL pH MONITORING AND EPITHELIUM ($N$ = 5)*

| | *Preoperative* | *Postoperative ($X$ = 31 weeks)* |
|---|---|---|
| 24-hr pH score‡ | 50 | 7.5 (<22.5)§ |
| Time pH < 4(%)‡ | 8 | 1 (<4%)§ |
| Papillary length (mm)‡ | 0.32 | 0.14 |
| Papillary extension (%)† | 76 | 53 |
| Basal zone hyperplasia (%) | 19 | 16 |

*$N$ = Number of patients.
†$P < 0.05$ between pre- and postoperative values.
‡$P < 0.01$ between pre- and postoperative value.
§Normal values (4).

epithelial values are comparable to those reported by Ismail-Beigi and co-workers (1, 2) in asymptomatic control subjects.

The low correlation coefficients ($r$ values) suggest that factors other than acid exposure during one 24-hr period may influence the epithelial reaction. For example, Johnson et al (14) found that the cigarette smokers in a patient group whose cardioesophageal junction was demonstrated to be competent by pH testing had significantly longer papillae than nonsmokers in the same group. Thus, some smokers in our present study could have had severe epithelial changes due to their daily cigarette consumption, but have low distal esophageal acid exposure during the 24 hr when they were monitored not smoking. The concentration of bile salts present in the refluxed acid gastric juice was another factor that may have been important but which we did not measure (15). In addition, the biopsies were obtained 2 cm from the squamocolumnar junction, a region which has recently been shown to have a significant incidence of papillary extension and basal zone hyperplasia in normal individuals (3). Also, larger biopsies, as obtained with the suction technique, could increase the tissue sampled enough to yield better correlations.

Despite these unmeasured variables, which would produce a bias against the correlations found, the direct linear relationship between papillary length and acid exposure was statistically significant. If our correlations were valid, these reactive epithelial changes would be expected to subside when exposure to acid gastric juice decreased. This reversibility was documented because papillary length and basal zone hyperplasia decreased in five patients after successful antireflux surgery (Table 3). Thus, the epithelial changes of papillary extension and basal zone hyperplasia were influenced by exposure to acid gastric juice. An analogy between this reaction and that seen in other chronically irritated stratified squamous epithelium has previously been drawn (1, 16, 17).

Desquamation of epithelial cells secondary to reflux of acid gastric juice may cause pyrosis by exposing the nerve endings contained in the papillae. This desquamation could account for the relative increase in percent papillary extension observed in those patients with gastroesophageal reflux symptoms (2); however, no absolute measure of these epithelial components has been made. Our data support the concept that acid reflux induces desquamation of epithelium, because those patients with abnormal 24-hr pH score had less suprapapillary epithelium than those with a normal score.

Patients with an abnormal 24-hr pH score had longer papillae than those with a normal score. This appears to be due to epithelial proliferation in the basal zone since we measured absolute papillary length from the basal lamina at the tip of the papillae to basal lamina beneath the basal zone. In support of this, Kalkay et al (18) showed increased new cell formation in the basal zone of patients with histologic esophagitis by using [$^3$H]thymidine autoradiography. Furthermore, total epithelial width in patients with abnormal 24-hr pH scores was comparable to those with normal 24-hr pH scores despite the loss of the suprapapillary epithelium. These studies suggest that preservation of total epithelial thickness in the face of surface desquamation results from cellular proliferation in the basal zone.

The 24-hr pH monitoring procedure affords an opportunity to observe the effects of reflux in different body positions on epithelial reaction. The recumbent posture is known to aggravate gastroesophageal reflux. An autopsy series has shown an increased incidence of esophagitis in patients dying after long illnesses with prolonged bedrest as opposed to those from accidental death (19). Rendal (29) characterized a "recliners reflux syndrome" and theorized a poor mechanical barrier to reflux during recumbency. We confirmed these observations by showing that those patients with the longest percent papillary extension had the greatest recumbent acid exposure (Figure 5).

