Three year follow up of patients with gastrooesophageal reflux disease

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Abstract
Data on the natural course of gastrooesophageal reflux disease are sparse. One hundred and sixty-six patients with typical reflux symptoms (heartburn and/or acid regurgitation) and pathologic pH monitoring (reflux time >8.2% upright and/or >3.0% supine) were studied. The patients were followed up by questionnaire and interview for a mean of 41 (seven to 86) months after diagnosis of reflux disease. Ten patients had died of diseases not reflux related. In 117 (75%) of the remaining 156 patients data on the course of gastroesophageal reflux disease could be obtained. In 12 patients anti reflux surgery had been performed. Forty one (39%) of the remaining 105 and 83 have stopped taking medical therapy, in 13 of these patients symptoms had completely disappeared. Sixty four patients continued on medication (40 on demand, 24 regularly). When asked how their symptoms would be if they completely stopped medication, 71 patients considered their symptoms to be equal or worse and 21 patients to be improved as compared with the initial investigation. Patients with persisting symptoms at follow up had significantly more supine reflux (p<0.05) at the initial pH monitoring as compared with patients with improved symptoms. The presence and grade of oesophageal erosions at initial endoscopy, duration of symptoms, age, sex, and smoking habits had no influence on the course of gastroesophageal reflux disease. In conclusion, reflux symptoms disappear only in a minority of patients with proven gastroesophageal reflux disease. More than half of all patients continue medication, either on demand or regularly. Severe supine reflux is an unfavourable prognostic factor.

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Occasional mild heartburn is one of the most common symptoms reported by otherwise 'healthy' subjects. The prevalence of heartburn has been estimated between 7% on a daily basis and 36% at least once a month. Until H2 blockers were generally available the medical treatment of chronic reflux symptoms was inferior to surgical management. Introduction of H2 blockers has substantially improved success of medical therapy. There are numerous studies which have shown that short term treatment with H2 blockers and omeprazole can effectively heal severe reflux oesophagitis and improve reflux symptoms. Relapse of oesophagitis and symptoms, however, is frequently observed.

Thus, gastroesophageal reflux disease obviously cannot be healed with short term treatment.

Data on long term outcome of gastroesophageal reflux are sparse. Available studies either were based on small samples or did not meet modern inclusion criteria of patients. The aim of the present study, therefore, is (i) to follow up a large and well defined patient sample with proven gastroesophageal reflux disease and (ii) to identify prognostic parameters which can predict the course of reflux disease.

Methods

PATIENTS
Between 1983 and 1990, 708 patients were investigated for gastroesophageal reflux disease in our laboratory. From these, all patients with typical symptoms of gastroesophageal reflux disease (heartburn and/or acid regurgitation) for at least one month before the study and a pathologic 24 hour pH monitoring (see below) were selected. Patients with previous upper gastrointestinal surgery such as cholecystectomy, gastric resection, or selective proximal vagotomy were excluded. One hundred and sixty six consecutive patients remained with proven gastroesophageal reflux disease were included in the study.

INDEX ASSESSMENT
A standardised questionnaire was completed for each patient during a personal interview with an experienced gastroenterologist who asked about age, smoking habits, and type, frequency and duration of symptoms.

TWENTY FOUR HOUR pH MONITORING
Ambulatory 24 hour pH monitoring was performed as previously described. Briefly, a combined glass electrode (440 M4, Ingold, Urdorf Switzerland, external diameter at the tip 4 mm) was connected to a pH meter and initially positioned in the stomach of the supine patient. It was then slowly withdrawn until a sudden rise of pH from acid (pH <4) to neutral (pH >6) was recorded on the pH meter. The pH rise could be identified in each case. The electrode was placed 5 cm above the sudden pH rise by anchoring the cable to the patients nose with adhesive tape. It is controversial whether the electrode in pH monitoring can be placed without prior manometry. In the present study, manometry has been replaced by the identification of the sudden pH rise at the oesophagogastric junction, as the accuracy of this simple method to position the electrode has been validated compared with manometric, endoscopic, and radiologic methods. Finally, the electrode was con-
### TABLE I  Type and outcome of anti reflux surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Reflux symptoms</th>
<th>Postoperative dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Improved</td>
</tr>
<tr>
<td>Fundoplication</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastrapexy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fundoplication + vagotomy</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrapexy + vagotomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Billroth II resection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>n=12, 8 men, 4 women</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

### TABLE II  Symptomatic success of medical treatment as assessed by the patient

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Success</th>
<th>None</th>
<th>Moderate</th>
<th>Good</th>
<th>Excellent</th>
<th>Σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>15</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>H₂ blocker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other drugs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3</strong></td>
<td><strong>1</strong></td>
<td><strong>17</strong></td>
<td><strong>33</strong></td>
<td><strong>10</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>

*= unknown/unclear.

