Occasional mild heartburn is one of the most frequent long-term adverse effects reported by patients after treatment of reflux disease with 

proton pump inhibitors. The prevalence of heartburn has been shown to vary from 10% to 30% at 1 year, and from 5% to 10% at 5 years. However, the frequency of heartburn is often underestimated, as many patients may not report it or may consider it minor. In the present study, therefore, it is to follow up on a large and well-defined patient sample with proven gastroesophageal reflux disease and to identify parameters which can predict the course of reflux disease.

Three year follow up of patients with gastrooesophageal reflux disease

Abstract

Data on the natural course of gastroesophageal reflux disease (GERD) are scant, and follow-up studies of patients with proven reflux disease are few. This paper presents a follow-up study of 136 patients who had been monitored by 

24-hour pH monitoring (reflux index > 8%) at least three times at 6-month intervals. The aim of the present study therefore is to follow up on a large and well-defined patient sample with proven gastroesophageal reflux disease and to identify parameters which can predict the course of reflux disease.

Methods

Between 1983 and 1990, 708 patients were included in this study. Follow-up was complete in 136 patients (8216 months after the initial monitoring session). The mean age of the patients was 55 years. The majority of patients had typical symptoms of gastroesophageal reflux disease (heartburn and/or acid regurgitation) for at least 6 months. The patients were selected for a large and well-defined patient sample with proven gastroesophageal reflux disease and to identify parameters which can predict the course of reflux disease.

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. The questionnaire was administered to all patients at the initial monitoring session and at each follow-up visit.
Three-year follow up of patients with gastrooesophageal reflux disease

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 gastroesophageal 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 antireflux 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 (33% 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).

ENDOSCOPY
Oesophagitis was graded using flexible endoscopes according to the Savary-Miller classification.24 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.

Table I

<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>1</td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fundoplication+Vagotomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastroscopy+Vagotomy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Billroth II resection</td>
<td>1</td>
<td>1</td>
</tr>
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</table>

n=12, 8 men, 4 women

Table II

<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></td>
<td>2</td>
<td>10</td>
<td>15</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>H₂ blocker</td>
<td></td>
<td>1</td>
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<td>4</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Omeprazole</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pirenzepine</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
<td>17</td>
<td>33</td>
<td>64</td>
</tr>
</tbody>
</table>

?= unknown/unclear.

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

Figure 1: Numbers of patients on different treatment schedules and symptomatic success of treatment.

- No symptoms
- Equal
- Improved
- Worse

Table of symptoms at follow up
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 gastroesophageal 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 have gastrooesophageal reflux disease at all and that the symptoms of true gastroesophageal reflux disease persisted in the majority of cases. This view is corroborated by other studies which based the diagnosis gastroesophageal 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 gastroesophaga-

<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 (0-4-58-2)</td>
<td>5-0 (0-0-96-6)*</td>
</tr>
<tr>
<td>Supine</td>
<td>2-3 (0-32-7)</td>
<td>2-0 (0-0-96-6)*</td>
<td>5-0 (0-0-96-6)*</td>
</tr>
</tbody>
</table>

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

Our 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 gastrooesophageal reflux disease is even more rare.

De Caestecker found that daytime gastro-oesophageal 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 longest 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 gastrooesophageal 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 gastrooesophageal reflux disease.

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