The induction of peptic esophagitis in animal models depends on duration of contact of the acid peptic juice on the esophageal mucosa (21–24). We have shown that those patients with long papillae had a delayed recumbent acid clearance time, re-

sulting in prolonged contact between mucosa and acid. Patients with short papillae had rapid acid clearance in the recumbent position and minimal acid mucosal contact. DeMeester et al (25) also found a higher incidence of endoscopic esophagitis and strictures in those patients with excessive recumbent reflux. Prolonged acid mucosal contact in the recumbent position may be due to the known decrease in esophageal peristalsis and salivary flow rates during sleep (26, 27), thus leaving a dry, nonperistaltic esophagus with no salivary buffer to acid. Upright acid exposure had little influence on changes in percent papillary extension because acid clearance was rapid even though the frequency of reflux episodes significantly exceeded those recumbent. In fact, upright refluxers had comparable total acid exposure to bipositional refluxers; but had a mean papillary extension comparable in length to those with normal 24-hr pH scores. Thus the esophageal acid clearance time was a more important determinant of reflux esophagitis than either the magnitude of total acid exposure to the esophageal mucosa or the frequency of reflux episodes.

The normal cardioesophageal junction permits more "physiologic reflux" in the upright position, generally after meals, than during recumbent sleep (4, 25, 28, 29). This postural influence on reflux frequency may in part result from a significantly higher DES pressure during supine posture than when sitting (30). Additionally, simultaneous pH and motility tracings have shown precipitation of reflux episodes after deglutition (26). The hourly rate of deglutition upright was 73/hr, increasing to 196/hr while eating and diminishing to only 7/hr during recumbent sleep (31). Therefore, we were not surprised to observe that the frequency of upright episodes significantly exceeded recumbent episodes. Factors other than gravity must influence upright reflux. Belsey (32) observed, during rigid endoscopy in the sitting position, that inspiration provoked a gush of gastric secretion into the esophagus in patients with an incompetent cardia. These observations suggest that in the upright posture a pressure differential favorable for reflux must exist from the stomach up to the mid-esophagus. Johnson et al (33) reported an erect gastroesophageal pressure profile and showed a graded pressure drop of 12 mm mercury from the stomach up to the mid-esophagus. Turlbeck and Marshall (34) have shown in animals that the recumbent intraesophageal pressure profile was less negative than that observed upright due to a loss of the gravitational tug on esophageal walls by a blood-filled heart and lungs. Thus a diminished recumbent gastroesophageal pressure gradient, higher recumbent sphincter pressure, and diminished deglutition during sleep may all account for fewer reflux episodes observed during recumbency.

We showed that patients with a hiatal hernia had longer papillae than those without a hernia. Reflux frequency, both upright and recumbent, was greater in patients with a hernia due to lower DES pressure. Furthermore, the presence of a hernia significantly increased the patient's acid clearance time during recumbency. Longhi and Jordan (35) have shown that the hiatal hernia sac impaired barium clearing from the recumbent esophagus because of retrograde flow of barium back into the esophagus immediately following the DES relaxation associated with a subsequent swallow. Thus, the presence of a hernia predisposes to a reflux pattern previously shown to cause long papillae, namely recumbent reflux episodes that were poorly cleared resulting in prolonged acid mucosal contact. Reflux frequency decreased during recumbency regardless of whether a hernia was present or absent (Figure 6C). DeMeester and co-workers (12, 13) have shown that both the frequency and duration of reflux episodes diminished after surgical antireflux procedures had reduced the anatomical hiatal hernia and had restored additional length of DES to the positive pressure environment of the abdomen. In most patients this resulted in an increased DES pressure.

Our studies suggest that the diagnosis of a hiatal hernia by endoscopy in a sedated patient during quiet respiration was more important than the more vigorous radiographic technique that may produce hernias of no functional significance. Indeed, those patients who had a hiatal hernia diagnosed only by endoscopy tended to have lower DES pressure, more frequent reflux, and longer papillae than those diagnosed only radiographically.

Dysphagia observed in patients without an anatomical stricture but with gastroesophageal reflux symptoms has been attributed to histologic esophagitis (20, 36, 37). Our studies support this observation by showing a significant correlation between the dysphagia section of the symptom questionnaire and percent papillary extension, even though only 8% of the patients in our series had an anatomical stricture. This correlation suggests that esophagitis causes increased sensitivity to the passage of a bolus or causes dysfunction of the esophageal wall resulting in a sensation of dysphagia.