In addition, data on actual symptoms as compared with index investigation, medication (type, duration, success), endoscopy, and eventual anti reflux surgery were obtained. If endoscopy or anti reflux surgery had been performed, the medical records were obtained.

**STATISTICAL ANALYSIS**

Data are given as means (SD) and, if appropriate, as medians and ranges. The Wilcoxon's rank-sum test for unpaired data and the χ² test were used to test for statistically significant differences.

**Results**

Ten patients had died unrelated to reflux disease. In 117 (75%, 85 men, 32 women) of the remaining 156 patients data on the course of gastrooesophageal reflux disease could be obtained. They were followed up for a mean of 41 (7–86) months. The mean age ranged from 19 to 80 years with a median of 52 years. In 12 patients anti reflux surgery had been performed. The type and outcome of surgery is summarised in Table I.

In the remaining 105 patients (77 men, 28 women) the median overall duration of symptomatic reflux disease was 10 (one to 50) years at follow up. Thirty-nine per cent of the patients had stopped medication, and in only less than one third of these patients symptoms had completely disappeared. Sixty-one per cent of the patients continued to take medication, either on demand or regularly (Fig 1). The success of the different types of medication is summarised in Table II. Antacids were significantly more often taken on demand, not regularly, than H₂ blockers (83% vs 36%, p<0.002).

Patients on medication (regular or on demand) were asked how their symptoms would be if they stopped all medication. Seventy one considered their symptoms to be equal or worse and 21 patients to be improved as compared with the index investigation (Fig 2).

Twenty four patients had an endoscopy both at the index assessment and at follow up. New appearance of erosions occurred as often as disappearance of erosions (Fig 3).

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**ENDOSCOPY**

Oesophagitis was graded using flexible endoscopes according to the Savary-Miller classification. Isolated oesophageal erosions (grade I) were found in 11%, linear confluent erosions (grade II) in 9%, circumferential erosions (grade III) in 7%, and an endobrachyoesophagus (grade IV) in 5% of the patients, respectively. Thus, in a total of 32% of the patients erosive oesophagitis was present. Patients with oesophageal erosions had significantly (p<0.05) more reflux (upright 18.2% (2.7%–59.6%), supine 10.1% (0.0%–98.6%)) as compared with patients without erosions (upright 12.4% (0.4%–69.4%), supine 4.2% (0.0%–80.7%)).

**FOLLOW UP**

Follow up interviews were carried out between February and December 1990. The patients were invited to the reassessment by letter and if necessary by phone. The interview of the index assessment was repeated either by telephone or by personal interview at our laboratory. The questions of the index interview were repeated.

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*Do you continue medical antireflux treatment and how are the symptoms as compared with index investigation?*

![Graph showing number of patients on different treatment schedules and symptomatic success of treatment.](http://gut.bmj.com/33.8.1016)
Prognostic factors
Patients with persisting symptoms at follow up had significantly more supine reflux (p<0.05) at the initial pH monitoring as compared with patients with improved symptoms (Table III). The presence and grade of oesophageal erosions at the initial assessment, duration of symptoms, age, sex, and smoking habits had no influence on the course of gastrooesophageal reflux disease.

Discussion
Anti reflux surgery was the most efficacious therapy for gastrooesophageal reflux disease until the advent of H2 receptor blockers. While studies on the success of short treatment with various drugs are numerous information on what happens after stopping scheduled treatment are sparse. In these few studies, erosive oesophagitis recurred in a large proportion of patients within six months. Therefore, we wondered how the symptoms and the need for treatment developed after the initial diagnosis irrespective of the presence or absence of oesophageal erosions.

