When is Esophagitis Healed?
Esophageal Endoscopy, Histology and Function Before and After Cimetidine Treatment

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In order to assess whether in reflux esophagitis morphological and functional disorders persist after macroscopic healing, cimetidine was given for 6–12 weeks at a dose of 1.6 g/day to 30 patients with acid gastroesophageal reflux and esophagitis. The mucosal defects healed in 6 patients, improved in 14 patients, and remained unchanged in 10 patients. Lower esophageal sphincter pressure, acid clearance, acid perfusion test, and histological signs of mucosal inflammation were assessed before and after treatment. The histological and functional findings did not improve after healing of the mucosal defects. Therefore, endoscopic normalization in patients with reflux esophagitis is not associated with the disappearance of inflammation and abnormal motor function. The persistence of these abnormalities might explain the tendency of esophagitis to recur after symptomatic and endoscopic "healing."

In patients with reflux disease it is still unknown what to treat and for how long. Possible endpoints of treatment are the healing of epithelial defects, the disappearance of inflammatory infiltrates, and the improvement of abnormal motor function. In four studies previously performed with cimetidine (1–4) it is difficult to determine which of these endpoints is best. In only two studies patients with endoscopically defined esophagitis were admitted (1, 2); in the two others endoscopy was either not performed (4) or patients with a normal esophageal mucosa were not excluded (3). Esophageal histology and function were not compared in any of the studies.

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The present study should answer the question of whether healing of epithelial defects of the esophageal mucosa is paralleled by disappearance of granulocytic infiltration and abnormal motility. Thus, the value of normalization of the endoscopic aspect as an endpoint to treatment was assessed.

MATERIALS AND METHODS

Admission Criteria. Thirty consecutive patients with esophagitis due to acid gastroesophageal reflux entered the study. Endoscopies were performed by the physicians managing the patients. Function tests were performed by "blinded" physicians who were unaware of the endoscopic and clinical findings. Esophagitis was diagnosed by fiberendoscopy. The lesions of the esophageal mucosa were defined as follows (5–8): mild, isolated round or linear erosions; severe, confluence of the erosions involving the total esophageal circumference; complicated, erosions as described above plus deep ulcers, peptic stenosis, and/or columnar epithelium-lined esophagus. Peptic stenosis was present in 10 cases. In all these cases, it was moderately severe, ie, a pediatric fiberendoscope with a diameter of 8 mm (Olympus GIF-P2) could be passed across the stenosis. Cases with more severe stenosis were excluded. Reddening, granularity, and friability of the

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esophageal mucosa without epithelial defects or other lesions than those described above were not considered signs of esophagitis. The histological aspect of the mucosa was not used as an admission criterion.

An intraesophageal pH-metry of 3-hr duration was performed while the patients were fasting. A transnasal pH electrode was positioned 5 cm proximal to the manometrically determined lower esophageal sphincter. At the beginning of the 3-hr pH measurement, acid clearance was determined as described in the next section. Only patients with abnormal reflux were admitted to the study. Reflux was considered abnormal when intraesophageal pH was below 4 for more than 5 min/hr in the supine position (9).

Patients with secondary gastroesophageal reflux, eg, due to outlet obstruction of the stomach or other causes of gastric retention, patients after surgery of the upper gastrointestinal tract, and patients with concomitant duodenal and gastric ulcers were excluded.

Treatment and Assessment of the Response to Treatment. The patients were treated with 4 times 400 mg cimetidine per day and were endoscoped after 6 weeks. When, on this occasion, the esophagitis was healed according to endoscopic appearance, the patient was discharged from treatment. When there was no improvement, treatment was discontinued and surgery was suggested. When improvement was noted, continuation of treatment for another 6 weeks was suggested to the patient and endoscopy was repeated after 12 weeks. Seven patients with symptomatic worsening in spite of endoscopic improvement were unwilling to continue medical treatment and were referred to surgery after the 6th week of treatment. Placebo was not given in this study since we (5), like others (1, 2), have shown previously that cimetidine is better than placebo in the treatment of reflux esophagitis. In the 11 patients with peptic stenosis, no dilatations were performed during cimetidine treatment.