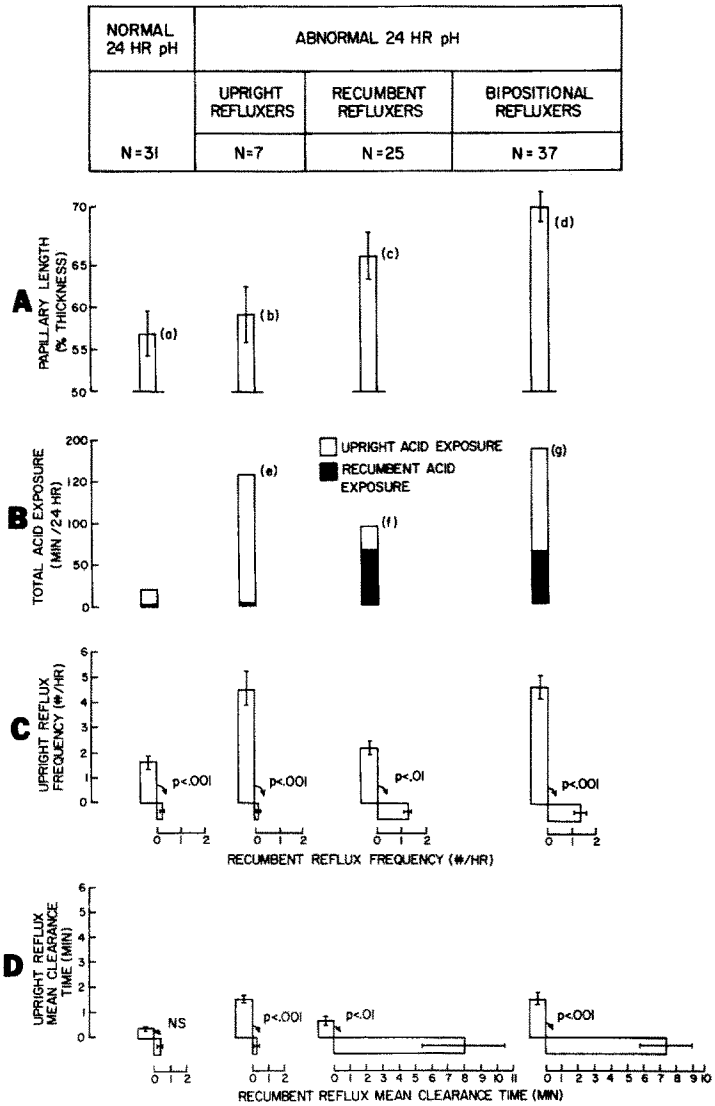


**Fig 5.** Influence of reflux characteristics on percent papillary extension. $N$ = number of patients. All bars show mean and 1 SEM. Papillary length (d) and (c) both more than (a) with $P < 0.001$ and 0.05, respectively; (d) more than (b) with borderline significance ($0.1 > P > 0.05$). Minutes of total acid exposure shown by the entire bar; unshaded area equals minutes upright, and shaded area equals minutes recumbent. Total acid exposure (f) is less than both (g) ($P < 0.001$) and (e) ($0.1 > P > 0.05$). The sign (↘) and adjacent "p" denote significance of change in reflux measure in each group after upright-to-recumbent posture change. Upright reflux frequency and clearance measures on vertical bar and comparable recumbent measure on horizontal bar. "NS" means not statistically significant.

Heartburn induced by the Bernstein test has failed to correlate with histologic inflammation (38); similarly papillary extension has not always agreed with the Bernstein test (1, 3). Our attempt to subjectively quantitate pyrosis by a symptom questionnaire and relate it to papillary extension similarly failed. The questionnaire score for regurgitation tended to increase with papillary length but, again, not with statistical significance. We feel the poor correlation between the subjective symptoms of

