

# Barrett's esophagus can develop after antireflux surgery

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## Barrett-Ösophagus nach Antireflux-Chirurgie

**Zusammenfassung.** *Grundlagen:* Antireflux-Chirurgie stellt eine gute Alternative zur medikamentösen Therapie der gastroösophagealen Refluxkrankheit (GERD) ohne Barrett-Ösophagus (BE) dar, bei denen sie die Entstehung eines BE verhindern soll. Diese Studie untersuchte die Entstehung von BE nach Antireflux-Chirurgie.

*Methodik:* Von 115 Personen ohne BE vor der Operation haben 12 (10,4 %) eine intestinale Metaplasie entwickelt und wurden mittels Endoskopie, Histologie und Funktionsdiagnostik untersucht.

*Ergebnisse:* Die 12 Personen hatten durchschnittlich 5 Endoskopien mit Biopsien. Symptome bestanden bei 10 (83 %) Patienten 80 Monate nach der OP. Die Nachsorge betrug im Mittel 135 Monate. Vier Personen hatten keinen Reflux beim pH und Bilitec Monitoring; 8 Patienten hatten pathologischen Reflux. Es gab keinen Unterschied zwischen jenen mit normaler und pathologischer Refluxaktivität bezüglich Endoskopie, Histologie und Manometrie. Eine intestinale Metaplasie entstand in 58–90 Monaten ausgehend von cardiac oder oxyntocardiac mucosa. Vier Personen hatten eine Regression von intestinaler Metaplasie zu cardaic mucosa nach intensiver medikamentöser Therapie.

*Schlussfolgerungen:* Antireflux-Chirurgie kann die Entstehung eines BE in 10 % der Fälle nicht verhindern, wobei 1/3 der Personen pathologischen Reflux hatten. Mittels Histopathologie kann eine Progression von oxyntocardiac und cardaic mucosa zur intestinalen Metaplasie bzw. Dysplasie und Karzinom bzw. Regression vom BE zur cardiac und odyntocardiac mucosa monitiert und mit der Funktionsdiagnostik korreliert werden.

**Schlüsselwörter:** Antireflux-Chirurgie, Barrett-Ösophagus, Histologie, Nissen Fundoplikatio, Refluxkrankheit.

**Summary.** *Background:* Surgical treatment in patients with gastroesophageal reflux disease (GERD) without Barrett's esophagus (BE) is an excellent alternative therapy to medical treatment, preventing the development of complications and the appearance of BE.

*Purpose:* To determine the newly developed BE in a group of patients without BE prior to surgery, the patients were submitted to a late subjective and objective follow-up.

*Methods:* From 115 non-BE patients submitted to surgery and followed up for a long period, 12 (10.4%) developed intestinal metaplasia after operation. They were submitted to endoscopic, histologic, manometric and functional studies (24-h pH and Bilitec).

*Results:* The 12 patients had an average of 5 endoscopies after surgery with several biopsy samples. Symptoms of recurrent reflux were present in only 10 patients (83%) at a mean of 80 months after surgery. The mean follow-up was 135 months. Four patients showed the absence of pathologic reflux measured by 24-h pH and Bilitec monitoring, while 8 had the presence of abnormal acid reflux. There were no significant differences between endoscopic, histologic and functional studies comparing patients with the presence or absence of pathologic reflux. The time of appearance to intestinal metaplasia from cardiac or oxynto-Cardiac mucosa was 58–90 months. Four patients showed regression of intestinal metaplasia to cardiac mucosa after intensive medical treatment.

*Conclusions:* Antireflux surgery in patients without BE does not prevent the late appearance of BE in near 10% of the cases, provided that a long-term follow-up is performed and several endoscopic and histologic evaluations are repeated. Near 2/3 of these patients showed the presence of acid reflux, while 1/3 showed no abnormal reflux. With this method of follow-up, metaplastic changes from cardiac to intestinal metaplasia and from intestinal metaplasia to low-grade dysplasia can be documented, as well as regression from intestinal metaplasia to cardiac mucosa.

