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HONORED GUEST'S ADDRESS

ESOPHAGEAL SURGERY AT THE END OF THE MILLENNIUM

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The "Smith Surgical Papyrus" transcribed in the years 3000 to 2500 bc contains the first written report on surgery of the esophagus. The papyrus was discovered by the American Egyptologist Edwin Smith in 1862 and further meticulously edited by Henry Breasted in 1930.¹ Case 28 of the 48 cases described in this work was entitled "A Gaping Wound of the Throat Penetrating the Gullet" and tells us: "... if thou examinest a man having a gaping wound in his throat, piercing through to his gullet; if he drinks water he 'chokes' (and) it comes out of the mouth of his wound; if it is greatly inflamed so that he develops fever from it, thou shouldst draw together that wound with stitching . . ."

Only 2000 years later in the seventeenth century cervical esophagotomy was first performed and resection of the thoracic esophagus had to wait

until the introduction of intratracheal anesthesia well into the twentieth century. The real progress came as a result of the development of thoracic surgery during and after the Second World War. Inasmuch as I had the privilege to be trained by Mr. Ronald Belsey in Bristol, I was able to stand on the shoulders of a true giant in esophageal surgery and witness the remarkable developments that were taking place. This unique experience allowed me to build up my own practice in esophageal surgery, thereby actively participating in the more recent evolutions and capturing my fascination until today. This honored guest address is the reflection of my thoughts on esophageal surgery at the end of the MILLENNIUM, thoughts in part based on my own experience now dealing with more than 2500 cases and in part on the work of so many other "esophagologists."

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Esophageal atresia

The earliest description of esophageal atresia with tracheoesophageal fistula was made in 1697, 300 years ago, by Gibson in London.² The condition was destined to remain an anatomic curiosity until the first half of the century, when on March 15, 1941, C. Haight at the University of Michigan was the first to perform a successful one-stage closure of the fistula and primary anastomosis.³ The further spectacular improvements in treating this condition are a remarkable example of the progress of modern tho-

Fig. 1. Esophageal atresia in 203 patients. Incidence of different types of atresia.

Table I. Esophageal atresia: Waterston classification and postoperative mortality in 201 patients

	1969-1979	1980-1981	1988-1996	Overall
A	2/17 (11.7%)	0/25 (0%)	0/23 (0%)	2/65 (3%)
B	4/31 (13%)	1/21 (4.7%)	0/28 (0%)	5/80 (6%)
C	8/21 (38%)	4/19 (21%)	3/16 (18.7%)	15/56 (26.7%)
Total	14/69 (20%)	5/65 (7.7%)	3/67 (4.4%)	22/201 (11%)

A, Birth weight greater than 2500 gm; good general condition. B, Birth weight 1800 to 2500 gm; good general condition. Birth weight greater than 2500 gm, moderate pneumonia, and/or non-life-threatening congenital malformations. C, Birth weight less than 1800 gm; good general condition. Birth weight 1800 to 2500 gm, severe pneumonia, and/or life-threatening congenital malformations.

racic surgery and preoperative and perioperative neonatal care: the epitome of modern surgery.

The most common form of esophageal atresia is combining the atresia with a tracheoesophageal fistula of the distal segment, occurring in approximately 85% of the cases, followed by atresia without a fistula, usually a long-gap atresia, occurring in approximately 10%, data that are confirmed by the experience that my colleagues and I obtained in dealing with 203 cases (Fig. 1).

Association with other congenital malformations is frequently seen and they can be life threatening in as much as 20% of the cases. Prematurity, associated malformations, and pulmonary status at the time of surgical correction are considered as the three essential prognostic parameters; therefore, since the sixties they have been incorporated in a classification named after Waterston.⁴ This classification remains a valid way to judge the progress that has been made over the years in controlling postoperative mortality.

Today, in patients who have no or non-life-threatening associated malformation(s) and who are in good general condition at the time of surgery, no

mortality is to be expected. In our own experience over the years, overall mortality decreased from 20% to 5.4% (Table I). The most difficult technical problem today relates to the long-gap atresia when primary anastomosis becomes impossible. In such a situation there are essentially two alternatives—elongation with delayed primary anastomosis⁵ or colon interposition.⁶ The first option fell into disfavor because of the high incidence of postoperative complications and severe gastroesophageal (GE) reflux in the late follow-up⁷; thus colon interposition now is preferred, with the technique described by Belsey. Twenty-five patients underwent a coloplasty.⁸ In the immediate postoperative period, anastomotic dysphagia (56%), regurgitation (40%), and diarrhea (28%) were frequent but gradually decreased to 16%, 20%, and 12%, respectively. At final evaluation, 85% of the patients were considered to have excellent or very good results and only four patients were judged to have a moderate result.