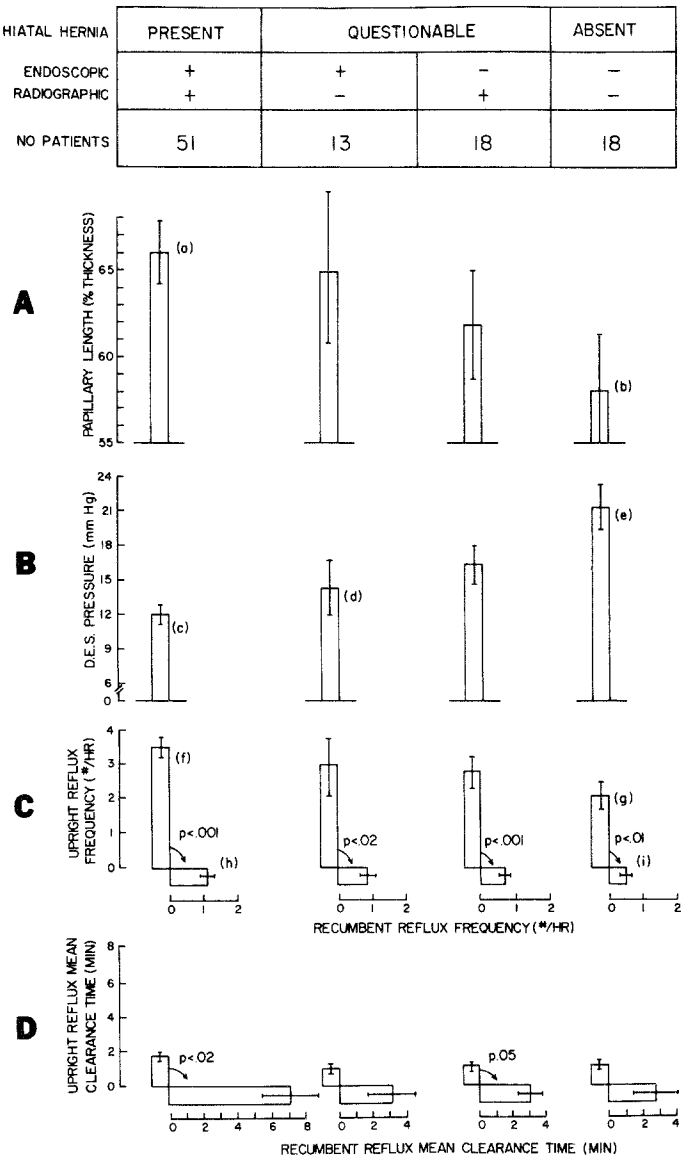


**Fig 6.** Relation of hiatal hernia to papillary extention (A), DES pressure (B), reflux frequency (C), and reflux clearance (D). All bars show mean and 1 SEM. The sign (↘) and adjacent p denote significant change in reflux measure after upright-to-recumbent posture change. Upright reflux frequency and clearance measured on vertical bars and recumbent on horizontal bars; for percent papillary extension (a) > (b), $P < 0.05$; DES pressure (c) < (e), and (d) < (e) with $P < 0.001$ and 0.02 respectively; reflux frequency (f) > (g) and (h) > (i), both $P < 0.05$.

heartburn and regurgitation and the severity of esophagitis was due to the observation that the most detrimental acid exposure to esophageal mucosa occurred at night while the patient sleeps. In contrast, frequent episodes of reflux during the day result in severe discomfort but cause little histologic alteration because they are rapidly cleared.

Various tests to determine reflux have been related to subjective symptoms (39) but seldom to histological esophagitis. We therefore related both

DES pressure and the standard acid reflux test to papillary length in order to determine the relative sensitivity of these reflux tests to reflect histologic change. DES pressure tended to relate inversely and the standard acid reflux test score directly to papillary length, but neither had statistical significance. This does not detract from their value for measuring reflux, for we have reported a significant inverse correlation between DES pressure and both SART and 24-hr pH score (40, 41) as well as a significant direct correlation between 24-hr pH score and results from the standard acid reflux test (40). Failure of the DES pressure and the standard acid reflux test to significantly correlate with reactive epithelial changes shows that these tests do not precisely measure gastroesophageal reflux as it affects distal esophageal histologic change. This results because both the DES pressure and standard acid reflux test measure only cardioesophageal competency and not acid clearance from the esophagus. In contrast, 24-hr pH monitoring quantitates acid gastric juice exposure to distal esophageal mucosa in a manner that significantly relates to the propensity for reflux esophagitis.

In conclusion, our population study showed that the pH of refluxed gastric juice served as a sensitive tag to assess two important determinants of reflux esophagitis: (1) reflux frequency secondary to incompetency of the cardioesophageal junction, and (2) esophageal clearing of the refluxed gastric juice. Both of these components must be assessed in the future in determining benefit from a potential therapeutic measure. Recumbent acid exposure during sleep appears to be the most important exposure to control both by diminishing reflux frequency and by improving acid clearance.

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