**Keywords:** Barrett's esophagus, antireflux surgery, fundoplication.

## Introduction

The initial management of patients with pathologic gastroesophageal reflux disease is based on medical treatment, with a long-term success rate between 50 and 100%, depending on the daily dose employed [1–3]. However, in near 25% of the patients surgical treatment is an excellent alternative therapy, which is indicated if the reflux symptoms recur very soon after stopping medication and if the presence of pathologic acid reflux into the esophagus is documented together with an incompetent lower esophageal sphincter [4]. In this group of patients, surgical treatment has good long-term results in near 80–90% of the patients, provided that they do not have Barrett's esophagus [5–16] and depending on the length of follow-up [5–8, 13, 15]. The majority of surgeons have employed a total 360° fundoplication (Nissen procedure) and some surgical groups a posterior gastropexy (Hill procedure) associated to the calibration of the cardia (Larraín procedure). After surgery, lower esophageal sphincter function is restored and acid or duodenal content into the esophagus is significantly reduced or even abolished [17]. One important point in the discussion is the fact whether surgery prevents the development of “de novo” Barrett's esophagus in patients in whom no Barrett's esophagus was present at the time of initial surgery. Several authors, such as DeMeester [18], Theisen [19], Gutschow [20] and Wetscher [21], believe that this fact is exceedingly rare in patients who have an effective anti-reflux procedure, and postulate that no reports of BE that has developed following a successful antireflux operation have been published.

The purpose of this prospective study was to perform a late follow-up (more than 10 years) after antireflux surgery in a group of patients without Barrett's esophagus, in whom several objective evaluations were performed, including several endoscopies and biopsy samples at the gastroesophageal junction.

## Methods

### *Patients studied*

This prospective trial started on March 1987, when a special protocol for patients with reflux esophagitis was designed which included a careful clinical questionnaire, endoscopy with several biopsy samples, esophageal manometry and 24-h pH monitoring. In the last 10 years we have incorporated Bilitec studies. From March 1987 until December 1996, a total of 125 patients with reflux esophagitis without BE were operated and followed up carefully. The end of the follow-up was December 2005. Therefore, this study took us 18 years to be completed. From the original 125 patients (no operative mortality occurred), the late follow-up was completed in 115 (92%). From them, in 12 patients (10.4%) the development of intestinal metaplasia at the distal esophagus was noted and constitutes the present evaluation. Patients with preoperative Barrett's esophagus, stricture or previous antireflux surgery or gastric surgery or other diseases as scleroderma were excluded.

### *Clinical questionnaire*

A careful clinical assessment was performed in each patient before and late after surgery asking for the presence of typical GER symptoms. At the late follow-up they were grouped as symptomatic or asymptomatic.

### *Endoscopic evaluation*

All endoscopic procedure was performed by one of the authors (AC), using an Olympus GIF XQ-20 endoscope (Tokyo, Japan). Special care was taken to measure the exact location of the squamous-columnar junction at the beginning and at the end of the procedure, avoiding the “push and pull” effect of the endoscope [22].

This procedure was performed in all patients before surgery and 61 times after operation in 12 patients included in this study, which is a mean of 5.1 endoscopies per patient after surgery. For this study, four quadrant biopsy specimens were taken 5 mm distal to the squamous-columnar junction, which were designated as “gastroesophageal biopsies”. Hiatal hernia was defined as the presence of a sac-like structure distal to the tubular esophagus and containing gastric rugal folds. The presence of erosions was evaluated proximal to the squamous-columnar junction, as well as the presence of a peptic ulcer. For this study, the length of the columnar lined esophagus was determined with great care by endoscopy, taking the proximal limit as the most proximal presence of a segment of columnar epithelium (if tongues were present, the most proximal limit was taken) and the distal limit corresponding to the lower esophageal sphincter, which is the place where the proximal gastric rugal folds join the tubular esophagus with the stomach decompressed.

### *Histologic analysis*

Each biopsy sample was immediately submerged in 10% formaline solution and sent for histological examination. They were stained with hematoxylin and eosin and Alcian blue stain at pH 2.5. Fundic mucosa was identified by the presence of parietal and chief cells at the deep glandular layer. Cardiac mucosa was defined by the presence of mucous-secreting columnar cells. Oxynto-Cardiac mucosa was defined by the presence of both parietal cells and mucous secreting cells. Intestinal metaplasia was defined by the presence of well-defined goblet cells. The presence of inflammatory component was also evaluated by the findings of acute and chronic inflammatory cells.

Low-grade dysplasia was diagnosed if the nuclear cytoplasmic rate was slightly increased with the stratification of the underlining epithelium, with the loss of polarities and mitotic figures with an increased nuclear-cytoplasmic ratio [23].

### *Manometric evaluation*

Manometric testing was carried out after a 12-h fast with patients in the supine position. The details of the procedure and equipment employed have been fully explained

in previous reports [23, 24]. Three manometric characteristics of the lower esophageal sphincter were determined: resting pressure, total length and abdominal length. An incompetent sphincter was defined by the presence of one or more of the following parameters: lower esophageal sphincter pressure less than or equal to 6 mmHg, total length less than 20 mm and abdominal length less than 10 mm [26, 27]. The location of the distal and proximal limit of the lower esophageal sphincter was carefully measured in cm from the incisors. The amplitude of the distal esophageal contractile waves was also determined in mmHg. This test was performed before and at a mean of 88 months after surgery.