During long-term follow-up after primary anastomosis, most of the residual symptoms are caused by the atresia-related motor disorders of the esophageal body, GE reflux, and pulmonary disorders, the

Table II. Esophageal atresia: Pulmonary status after corrected esophageal atresia

	TLC	VC	FEV ₁	FEV ₁ /VC
Gestational age				
< 37 wk, n = 10	72	69	70	87
≥ 37 wk, n = 37	86	82	82	87
	‡	†	†	
Birth weight				
< 10th percentile (n = 10)	75	69	71	84
> 10th percentile (n = 37)	82	77	80	86
	*	*	*	
Use of contrast				
+ (n = 32)	76	74	78	88
- (n = 13)	84	79	79	82
	*			†
Type of operation				
Colon (n = 7)	68	65	67	88
Anastomosis (n = 34)	83	80	80	86
	*	*	†	

Figures are given as the percent of normal values. TLC, Total lung capacity; VC, vital capacity; FEV₁, forced expiratory volume in 1 second.

**p* < 0.05.

†*p* < 0.005.

‡*p* < 0.0005.

latter enhanced by congenital deficiency of the ciliated epithelium in the trachea. However, most frequently the combination of both esophageal and pulmonary symptoms is noticed. This is mainly caused by GE reflux resulting in inflammation and recurrent anastomotic stricture on one hand and in regurgitation and aspiration on the other hand.

In a group of 63 patients followed up for at least 3 years, 57% became completely symptom-free. Of the 27 patients who had symptoms, 20 (74%) had both esophageal and pulmonary symptoms. In that subset of 20 patients, 15 (75%) had a documented GE reflux necessitating either aggressive medical treatment (11 patients) or antireflux surgery (4 patients). The treatment resulted in cure or clear improvement of the symptoms in 11 of the 15 patients (73%).

The importance of an aggressive policy to stop any further damage of the lungs is well illustrated by an analysis of pulmonary function tests in a group of 47 patients followed up between 6 and 13 years after surgery.⁹ Only 23% had normal function tests, and as many as 25% of the patients who had abnormal function tests also had symptoms.

Factors influencing significantly pulmonary function were prematurity, low birth weight reflecting prematurity, use of preoperative contrast medium, and colon interposition, the latter because of two thoracotomies in a number of patients. All these

Fig. 2. Contractility pattern of the musculus cricopharyngeus in control specimens (A) and Zenker's diverticulum (B).

factors had a mostly restrictive effect on pulmonary function (Table II).

Because today more and more children treated for esophageal atresia are now entering their adult life, it is to be expected that many of them will be found with a number of potentially severe and complex functional esophageal and/or pulmonary problems necessitating intense long-term follow-up on a regular basis to remedy their problem.

Zenker's diverticulum

Pharyngoesophageal diverticulum originally was believed to be a pulsion diverticulum enlarging over time and causing dysphagia by compression of the esophagus.¹⁰

Belsey,¹¹ at the occasion of his honored guest lecture before The American Association for Thoracic Surgery in 1966, emphasized a dysfunction of the cricopharyngeal muscle as the underlying cause and presented a series of 45 patients, the majority of them treated with myotomy and diverticulopexy resulting in a complete symptomatic relief in 43 patients.

Belsey's hypothesis later became endorsed through the developments of manometry. Ellis and associates¹² identified premature relaxation and contraction as the possible cause of the cricopharyngeal dysfunction, while Duranceau¹³ and Migliore, Payne, and Jeyasingham¹⁴ recorded a more general dysfunction of the upper esophageal sphincter.

More recently, Cook and coworkers¹⁵ proved a noncompliance of the upper sphincter with an in-

Table III. *Contractility studies in five patients with Zenker's diverticulum and five controls*

	<i>TPT</i> (msec)	$\frac{1}{2}$ <i>RT</i> (msec)	<i>Amp</i> (gm)	<i>dP/dT</i> (gm/msec)
Control	84	70	8.3	0.2
	72	70	1.4	0.05
	123	165	3	0.06
	61.5	123	6	0.08
	172	193	4.1	0.5
Total	102.5	124		0.32
	(± 45.2)	(± 55.4)		(± 0.01)
ZD	324	188	0.9	0.006
	126	120	1.2	0.07
	490	312	0.7	0.01
	126	178	0.8	0.05
	72	193	0.5	0.01
Total	225	189		0.03
	(± 156)	(± 66)		(± 0.001)
	$p < 0.05$	$p < 0.05$		$p < 0.05$

ZD, Zenker's diverticulum; *TPT*, time to peak twitch; $\frac{1}{2}$ *RT*, half relaxation time; *AMP*, amplitude; *dP/dT*, velocity of force increment.

creased intrabolus pressure, reflected by the appearance of a large shoulder on the manometric tracing, to be the underlying pathogenic mechanism.

