Clinical Significance of Esophageal Histologic Findings After Antireflux Surgery

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Hypothesis: Only limited and controversial information exists regarding the histologic effect of successful antireflux surgery on esophageal mucosa and its clinical significance.

Design and Settings: A randomized, blinded follow-up study conducted in a university hospital between January 1, 1992, and December 31, 1997, with a mean follow-up of 8 months.

Patients: Forty patients with severe symptomatic gastroesophageal reflux disease (24 men and 16 women; mean age, 50 years).

Main Outcome Measures: Microscopic signs and severity of esophagitis analyzed by 2 blinded histopathologists.

Results: Histopathologist 1 interpreted 22 (69%) of 32 postoperative biopsy specimens as normal; 7 (22%), as showing mild changes; 1 (3%), moderate changes; and 2 (6%), severe changes of reflux esophagitis. Histopathologist 2 interpreted 25 (78%) of 32 postoperative biopsy specimens as normal ($P = .001$); 1 (3%), as showing mild changes ($P = .003$); 4 (13%), moderate changes; and 2 (6%), severe changes. Between histopathologist 1 (90.6%) and histopathologist 2 (81%), the absence of esophageal mucosal inflammation correlated best with normalized pH monitoring.

Conclusions: These findings suggest that, if other findings such as those from fundic wrap at endoscopy and 24-hour pH monitoring are normal, the clinical significance of routine esophageal histologic examination after successful fundoplication is limited.

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HE SIGNIFICANCE of the histologic appearance of esophageal mucosa after healing of gastroesophageal reflux following successful antireflux surgery is still obscure. The few previous studies have yielded inconclusive results, with some reports suggesting either no or only temporary effect of treatment, and others showing marked improvement in esophageal histologic findings. The reason for conflicting data remains obscure, but many shortcomings in these studies, including the use of patients without a well-established diagnosis of gastroesophageal reflux disease (GERD), small numbers of patients, or great variation in operative technique, may be some of the causes.

After introduction of the laparoscopic technique, the number of antireflux operations performed has increased. Postoperatively, these patients are studied for several reasons, and biopsy specimens of esophageal mucosa are often taken. However, the significance of these postoperative specimens is obscure for clinicians. Therefore, we conducted the present study, in which 2 experienced blinded histopathologists estimated the effect of successful antireflux surgery on esophageal mucosa.

RESULTS

HISTOPATHOLOGIST 1

Thirty-nine (20%) of 191 biopsy specimens (from 14 patients) were interpreted as insufficient for analysis. At least 1 specimen for each of 32 patients could be histologically evaluated both preoperatively and postoperatively (Table 2). The differences in the prevalence of different grades of histologic esophagitis between preoperative and postoperative specimens (normal, 50% vs 69%; mild, 16% vs 22%; moderate, 12.5% vs 23.1%; and severe, 21.9% vs 6.3%) were nonsignificant.

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PATIENTS AND METHODS

Forty consecutive patients (24 men and 16 women; mean age, 50 years; range, 27-73 years) were operated on for severe symptomatic GERD between January 1, 1992, and December 31, 1997, at the Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland. Each patient had had long-term conservative treatment with proton pump inhibitors or histamine blockers and had a pathologic preoperative 24-hour pH recording (mean pH < 4 in 13.3% [range, 3.7%-51.1%] of registration time). On esophageal manometry performed on 34 patients preoperatively, the mean lower esophageal sphincter pressure was 11.48 mm Hg (range, 0-34 mm Hg; SE, 1.37 mm Hg). Esophagoscopy were performed by persons who had not previously been involved in the patients’ care. In 37 patients, upper gastrointestinal tract endoscopy had demonstrated erosive esophagitis, but 3 patients (all taking omeprazole) had no macroscopic esophagitis. Patients with Barrett esophagus, defined as intestinal metaplasia in tubular esophagus, were excluded.