#### 24-h intraesophageal pH

This test was performed after a 12-h fast and always after a manometric evaluation in order to precisely determine the location of the lower esophageal sphincter [28, 29]. All patients were off PPI's at least 7 days before this test.

The details of the methods and equipment employed have been previously published [23, 29]. The digitrapp equipment from Synectics (Sweden) was used. The most practical way to express the results is the percentage of time during 24 h with a pH less than 4 at the distal esophagus. This test was performed before and at a mean time of 88 months after surgery.

#### 24-h monitoring of esophageal exposure to duodenal juice

This technique was developed to spectrophotometrically measure the intraluminal bilirubin concentration. It consists of a portable optoelectronic data logger (Bilitec 2000, Synectics, Sweden) connected to a fiberoptic probe that is located 5 cm proximal to the lower esophageal sphincter. The details of this procedure have been extensively published previously [23, 30]. This test was performed only late after surgery (mean 100 months). The final results are expressed as the percentage of time during 24 h in which bilirubin is measured at the distal esophagus, with an absorbance greater than 0.2.

#### Statistical analysis

For statistical evaluation Fisher's exact test and Chi square test were employed and a  $p < 0.05$  was considered as significant.

#### Surgical procedure

From the 12 patients included in this investigation, classic open posterior gastropexy with cardial calibration was performed in 6 and a total 360° Nissen fundoplication in 6 patients (3 laparoscopic and 3 open).

#### Definition of regression

- The loss of intestinal metaplasia with the presence of only cardiac or oxynto-Cardiac mucosa.
- The loss of low-grade dysplasia to non-dysplastic mucosa.

## Results

The group of 12 patients had a mean age of 56.8 years (range 35–76), being 7 women and 5 men. Symptoms of GERD were present at the late control in 10 patients (83%). However, with the use of permanent PPI's, 8 of the 10 patients were asymptomatic and only 2 persisted with mild heartburn during medical treatment, probably due to the fact that they were using only 20 mg of Omeprazole. The mean follow-up of the whole group is 135 months after the initial antireflux surgery (range 36–208 months) and the mean time of recurrence of reflux symptoms was 82 months (range 12–180), when PPI's were started. The main endoscopic and histologic findings are shown in Table 1, according to the presence or absence of pathologic acid reflux. Four patients showed no abnormal acid reflux, while 8 (67%) exhibited abnormal acid reflux. There were no significant differences in endoscopic and histological findings comparing both groups. The distribution of *H. pylori* both at the antrum and at the cardia was similar. Table 2 shows the main results of functional studies performed at a mean time of 88 months after surgery. There was no significant difference in preoperative 24-h pH values comparing patients with the absence or presence of reflux after surgery ( $p < 0.3$ ), as well as in the resting lower esophageal sphincter pressure ( $p < 0.8$ ). Among patients with the absence of postoperative reflux, there was a significant decrease in 24-h pH values compared to preoperative values ( $p < 0.001$ ), while no significant change was documented in patients with the presence of reflux after surgery compared to preoperative values ( $p < 0.3$ ). However, in both groups there was a significant increase of resting lower esophageal sphincter pressure after surgery ( $p < 0.01$ ). The total length of LES did not change significantly after surgery in the group with the absence of pathologic reflux; however, there was a significant increase among patients with the presence of pathologic reflux ( $p < 0.007$ ).

Table 3 shows the histological changes in the columnar mucosa distal to the squamous-columnar junction in patients who developed short-segment Barrett's esophagus late after surgery. Before operation 3 patients had oxynto-Cardiac mucosa, 3 patients had fundic mu-

**Tab. 1: Endoscopic and histologic findings among patients who developed Barrett's esophagus late after antireflux surgery (mean 88 months)**

	Pathologic reflux absent <i>n</i> = 4	Pathologic reflux present <i>n</i> = 8	<i>p</i>
Hiatal hernia	1	1	n.s.
Endoscopic esophagitis	1	2	n.s.
<i>H. pylori</i> GE junction	4(-)	8(-)	n.s.
Inflammatory cells GE junction	1(-) 3(+)	1(-) 7(+)	n.s.

GE gastroesophageal; n.s. not significant.