An improvement of esophagitis was diagnosed when the circumferential epithelial defects had become patchy or the longitudinal defects had disappeared in some, but not all, segments of the esophagus. Healing was diagnosed when epithelial defects had disappeared completely. Endoscopic photographs were taken during all endoscopies in order to allow reassessment of the findings by examiners not present at endoscopy. During every endoscopy at least 5 biopsies were taken from the macroscopically intact esophageal mucosa near the epithelial defects. They were read "blindly" by a pathologist who was not aware of the findings. The presence of neutrophilic and/or eosinophilic granulocytes in the lamina propria was regarded as a positive sign of esophagitis as defined by histological criteria. Further details on this histological criterion have previously been published (9). Papillar length and basal cell thickness were also evaluated, but we failed again to correlate these criteria with reflux and esophagitis.

Before and 24–48 hr after discontinuation of cimetidine treatment three esophageal tests were performed in every patient: acid clearance, manometry of the lower esophageal sphincter pressure (LESP), and acid perfusion test. The acid clearance test was modified as described previously (11) by counting the number of swallows necessary to clear a 15-ml bolus of 0.1 N HCl from the esophagus. The test was performed in the sitting position. LESP was assessed by the continuous withdrawal method in the supine position with perfused catheters. Details of the method have been described elsewhere (11, 12). Six profiles were recorded and the mean of the pressure was taken. Acid perfusion was performed as described by Bernstein and Baker (13). The test was considered to be positive when, during acid perfusion, the subject experienced discomfort (pain and/or heartburn) which disappeared during subsequent perfusion of saline solution.

Studies in Healthy Controls and Patients Without Endoscopic Esophagitis. Twenty-four healthy members of the medical staff served as a control population for pull-through manometry, esophageal acid clearance, and acid perfusion tests. Suction biopsies were also performed in these subjects. The results have in part been previously published (10, 11). In 13 healthy staff members a 3-hr intraesophageal pH-metry was performed. The patients and the healthy controls gave informed consent before entering the trial. The study protocol was approved by the local ethics committee.

RESULTS

Clinical Course and Endoscopic Appearance. Mean age of the 30 patients was 57 years. There were more males (25) than females (5). Eighteen patients were smokers, 15 had moderate alcohol intake (less than 80 ml of ethanol per day). There were no alcoholics in this group.

In 6 patients the macroscopically visible lesions healed completely, in 14 patients they improved, and in 10 patients they remained unchanged or worsened (Table 1). Of the 6 patients with healing, 5 had mild esophagitis at the beginning of the study, and 1 had complicated esophagitis. The tendency of mild esophagitis to heal better than severe and complicated esophagitis is statistically not significant ($\chi^2 = 3.77$, $df = 2$, $P > 0.1$). In no single case did the columnar-lined epithelium recede during treatment. On the contrary, there was an increase of columnar-lined epithelium appearing at sites of healing esophageal ulcers. The endoscopic response was on the average paralleled by the symptomatic response ($P < 0.02$). The 6 patients with healed esophagitis became symptom-free. Of the 14 patients with improved esophagitis, 4 became symptom-free, 3 had fewer symptoms, and in 7 the symptoms became worse. Of the 10 patients without endoscopic improvement, 2 became symptom-free, 1 had fewer symptoms, and 7 had no symptomatic improvement or had more symptoms.