Thirty-five patients were operated on by the standardized floppy technique (including fundic mobilization, hiatal repair, and 2-cm-long wrap) with the use of either a transabdominal (33 patients; laparoscopic in 22 and open in 11) or a transthoracic (2 patients) approach, and 5 operations were laparoscopic partial fundoplications (Toupet). There were no postoperative complications. All operations were primary ones.

In all 40 patients, preoperative and postoperative biopsies were taken from macroscopic lesions with the use of a biopsy forceps (Rebit [2.3 mm]; Gip/MediCare, Grassau, Germany) or, if there was no lesion, 3 to 5 cm above the esophagogastric junction. Preoperatively, a total of 97 biopsy specimens were taken (range, 1-4 [mean, 2] per patient).

Postoperatively, histologic changes progressed in 7 specimens (21.9%) (6 changed from normal to mild and 1 from moderate to severe), remained unchanged in 11 (34.4%), and diminished in 14 (43.8%). Of the biopsy specimens in which esophagitis diminished, 5 changed from mild to normal, 5 from severe to normal, 2 from moderate to normal, 1 from moderate to mild, and 1 from severe to moderate. Histologic signs of esophagitis diminished significantly after the operation (normal or mild changes, 66% vs 91%; P = .04). The length of follow-up had no effect on the number of normal postoperative biopsy specimens. The absence of esophageal mucosal inflammation (grade III-V) correlated best with normalized pH monitoring postoperatively, which occurred in 29 patients (90.6%).

Postoperatively, healing of GERD was verified by 24-hour pH recording in each patient (mean pH < 4 in 1.1% [range, 0.0%-4.5%] of registration time). In addition, mean lower esophageal sphincter pressure was 17.05 mm Hg (range, 8.5-37.0 mm Hg; SE, 1.21 mm Hg) on esophageal manometry (34 patients). At the follow-up endoscopy, after a mean period of 8 months (range, 3-48 months), fundic wrap was normal in all cases, but in 3 cases grade I esophagitis was detected. One patient had a peptic esophageal stricture that had been present preoperatively. Postoperative biopsy specimens were taken from every patient (94 specimens; 2-4 per patient; mean, 2) by the same criteria as preoperatively.

Both preoperative and postoperative biopsy specimens were fixed in 10% buffered formalin solution and stained with hematoxylin-eosin and periodic acid–Schiff in all cases, and also with Giemsa in 15 cases. All biopsy specimens were coded, randomized, and read blindly by 2 experienced histopathologists (P.I.S. [histopathologist 1] and J.E.M. [histopathologist 2]) without knowledge of each others’ evaluations, the clinical situation, or whether specimens had been taken before or after the operation. The biopsy specimens were graded and scored according to microscopic signs and severity of esophagitis by a modified version of the previously presented criteria (Table 1). When the effect of antireflux surgery on mucosal histologic findings was analyzed, the score of the most abnormal finding was used. However, according to both histopathologists, preoperative and postoperative specimens included inadequate squamous epithelium for evaluation in 8 and 9 patients, respectively. Thus, 32 and 31 patients were included.

This study was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital.

Fisher exact test, Mann-Whitney test, 7 test, and Spearman rank correlation test were used for statistical comparisons as indicated. A P value of less than .05 was considered significant.

### Table 1. Histologic Features of Reflux Disease

<table>
<thead>
<tr>
<th>Description</th>
<th>Grade</th>
<th>Features</th>
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<tbody>
<tr>
<td>No or indefinite</td>
<td>0</td>
<td>No features of esophagitis</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Elevation of papillae to &gt;30% of mucosal length and basal zone increase to &gt;15% of mucosal length</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Elevation of papillae to &gt;50% of mucosal length and basal zone increase to &gt;15% of mucosal length</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>1 of the above plus neutrophilic exudate</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>Severe inflammatory exudate, granulation tissue, or marked reparative changes</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Necrotic mucosa with dense inflammation</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Fibrosis</td>
</tr>
</tbody>
</table>

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in 12 patients (38%), and diminished in 14 patients (44%) (in 7 from mild to normal, in 2 from severe to normal, in 4 from moderate to normal, and in 1 from severe to moderate). The histologic signs of esophagitis diminished significantly after the operation ($P=.02$). The absence of esophageal mucosal inflammation (grade III–V) correlated best with normalized pH monitoring postoperatively, which occurred in 26 patients (81%).