**Tab. 2: Functional studies before and late after antireflux surgery in patients who developed Barrett's esophagus (mean 88 months after surgery)**

Patients	Symptoms of GER	24 h pH studies		24 h Bilitec Post	LESP (mmHg)		Total length (mm)			
		Pre	Post		Pre	Post	Pre	Post		
Case No.		The absence of pathologic reflux <i>n</i> = 4								
1	(+)	13.9	1.1(108)	0.8	5	6	20	25		
2	(+)	19.5	0.3(96)	0	9	6	25	30		
3	(+)	12.6	0.5(84)	0.8	4	10	20	35		
4	(-)	25.4	4.1(84)	2.5	10	25	40	25		
Mean ± S.D		17.8 ± 5.8	1.5 ± 0.5	1.0	7 ± 2.9	11.7 ± 9	26.2 ± 9.4	28.7 ± 4.7		
		The presence of pathologic reflux <i>n</i> = 8								
5	(+)	14.8	16(168)	60	7	11	25	30		
6	(-)	22.5	31(96)	-	7	25	25	40		
7	(+)	21.5	36(96)	6.5	4	-	35	?		
8	(+)	85	37(36)	-	3	9	25	40		
9	(+)	64	10.8(72)	-	5	7	30	40		
10	(+)	18.6	15(96)	-	7	20	20	30		
11	(+)	14	17(24)	-	12	13	25	40		
12	(+)	19.5	20.8(96)	-	6	8	20	25		
Mean ± S.D		32.5 ± 26.7	22.9 ± 15	-	6.3 ± 2.7	13.3 ± 6.7	25.6 ± 4.9	35.0 ± 6.4		

LESP Lower esophageal sphincter pressure. Parentheses indicate the time after surgery; S.D. Standard deviation; 24-h pH studies expressed as % of time in 24 h with intraesophageal pH < 4.

**Tab. 3: Histologic findings at the columnar mucosa lining the distal esophagus before and after antireflux surgery among patients who developed Barrett's esophagus**

Cases	Follow-up (months)	ARS	Before op	I postop	II postop	III postop	IV postop	V postop	VI postop	VII postop	VIII Observation
Absence of acid reflux											
1	108	Nissen	O-C	C (36)	C (60)	IM (108)					
2	156	Nissen	C	C (24)	C (60)	IM (96) + LGD	IM (108)	IM (156)			
3	144	Nissen	C	C (24)	C (60)	IM (96)	IM (108)	IM (120)	IM (144)		
4	220	Hill	O-C	C (24)	C (48)	IM (60)	IM + LGD (96)	IM (108)	C (144)		Regression
Presence of acid reflux											
5	168	Hill	C	C (12)	C (36)	C(60)	IM (108)	IM (120)	IM (168)		
6	180	Hill	F	F (12)	O-C (24)	IM (48) + LGD	IM + LGD (96)	OC (120)	OC (168)		Regression
7	206	Hill	C	C (36)	C (60)	IM (96)	IM (120)	IM (156)	C (206)		Regression
8	36	Nissen	F	IM (12)	IM (36)						
9	120	Nissen	C	C (12)	C (48)	IM (60)	IM (96)	IM (120)			
10	208	Hill	F	F (24)	F (36)	O-C(48)	IM (72)	IM (84)	IM (96) + LGD	MI (120)	MI (208)
11	96	Nissen	C	C (12)	C (24)	C (36)	C (48)	IM (60)	IM (84)	C (96)	Regression
12	96	Hill	O-C	C (12)	C (60)	IM (96)					

ARS Antireflux surgery; IM intestinal metaplasia; O oxyntic; LGD low-grade dysplasia; F fundic. Parentheses indicate the time in months after surgery; C cardiac 2 patients (11 and 12) had 7 postoperative endoscopies. Regression means the change from intestinal metaplasia to cardiac mucosa.

**Tab. 4: The time of appearance of metaplastic changes among patients who developed Barrett's esophagus late after antireflux surgery**

The absence of pathologic reflux <i>n</i> = 4	The presence of pathologic reflux <i>n</i> = 8	
1. The development of intestinal metaplasia after initial surgery <i>n</i> = 12		
90 ± 21 months (4)	70 ± 28 months (8)	<i>p</i> < 0.3
2. The development of low-grade dysplasia <i>n</i> = 4		
96 months (2)	72 months (2)	<i>p</i> < 0.4
3. Regression to cardiac mucosa <i>n</i> = 4		
144 months (1)	133 ± 36 months (3)	<i>p</i> < 0.4
4. Persistence of intestinal Metaplasia <i>n</i> = 8		
136 ± 25 months (3)	105 ± 54 months (5)	
Parentheses indicate the number of patients. Pathologic reflux is defined as a % of intraesophageal pH < 4 ≥ 4.2% in 24 h.		

cosa and 6 patients had only cardiac mucosa. After surgery, a mean of 5.2 postoperative endoscopies together with several biopsy samples was performed in each patient. After surgery, the appearance of intestinal metaplasia occurred at a mean time of 90 months in the 4 patients with the absence of acid reflux and in 70 months among patients with the presence of pathologic acid reflux (Table 4). This value correlates with the appearance of reflux symptoms after antireflux surgery (82 months after surgery). The length of the specialized columnar epithelium varied between 10 and 25 mm, with a mean of 18 mm. Four patients (2 in each group) developed low-grade dysplasia. Two patients with the absence of reflux developed low-grade dysplasia 96 months after surgery. None of them was under PPI treatment, which started at that time. In one of them, low-grade dysplasia disappeared with aggressive medical treatment, remaining intestinal metaplasia. The other patient showed regression to IM 108 months after surgery and regression to cardiac mucosa 144 months after surgery, with continuous medical treatment.