Esophageal Function. Initial LESP in the 30 pa-

TABLE 1. PRE/POST TREATMENT DATA

Number	Sex	Duration of treatment (weeks)	Age (years)	Duration of disease (years)	Complications (ulcer, stenosis, or columnar epithelium)‡	Endoscopic aspect*	LESP (mmHg)	Acid clearance (no. of swallows)	Bernstein-test	Histology	Symptoms†
Healed											
1	m	6	69	6	–	1/0	17/15	38/40	+/+	+/–	1/0
2	m	6	51	8	–	1/0	8/9	13/20	–/–	–/–	3/0
3	m	6	55	3	–	1/0	4/5	27/28	+/+	+/+	3/0
4	m	6	69	3.5	–	2/0	9/8	30/30	+/+	+/+	3/0
5	m	12	70	3.5	–	1/0	5/7	60/57	+/+	–/–	3/0
6	m	12	60	0.5	ulc	4/0	9/10	35/25	+/+	+/+	2/0
Improved											
7	m	6	63	17	–	2/1	15/15	25/25	+/+	+/+	2/3
8	m	6	34	2.5	–	2/1	9/3	44/26	+/+	+/+	1/3
9	f	6	59	3	ulc	4/2	23/25	31/30	+/+	–/–	3/3
10	f	6	28	1.5	ste+col	4/3	16/16	13/15	+/+	+/+	2/3
11	m	6	76	8.5	ste+col	4/3	13/13	52/51	+/+	+/+	1/2
12	m	6	57	5	ulc	4/1	10/11	24/26	+/+	+/+	3/3
13	f	6	55	8	ulc+col	4/2	10/9	36/38	+/+	+/+	0/1
14	m	12	51	3	–	2/1	12/11	30/30	+/+	+/+	3/1
15	m	12	74	2	–	2/1	15/15	45/32	+/–	+/+	3/1
16	f	12	67	9	–	2/1	4/8	29/28	+/+	+/+	2/1
17	m	12	38	3	ulc+ste+col	4/3	18/17	27/29	+/+	+/+	2/0
18	m	12	49	0.2	ste+col	4/3	12/10	20/18	+/+	+/+	3/0
19	m	12	71	2.5	ste+col	4/3	7/6	27/40	+/+	+/+	3/0
20	m	12	55	1.5	ste+col	4/3	5/4	31/60	+/+	+/+	2/0
Unchanged or worsened											
21	m	6	47	5	–	2/4	7/5	55/45	+/+	+/+	1/1
22	m	6	53	22	ste+col	4/4	10/10	27/28	+/+	+/+	1/1
23	m	6	49	16	ste+col	4/4	5/5	45/47	+/+	+/+	0/3
24	m	12	75	10	–	1/2	19/15	13/13	+/–	–/+	3/1
25	m	12	54	0.5	–	1/1	12/14	34/33	+/+	+/+	3/0
26	m	12	67	4	–	1/2	11/8	40/41	+/+	+/+	2/3
27	m	12	59	22	–	1/1	10/11	24/26	+/+	+/+	3/0
28	m	12	27	7.5	ste+col	4/4	20/22	26/27	+/–	+/+	1/1
29	m	12	70	20	ste	4/4	13/11	30/30	+/+	–/+	3/3
30	f	12	71	25	ste+col	4/4	9/13	34/24	+/+	+/+	0/2

*Endoscopic aspect of esophagitis: 0 = healed, 1 = mild, 2 = severe, 3 = complicated esophagitis with mild mucosal defects, 4 = complicated esophagitis with severe mucosal defects.
†Symptoms: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
‡ulc = transition ulcer, ste = peptic stenosis, col = columnar epithelium-lined esophagus.

tients was on the average 11.2 mm Hg ± 4.8 SD. This value was lower than 24.3 mm Hg ± 5.1 measured in the 24 controls (in Student's t test, $P < 0.001$). The outcome of treatment could not be predicted by LESP. At the end of treatment, LESP remained unchanged as compared to the initial values. Acid clearance required more swallows in patients than in healthy controls (33 ± 12 and 12 ± 4 swallows, $P < 0.01$). Initial acid clearance was not affected by treatment. Acid perfusion produced pain in 29 of the 30 patients. Ten of the 24 controls had symptoms during acid perfusion ($\chi^2 = 17.46$, $P < 0.001$). After treatment 26 patients still had a positive test (Figure 1).

Histology. In 25 patients histology of the macroscopically intact esophageal mucosa surrounding the macroscopic lesions revealed granulocytic infiltrates. Initial histology was normal in 3 patients with mild esophagitis and 2 patients with complicated esophagitis. Treatment had no effect on the histological appearance. The extension and density of granulocytic infiltrates was similar before and after treatment. The infiltrates tended to be less frequent in responders than in nonresponders, but the difference was not statistically significant.

Three-Hour pH Measurement in Healthy Controls. In the 13 healthy subjects the median 1-hr reflux time (pH < 4) was 73 sec (range 0–374 sec).