Our study confirms the hypothesis of Richardson and colleagues that successful antireflux surgery diminishes the histologic signs of reflux esophagitis. In 78% (histopathologist 1) and in 84% (histopathologist 2) of patients, esophageal histologic changes were the same as preoperatively or had improved. In 7 and 6 patients, remarkable recoveries from severe or moderate changes to a normal histologic picture had occurred. Esophageal mucosal inflammation was absent in 90.6% and 81% of patients. Nonetheless, changes did progress in 22% (histopathologist 1) and 16% (histopathologist 2) of cases; however, progression occurred only to the nearest grade. According to histopathologist 1, 6 changed from normal to mild and 2 from moderate to severe; according to histopathologist 2, 3 changed from mild to moderate and 2 from moderate to severe.

On average, 2 biopsy specimens per patient were taken both preoperatively (range, 1–4) and postoperatively (range, 2–4). In other studies investigating changes in esophageal mucosa after the operation, the number of specimens taken varied. The study by Johnson et al had no information about the number of biopsy specimens. In addition, Richardson et al mentioned only that multiple specimens were taken, and the exact number was not stated. In the study by Brand et al, on average 2.6 (range, 1–5) specimens were obtained preoperatively, 3.6 (range, 1–5) early postoperatively, and 4.1 (range, 2–5) late postoperatively. Five to 6 specimens per patient were obtained in the study by Behar et al. To the best of our knowledge, no trials exist in which the number and clinical significance of postoperative esophageal biopsy specimens have been investigated. Moreover, we found no recommendation about when and how many postoperative esophageal specimens should be obtained. However, Collins et al found that the accuracy of histologic diagnosis of reflux esophagitis seems to be limited unless multiple specimens are examined.

In previously presented series, somewhat conflicting data have emerged concerning esophageal changes after antireflux surgery. Behar and colleagues found that, despite asymptomatic response and normal findings at postoperative endoscopy (15 patients, 1 year; 13 patients, 2 years; and 10 patients, 3 years), papillary elongation and basal cell hyperplasia did not return to normal. However, symptomatic improvement was accompanied by the disappearance of neutrophil infiltrate. In the report by Brand and colleagues, esophageal histologic findings were significantly improved in early postoperative studies. However, at the later follow-up, all 5 patients whose preoperative abnormal histologic findings had become normal at early follow-up had regressed to their abnormal status. In that study, 14 patients had normal findings, 5 abnormal, and 2 abnormal with leukocytes at the early follow-up. In contrast, at the later follow-up, 1 had normal findings, 5 abnormal, and 3 abnormal with leukocytes. The mean follow-up was 69.2 months. In the other 2 reports, significant histologic improvement was found in the esophageal mucosa after fundoplication. In the study by Johnson et al, both absolute and relative papillary lengths decreased after mean follow-up of 31 weeks. Absolute papillary lengths experienced the largest change, from 0.32 to 0.14. According to Richardson and colleagues, dramatic improvement in esophageal histologic findings was found after fundoplication; only 2 (11%) of the 19 patients who preoperatively had had histologic esophagitis typified by leukocytic infiltration had these findings postoperatively. Nevertheless, epithelial changes were evident postoperatively in 15 patients (71%). In our study, the incidence of normal findings or epithelial changes was similar to that of Richardson et al.