Two patients with the presence of pathologic acid reflux developed low-grade dysplasia 48 and 96 months after surgery, which showed regression to intestinal metaplasia and then to cardiac mucosa 120 months after surgery with intensive medical treatment. One patient (No. 6) started PPI at the time of appearance of dysplasia, while the other patient (No. 10) was under PPI treatment. All patients were treated with daily base PPI's permanently. In four patients, regression from intestinal metaplasia to cardiac mucosa occurred. One patient from the non-reflux group showed this regression to cardiac mucosa at 144 months after surgery, which means 54 months after the development of intestinal metaplasia. Three patients

from the reflux group showed this regression at 133 months after surgery, 2 to cardiac mucosa and 1 to oxynto-Cardiac mucosa, which means 63 months after the development of intestinal metaplasia. A total of eight patients persisted with IM.

At the current control, only 1 patient was re-operated, performing an acid suppression and duodenal diversion procedure. One patient was lost from the follow-up, while 10 patients remained under continuous PPI's, being asymptomatic while taking medication.

## Discussion

The results of this prospective study suggest that a short-segment Barrett's esophagus can develop after classic antireflux surgery, provided that a very long-term follow-up is performed (more than 10 years) and several endoscopic and histologic studies are performed in order to demonstrate the presence of intestinal metaplasia. Besides, this investigation for the first time has proved the progressive metaplastic changes in the same human subject that can occur until the appearance of intestinal metaplasia or even low-grade dysplasia.

We have reviewed several hundreds of surgical publications since 1980 up to date concerning antireflux surgery. In the great majority of publications, no clear distinction is made before operation between Barrett's and no Barrett's patients. Besides, the follow-up is too short (5 years or less) and objective data are seldom shown such as postoperative pH studies, manometric evaluation and endoscopic controls. Histological findings after surgery are even less. Therefore, it is difficult to conclude based on scientific evidences what really happens to patients 10 or 20 years late after surgery. As DeMeester states [18], very few authors have recorded the presence of Barrett's metaplasia following antireflux surgery when it was absent preoperatively. We have carefully reviewed the literature and found 6 publications with more than 5-year follow-up, with some objective evidences (Table 5).

Loustarinen in 2 reports [5, 7] refers with some detail to this particular aspect. In one publication [7] he followed up 105 patients for 77 months, with a clinical success rate of 63%. He performed endoscopy before surgery and at a late control in all patients, demonstrating erosive esophagitis in 5% of 81 patients with an intact wrap and 58% of esophagitis in the presence of a defective wrap. No clear histological studies were performed, but endoscopically he found a long segment BE (more than 3 cm) in 17% of the patients. This value is close to our results. This development of BE occurred in 33% of patients with a defective wrap and in 12% after an intact wrap. 24-h pH was performed in 46 patients, demonstrating an abnormal reflux in 7% with an intact wrap and in 69% with a defective wrap. These data are a little confusing, because in results section he states that Barrett's esophagus was observed in 18 patients at the follow-up, but in only 6 patients before operation. In the following section he states that seven of the 17 patients with newly detected Barrett's esophagus showed the absence of re-

**Tab. 5: The development of Barrett's esophagus following antireflux surgery in patients without Barrett's esophagus before operation**

Author	No. of operated patients	Criteria BE	% Clinical success	Endoscopy	Histology	Pathologic acid reflux	Development BE	Follow-up (months)
Loustarinen (1993)	25	> 3 cm CE Histology	14(56%)	25	21	4/14(29%)	7(33.3%) Intact wrap 4 Defective wrap 3	144
Loustarinen (1993)	105	> 3 cm CE	66(63%)	105 Esophagitis Defective wrap 14/24 = 58.3% Intact wrap 4/81 = 4.9%	No	15/46(33%) Intact wrap 7% Defective wrap 69% 7 BE (-) 10 BE (+)	18(17.1%) Intact wrap 10/81 = 12% Defective wrap 8/24 = 33.3%	77
Johansson (1993)	39	>3 cm CE	32(82%)	No defective wrap	No	36 3(+) = 8.3%	1(2.5%)	60
Isolauari (1997)	37	>3 cm CE	84%	35	No	No	7(19%)	132
Rantanen (1999)	39	>3 cm CE	Intact wrap 96% Defective wrap 67%	35 Esophagitis Intact wrap 3/22 = 14% Defective wrap 7/13 = 54%	No	8 4(+) 50%	5(14%) Intact wrap 2/22 = 9% Defective wrap 3/13 = 23%	78
Oberg (2001)	20	I.M.	100	20	20	5%	4(20%)	65
Wetscher (2001)	42	I.M.	100%	All	No	All normal	0	40
Csendes (2007)	115	I.M.	67%	All patients	All patients	18%	12(10.4%)	135