Some earlier treatment studies before modern medical treatment with H2 blockers, omeprazole, or prokinetics, may give some information on the 'natural course' of reflux disease. A study of Rex published in 1961 provided a 10 year follow up of patients with hiatal hernia (diagnosed by radiography) treated conservatively. During the 10 year follow up approximately 60% patients improved or became asymptomatic. Patients with minimal symptoms (dyspepsia, vague distress) showed improvement in 82% compared with only 39% of patients with 'oesophagitis' and symptoms such as dysphagia and regurgitation. Another study reported a disappearance of reflux disease in 35% of the patients. The major limitation of all these investigations was that the inclusion criteria have been based on radiographic findings of an hiatal hernia or on unspecific symptoms. Thus, one may argue that the patients with vague symptoms did in fact not have gastrooesophageal reflux disease at all and that the symptoms of true gastrooesophageal reflux disease persisted in the majority of cases. This view is corroborated by other studies which based the diagnosis gastrooesophageal reflux disease on reliable diagnostic standards – for example, endoscopy and/or oesophageal pH-metry. A randomised prospective study compared surgical therapy with a conservative management of patients with gastrooesophageal reflux disease over a period of 36 months. Excellent or good results were obtained in 73% of the surgically treated patients as compared with 19% of those treated conservatively. A study of Lieberman analysed the course of 20 medically treated patients with proven reflux disease during a 26 month follow up. After an initial intensive therapy with cimetidine and metoclopramide, 12 patients experienced a relapse of symptoms (nine patients when drug dosage were tapered or discontinued, three patients after a remission of longer than two years). Seven of the remaining eight patients were maintained 'asymptomatic' with occasional antacids (five patients) or cimetidine, 300 mg at bedtime (two patients). In this study, therefore, only one patient really remained asymptomatic without any medication. Another study analysed a six months maintenance treatment with cimetidine or placebo in 24 patients. Sustained symptomatic relief was similar in both groups when only patients were considered who completed the observation period. Because four of 10 patients in the placebo group dropped out because of worsening symptoms, their data are therefore in accordance with our results. As a result of our inclusion criteria, namely pathologic pH monitoring and the specific symptoms heartburn and acid regurgitation, our patient sample consists of proven cases with reflux disease. About one third had erosive oesophagitis initially. Hence, our sample seems to be representative for patients with gastrooesophago-

Table III

<table>
<thead>
<tr>
<th>Symptoms in the course</th>
<th>% Reflux time</th>
<th>None or improved (n=34)</th>
<th>Equal or worse (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upright</td>
<td>12-4 (4-69-4)</td>
<td>12-3 (4-58-2)</td>
<td>5-0 (6-96-6)</td>
</tr>
<tr>
<td>Supine</td>
<td>2-3 (0-32-7)</td>
<td>5-0 (0-96-6)</td>
<td></td>
</tr>
</tbody>
</table>

Medians (range); * = p<0.05 e group with symptoms improved.

Figure 2: Development of symptoms without medication as estimated by the patients. The figures of the group with no medication are necessarily the same as in Figure 1.

Figure 3: Correlation between endoscopic findings at the start of follow-up and in the course in 24 patients. An endobrachyoesophagus (*) was present in three patients.
Three-year follow-up of patients with gastroesophageal reflux disease. In one third of the patients with repeat endoscopy this gave discrepant results. Hence, erosions disappear and develop with similar frequency: they wax and wane. This explains the placebo healing rates in controlled drug studies in oesophagitis, which can be estimated at about 20%, and that healing of oesophagitis is not equivalent to healing of reflux disease. Less than one fourth of the patients treated conservatively had improved at follow-up. About two thirds of our patients continued drug treatment during the observation period, either continuously or on demand. Similar results were obtained in a much smaller sample of reflux patients. About half of our patients used antacids (Table II). The reason may be that German practitioners are reluctant to prescribe H2 blockers and omeprazole because of their high cost. In addition, omeprazole is not approved for long-term treatment. Finally, the mode of administration and action of antacids seems more logical for occasional reflux symptoms than treatment with a drug with systemic action.

Patients with anti-reflux surgery in the follow-up had severe symptoms, which did not sufficiently improve on medical therapy. Thus, if the operated patients are considered with the entire sample, spontaneous improvement of gastroesophageal reflux disease is even more rare.

De Caestecker et al. found that daytime gastroesophageal reflux is an important factor for the development of erosive oesophagitis. We could confirm these results. In addition, we found that the severity of reflux is correlated with erosive oesophagitis, irrespective of the body position and the intake of meals. For the long-term outcome, however, only high supine reflux proved to be an unfavourable prognostic factor in reflux disease. We were unable to define other prognostic factors - for example, the duration of symptomatic reflux disease and the grade of oesophageal erosions did not correlate with the course of symptoms. This confirms previous findings that neither the duration of symptoms before diagnosis nor the endoscopic findings had an influence on the course of reflux disease.

In conclusion, reflux symptoms disappear only in a minority of patients with proven gastroesophageal reflux disease over the years. More than half of all patients continue medication, either on demand or regularly. High supine reflux is an unfavourable prognostic factor in gastroesophageal reflux disease.

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