The causes of persistent postoperative epithelial changes are unknown. Some changes in esophageal mucosa may be irreversible, particularly because many of our patients had a long history of GERD. Richardson et al speculated that some of the postoperative epithelial changes may require a longer time (mean, 39 months) for full recovery. However, in our study, the length of follow-up (mean, 8 months) had no effect on the incidence of normal postoperative biopsy specimens.

The operative techniques of antireflux procedures in previously presented studies varied markedly, including Belsey partial fundoplication (10 patients) and Hill gastroscopy (5 patients) in the study by Behar et al and

### Table 2. Esophageal Histologic Findings Preoperatively and Postoperatively

<table>
<thead>
<tr>
<th>Histopathologist 1</th>
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<tr>
<td>Preoperative</td>
<td>6</td>
<td>10</td>
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<tr>
<td>Postoperative</td>
<td>11</td>
<td>11</td>
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</table>

<table>
<thead>
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<th>Histopathologist 2</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Postoperative</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic Grade of Esophagitis</th>
<th>No/Indefinite</th>
<th>Mild: 2</th>
<th>Moderate/Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
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</table>

*Data are given as number of patients.
Nissen fundoplication (18 patients), Hill gastropexy (4 patients), and Allen procedure (3 patients) in the study by Brand et al.13 In the studies by Johnson et al.14 (5 patients) and Richardson et al.15 (21 patients), all patients were operated on with Nissen fundoplication. The reasons for conflicting data in the above-mentioned studies are obscure. One explanation may be the relatively small numbers (5-25) of patients and the different surgical techniques used without objective proof of healing of GERD. Differences may also be due to variation in control methods, which have different specificities and sensitivities.

The sensitivity and specificity of the acid perfusion test were 59% to 85% and 59% to 67%, respectively.12 In contrast, the sensitivity of barium radiology has ranged from 30% to 71%,13,14 and specificity, from 75% to 88%.14 The sensitivity of endoscopy has ranged from 30% to 62%,14,15 and specificity, 94%.14 In the diagnosis of GERD, the manometric measurement of the lower esophageal sphincter has a sensitivity of 84% and specificity of 89%.13 Ambulatory 24-hour esophageal pH monitoring has been proposed as the gold standard for the diagnosis of GERD,16 its sensitivity being 96% to 98%,15,17 and specificity, 96% to 100%,15,17 which we also confirm. Therefore, the relatively small number of pH measurements performed and the older methods used with low specificity and sensitivity may be other reasons for conflicting data between earlier studies. In our study, the operative results were objectively documented by endoscopy (including intact wrap) and 24-hour pH monitoring in all cases, and by esophageal manometry in 34 cases. All 40 patients had abnormal results of 24-hour pH monitoring preoperatively and normal values after the operation. In the study by Behar and colleagues,1 all 15 patients had abnormal pH measurements (not 24-hour pH recording) and acid infusion tests preoperatively. Postoperatively, 11 patients had no reflux symptoms and 10 had negative results of acid infusion tests. All 4 symptomatic patients had pathologic results of acid infusion tests postoperatively.1 In another study, all patients had positive results of acid reflex tests (sensitivity, 59%-85%; specificity, 59%-67%).12 Preoperatively, an acid reflux test was performed on all of these patients at early postoperative follow-up and on 12 patients at late postoperative follow-up. The result of the acid perfusion test was positive in the early postoperative period in 12 of the 24 patients and at late postoperative follow-up in 6 of the 12 patients. The reason for the worsening of histologic findings at late postoperative follow-up in this study remains unknown.2 Because 24-hour pH recording was not used, some failures may have been missed. In the study by Richardson et al.,4 the number of pH recordings performed was not mentioned. Postoperative pH measurements were performed on only symptomatic patients, with 21 patients being symptom free.

Our study shows that successful antireflux surgery reduces the histologic signs of reflux esophagitis. However, normal postoperative biopsy specimens were found in only 69% to 77% of patients. The absence of esophageal inflammation correlated best with normalized results of pH monitoring postoperatively.

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REFERENCES