CE columnar epithelium; BE Barrett's esophagus; IM intestinal metaplasia.

flux. In another report [5] he referred to 25 patients with a mean follow-up of 144 months after Nissen fundoplication, finding a Visick I and II grading in only 56% up to 20 years of control. In 21 patients histological specimens were obtained and in 7 (33.3%) Barrett's metaplasia appeared, 4 in an intact wrap and 3 in a defective wrap. These 2 long-term papers clearly demonstrate that a de novo BE can appear in asymptomatic patients, with an intact wrap, providing a long-term endoscopic and histologic evaluation.

Johansson [9] evaluated 40 patients submitted to fundoplication and followed up for 60 months. Clinical success was achieved in 85% of the patients. No defective wrap was found by endoscopic evaluation, which is extremely rare for us. No histological analyses were performed. 24-hr pH was + in 3 of 36 cases (8.3%). Barrett's metaplasia appeared in 1 case (2.5%).

Isolauari [6] found that 37 patients were controlled at 132 months after fundoplication. No histologic or 24-h pH studies were performed. He found 7 new cases of Barrett's esophagus at the late control (19%), which again is similar to our findings. Rantanen [8] found that a group of 39 patients were submitted to surgery and followed up for 78 months. He described 96% success in the presence of an intact wrap and 67% with a defective wrap. Very few patients had manometric, 24-h pH and radiological stud-

ies. He found 5 patients (14%) with Barrett's esophagus appearing late after surgery, 9% after an intact wrap and 23% after a defective wrap. Oberg [11] reported 20 patients submitted to fundoplication and followed up for 65 months. In all patients, complete objective evaluations were performed. He obtained 100% clinical success and 24-h pH and endoscopy were normal in 95%. It is not clear whether this was a selected group in which a 100% success was obtained (which is extremely rare) or it was an unselected consecutive group. These patients had a columnar-lined mucosa of the distal esophagus of 2-cm length before surgery. However, having all parameters normal, they found 4 patients (20%) who developed intestinal metaplasia at the distal esophagus, and they have no clear explanation for this fact. The final publication is from Wetscher et al. [21] who operated 42 patients who were followed up for 3.5 years. They clearly state in the surgical group that only patients free from reflux symptoms after surgery were included. They had no acute esophagitis on endoscopy, had a normal LES on manometry and normal 24-h pH studies. Even 19% of the patients had a normal pH study before surgery. This is clearly an ideal and exceptional group and is of no use for scientific purposes, because it does not reflect the reality of antireflux surgery. They did not find any patient developing BE, but they were followed up for 3.5 years after surgery.

There is 1 more paper, which was not included in Table 5. It is from Thor et al. [10] who performed a 5-year follow-up in 31 patients submitted either to Nissen or to Toupet fundoplication, performing endoscopic and biopsy specimens. However, they only mention some endoscopic results without any reference to BE or histological findings. No 24-h pH studies were performed and only some mention about a newly formed hiatal hernia is made. Therefore this study is not useful for our purpose.

Our study represents a careful objective follow-up at a very late control, and shows exactly what other authors as Loustariven, Isolauri, Rantanen and Oberg have found. Near 10 to 20% of patients without BE submitted to surgery can develop Barrett's metaplasia, only if a late objective follow-up is performed. This "de-novo" appearance of BE can be sometimes seen in asymptomatic patients, in the presence of an intact wrap by endoscopy and in the presence of a normal 24-h pH study, although it is clearly more prevalent if these mentioned parameters are abnormal. Ours is the only study evaluating bile reflux in these patients.