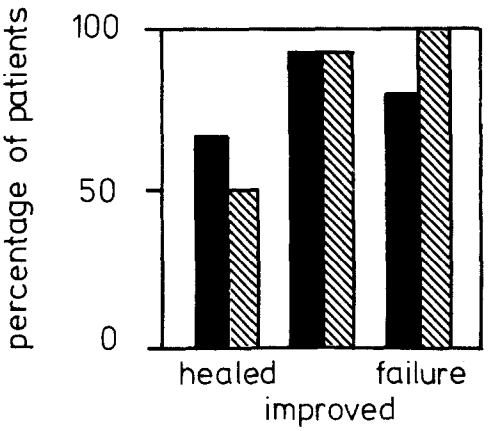

Fig 1. Percentage of patients with granulocytic infiltrates in the lamina propria. The black columns represent the percentage before and the hatched columns after cimetidine treatment, respectively. The patients are divided into three groups according to endoscopic response.

DISCUSSION

Studies in patients with reflux disease are difficult to conduct and to assess because of the many different ways to define the disorder. Some authors still look for axial hiatal hernia (14, 15), in spite of its questionable pathogenetic significance (16). Others define the disorder by heartburn or by tests mainly based on the patient's sensations (4), although the leading symptom in many refluxers is not heartburn (17), and heartburn, as well as an abnormal acid perfusion test, might also occur in patients with disorders other than reflux disease (18). Still others feel that abnormal function is the essential characteristic (3, 19, 20). These authors do not differentiate between subjects with and without peptic mucosal defects. Since such a failure to consider morphological changes is not accepted in disorders of the stomach and duodenum (21), it should also not be tolerated in the esophagus. There is even more confusion about the appropriate morphological criteria. At endoscopy, the only reliable signs of esophagitis are, according to our previous studies (5, 8), mucosal defects. Reddening, friability, granularity, and loss of glistening of the mucosa in the absence of mucosal defects are used as criteria of esophagitis by other authors (3, 22–24), while we have shown that these signs do not reflect either reflux or esophagitis (25, 26). Histology of patients with gastroesophageal reflux and esophagitis reveals granulocytic infiltrates even in areas with intact epithelium (9, 10). Others such as Ismail-Beigi et al (27) rely on epithelial thickness and papillar length as criteria of reflux. We have found similar values for epithelial thickness and papillar length in patients with reflux and in asymptomatic subjects (9). Interestingly, some authors who rely on epithelial data in American refluxers were unable to predict reflux in Swiss suction biopsies (CE Pope, personal communication).

In the present study, all 30 patients had esophageal peptic mucosal defects. Granulocytic mucosal infiltrates persisted together with an abnormal sensitivity to acid after normalization or improvement of endoscopic findings. Thus, the mucosa remains abnormal at a time when the disappearance of subjective symptoms and the normalization of the endoscopic picture would indicate healing. This signifies that the inflammatory infiltrates—together with the abnormal acid sensitivity—take much more time to disappear than the macroscopic lesions.

Abnormal sensitivity to acid in spite of endoscopic improvement has previously been reported (2). The Bernstein test is an unreliable method for the evaluation of reflux and esophagitis. Depending on criteria of a "positive response" the test is either frequently false positive, as in the present series, or false negative (31). Modifications of the test such as measuring the time for symptoms to appear or the electrical potential difference were not used in the present series.

There is some evidence that mucosal inflammation slowly disappears after antireflux surgery (28). Cimetidine treatment might not be sufficient to exert the same effect, even when given for a longer time period (1) than in the present study. Cimetidine has little or no effect on additional factors such as duodenogastric reflux (14, 15, 20) and slowed gastric emptying (31) which may aggravate reflux esophagitis. In addition, in the present study esophageal function did not improve while the macroscopic lesions healed. A drug-induced effect on motor function (32, 33) was excluded by performing the tests before starting and 24–48 hr after stopping of cimetidine. Similar results have previously been reported in reflux patients without proven reflux esophagitis (3, 4). Here, such a failure of abnormal motility to improve is not surprising. In feline esophagitis produced by acid perfusion of the esophagus, esophageal function deteriorates in parallel with mucosal damage (34, 35) and becomes normal again when the morphological damage disappears (36). A similar mechanism might be expect-

ed in human reflux disease. Our failure to observe this phenomenon might have one of two reasons: (1) treatment was not efficient enough or not given long enough, or (2) in human reflux esophagitis, in contrast to experimental esophagitis, the abnormal motility pattern is in fact irreversible.

For the time being, it would appear advisable to give drugs like cimetidine longer than to the point of endoscopic normalization and symptomatic relief, in an attempt to improve mucosal inflammation and possibly also esophageal function. This might interrupt a vicious circle and improve the very high recurrence rate (6) of this disease.

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