The second important point in this study is the progressive development of histological changes, demonstrating 2 consecutive histological changes that can occur in patients with GERD: the first metaplastic change from cardiac mucosa to intestinal metaplasia can occur around 80 months after surgery, maybe earlier in patients with the presence of reflux (70 months) compared to patients with the absence of reflux (90 months). A second histological change, appearing only in 4 patients, is the appearance of low-grade dysplasia. We are not aware of any other surgical report concerning these progressive stages, except in a previous paper by us [23] in which we demonstrated that low-grade dysplasia could appear in patients with Barrett's esophagus 2 to 4 years after initial classic antireflux surgery. However, there is an important point regarding the measurement of acid reflux by 24-h pH monitoring. The pH probe is placed 5 cm proximal to the proximal limit of the LES, thereby missing the eventual reflux due to this proximal placement. In spite of having a fundoplication, Barrett's esophagus developed because fundoplication probably was not able to prevent reflux into the distal esophagus. As a consequence we completely agree with the group of DeMeester [31] in the sense that cardiac mucosa represents an objective histological marker for reflux disease [32]. In fact, 9 of 12 of our patients had cardiac mucosa at the time of antireflux surgery and only 3 had fundic mucosa. Therefore, effective fundoplication could be defined maybe better by histopathology than by pH studies. However, the possibility of biopsy sampling error must always be considered. That is why we performed at least 5 endoscopic and histological evaluations in each patient.

This study stresses again the urgent necessity that the late results after antireflux surgery must be reported employing subjective and several objective analyses such as endoscopy, histological samples, manometry, 24-h pH studies and Bilitec studies. The need for a close endoscopic surveillance, especially if a Barrett's esophagus is present, is clearly demonstrated.

For us it is of questionable value to show results 1 or 2 years after surgery, evaluated only by a telephone call, asking whether he or she is under some medication. At an early control, almost all patients feel well and this finding is not representative to what will happen 15 or 20 years after surgery, when a progressive deterioration of the antireflux surgery is clearly observed [5, 13]. The final important point is that intestinal metaplasia is a dynamic and changing mucosa, dependent from the presence of acid and duodenal reflux. It can regress to cardiac mucosa, if reflux is completely abolished. However, some poorly understood issues remain, concerning the late appearance of specialized metaplasia after antireflux surgery, even in the absence of reflux symptoms and when acid or biliary reflux is not found by objective methods.

## References

- [1] Klinkenberg-Knoll EC, Festen HP, Jansen JB, Lamers CB, Nelis F, Snel P, Luckers A, Dekkers CP, Havu N, Meuwissen SG. Long term treatment with omeprazole for refractory reflux esophagitis. Efficacy and safety. *Ann Inter Med* 1994;121:161-7.
- [2] Hallerback B, Unge P, Carling L, Edwin B, Glise H, Havu N, Lyrenas E, Lundberg K. Omeprazole or Ranitidine in long term treatment of reflux esophagitis. The Scandinavian Clinics for United Research Group. *Gastroenterology* 1994; 107:1305-11.
- [3] Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di Mario F, Battaglia G, Mela GS, Pilotto A, Plebani M, Davi G. A comparison of five maintenance therapies for reflux esophagitis. *New Eng J Med* 1995;333:1106-10.
- [4] Campos GM, Peters JH, DeMeester TR, Oberg S, Crookes PF, Tan S, DeMeester SR, Hagen JA, Bremner CG. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastroint Surg* 1999;3:292-300.
- [5] Loustarinen M, Isolauri J, Laitinen J, Koskiven M, Keyrilainen O, Markkula H, Lelintinen E, Clusitalo A. Fate of Nissen fundoplication after 20 years. A clinical, endoscopic and functional analysis. *Gut* 1993;34:1015-20.
- [6] Isolauri J, Loustarinen M, Viljakka M, et al. Long term comparison of antireflux surgery versus conservative therapy for reflux esophagitis. *Ann Surg* 1997;225:295-9.
- [7] Loustarinen M. Nissen fundoplication for reflux esophagitis long term clinical and endoscopic results in 109 of 127 consecutive patients. *Ann Surg* 1993;217:329-37.
- [8] Rantanen TK, Halme TV, Loustarinen ME, Karhumaki LM, Kononen EO, Isolauri JO. The long term results of open antireflux surgery in a community based health care center. *Am J Gastroint* 1999;94:1777-81.
- [9] Johansson J, Johnsson F, Joelsson B, Floren CH, Walther M. Outcome 5 years after 360° fundoplication for gastroesophageal reflux disease. *Brit J Surg* 1993;80:46-9.
- [10] Thor KBA, Silander T. A long term randomized prospective trial of the Nissen procedure versus a modified Toupet technique. *Ann Surg* 1989;210:719-24.
- [11] Oberg S, Werner J, Johnsson F, Zilling TH, Van Holstein CS, Nilsson J, Walther B. Endoscopic surveillance of columnar lined esophagus. Frequency of intestinal metaplasia detection and impact of antireflux surgery. *Ann Surg* 2001;5:619-26.
- [12] Csendes A, Braghetto I, Korn O. Late subjective and objective evaluation of antireflux surgery in patients with reflux esophagitis: analysis of 215 patients. *Surgery* 1989;374-82.
- [13] Csendes A, Burdiles P, Korn O, Braghetto I, Huertas C, Rojas J. Late results of a randomized clinical trial comparing total fundoplication versus calibration of the cardia with posterior gastropexy. *Brit J Surg* 2000;87:289-97.
- [14] Low DE, Anderson RP, Ives R, Ricciardelli E, Hill LD. Fifteen to twenty years results after the Hill antireflux operation. *J Thorac Cardiovasc Surg* 1989;48:444-50.
- [15] Negre JB, Markkula HT, Keyrilainen O, Matikainen M. Nissen fundoplication. Results at 10 year follow up. *Am J Surg* 1983;146:635-8.

- [16] DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. *Ann Surg* 1986;204:9–20.
- [17] Stein HJ, Kauer WKJ, Feussner H, Siewert JR. Bile reflux in benign and malignant Barrett's esophagus. Effect of medical acid suppression and Nissen fundoplication. *J Gastroent Surg* 1998;2:333–41.
- [18] DeMeester TR. Surgical therapy for Barrett's esophagus: prevention, protection and excision. *Dis Esoph* 2002;15:109–16.
- [19] Theisen J, Oberg S. Surgical and medical therapies for GERD. Can we see into the future? *Am J Gastroent* 1998;93:1008–9.
- [20] Gutschow CA, Schroder W, Prenzel K, Boelschweiler E, Romagnoli K, Collard JM, Holscher AH. Impact of antireflux surgery on Barrett's esophagus. *Langenbeck's Arch Surg* 2002;387:138–45.
- [21] Wetscher GJ, Gadenstaetter M, Klinger PJ, Weiss H, Obrist P, Wykypiel H, Klaus A, Profanter C. Efficacy of medical therapy and antireflux surgery to prevent Barrett's esophagus in patients with gastroesophageal reflux. *Ann Surg* 2001;234:627–32.
- [22] Csendes A, Coronel M, Avendaño H. Endoscopic location of the squamous columnar junction in patients with gastroesophageal reflux. *Rev Méd Chile* 1996;124:1320–4.
- [23] Csendes A, Burdiles P, Braghetto I, Smok G, Castro C, Korn O, Henríquez A. Dysplasia and adenocarcinoma after classic antireflux surgery in patients with Barrett's esophagus. *Ann Surg* 2002;235:178–85.
- [24] Csendes A, Maluenda F, Braghetto I, Csendes A. Location of the lower oesophageal sphincter and the squamous columnar junction in 109 healthy controls and 778 patients with different degrees of endoscopic esophagitis. *Gut* 1993;34:21–7.
- [25] Csendes A, Braghetto I, Burdiles P, Díaz JC, Maluenda F, Korn O. A new physiological approach for the surgical treatment of patients with Barrett's esophagus. *Ann Surg* 1997;226:123–33.
- [26] Zaninotto G, DeMeester TR, Seenger W, Johansson KE, Cheung SC. The lower esophageal sphincter in health and disease. *Am J Surg* 1988;155:104–11.
- [27] Csendes A, Burdiles P, Alvarez F, Maluenda F, Henríquez A, Quesada S, Csendes P. Manometric features of mechanically defective lower esophageal sphincter in control subjects and in patients with different degrees of gastroesophageal reflux. *Dis Esoph* 1996;9:290–1.
- [28] DeMeester TR, Wang CI, Wernly JA, et al. Technique indications and clinical use of 24 hour intraesophageal pH monitoring. *J Thorac Cardiovasc Surg* 1980;79:656–670.
- [29] Csendes A, Alvarez F, Burdiles P, Braghetto I. Magnitude of gastroesophageal reflux measured by 24-hour esophageal pH monitoring according to the degrees of endoscopic esophagitis. *Rev Méd Chile* 1994;122:59–67.
- [30] Csendes A, Braghetto I, Burdiles P, Puente J, Korn O, Díaz JC. Long term results of classic antireflux surgery in 152 patients with Barrett's esophagus: clinical, radiologic, endoscopic, manometric and acid reflux analysis before and late after operation. *Surgery* 1998;126:645–57.
- [31] Oberg S, Peters JH, DeMeester TR. Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastroesophageal reflux disease. *Ann Surg* 1997;226:522–30.
- [32] Csendes A, Smok G, Burdiles P, Sagastume H, Rojas J, Puente G, Quesada F, Korn O. "Carditis": an objective histological marker for pathologic gastroesophageal reflux disease. *Dis Esoph* 1998;11:101–5.