Systematically taking large biopsy specimens of the cricopharyngeal muscle and proximal esophageal muscle wall at the time of operation allowed our group to perform a number of different studies.¹⁶ In a first setting, contractility studies were performed showing a significant decrease in time-to-speak twitch, half-relaxation time, and velocity of force increment (Table III) in specimens taken from patients with Zenker's diverticulum as compared with specimens obtained from control subjects (Fig. 2).

In a subsequent series of biopsy specimens, enzymohistochemistry and enzymoimmunology were studied for analysis of a series of parameters routinely used in evaluating neuromuscular disorders. Almost all parameters were judged normal in the control specimens, whereas clear abnormalities were found in the vast majority of biopsy specimens taken from patients with Zenker's diverticulum (Table IV).

Muscle biopsy tissue from Zenker patients showed a chaotic pattern of the muscle fibers, with hypertrophy and atrophy, necrosis, inflammation, and fibrosis between the fibers (Figs. 3 and 4). Acetylcholinesterase and neurofilament staining showed a pathologic absence of coloration in over

50% of the muscle fibers, indicating a more neurogenic induced disorder (Fig. 5).

In a final and third setting of biopsies, adenosine triphosphate metabolism, that is, energy charge, was measured (Table V). This energy charge appeared to be decreased and below the normal expected values in Zenker's diverticulum as compared with control specimens, pointing perhaps more toward a primary myogenic disorder. However, all three of these studies seem to endorse the concept of the noncompliant cricopharyngeal and upper cervical esophageal muscle as the underlying mechanism underscoring the importance of the extramucosal myotomy of the cricopharyngeal muscle and proximal 3 to 4 cm of the cervical esophageal muscle wall, as was described 30 years ago by Belsey.

From the clinical aspect, patients with Zenker's diverticulum have a wide variety of symptoms. Dysphagia and regurgitation are the most prominent ones and resulted in cachexia and aspiration pneumonia in 19% and 32%, respectively, in our experience with 225 patients.

Impressive in this series is the high incidence of associated disease of the upper gastrointestinal tract, especially GE reflux. In a group of 67 patients who underwent 24-hour pH study, 37 (55%) had a clear pathologic tracing and 21% had, on endoscopy, at least esophagitis grade II. The incidence of documented reflux necessitating a specific antireflux therapy was 44%.

Historically, treatment of patients with Zenker's diverticulum in my institution consisted in a simple diverticulectomy, but from 1975 onward patients were systematically treated by myotomy with diverticulopexy (Fig. 6). More recently, with the development of videoscopic surgery, a subset of patients were treated by an endoscopic esophagodiverticulectomy by means of the endoscopic stapler technique (Table VI).

Among the 36 patients treated with a simple diverticulectomy between 1953 and 1975, seven surviving patients were traced back. Five were free of symptoms, but in all five barium swallow showed either a recurrence or a spastic ring-like indentation at the level of the cricopharyngeus muscle. Two patients had symptoms: One had stenosis related to the operation; the second patient's symptoms developed 16 years after diverticulectomy and necessitated reintervention, that is, myotomy and diverticulopexy, to solve the problem.

In the 174 patients who underwent myotomy and diverticulopexy and four who had only myotomy for

Table IV. Enzymohistochemical and enzymoimmunologic findings in 15 control specimens and 62 specimens of Zenker's diverticulum

Dominant fiber type	Hypertrophy	Atrophy	Necrosis	Size variety	Fibrosis	Central nucleus	Inflammation	Nemaline rods	Ragged red fibers	Acetylcholinesterase	Neuro filam.
Control											
I:9	1/15	1/15	0/15	2/15	2/15	1/15	0/15	0/15	2/15	0/9	0/9
II:3											
Zenker											
I:40	32/41	37/41	33/41	40/41	31/41	30/41	21/41	4/41	23/41	33/44	33/44

The denominator gives the number of patients in whom a given parameter was examined.

a very small but symptomatic Zenker diverticulum, 96.5% had an excellent or very good result. Only 3.5% had a bad result, one patient requiring a reintervention. In this patient the muscle biopsy was strongly suggestive for a primary myogenic disease.

Twenty-eight patients have now been followed up for more than 10 years and up to 19 years, and 27 of them are completely free of symptoms. More recently, videoscopic esophagodiverticulostomy was performed in 11 patients by applying a specially adapted endoscopic stapler on the cricopharyngeal bar and stapling the diverticular sac to the cervical esophagus. This endoscopic stapling results in a V-shaped retraction of cricopharyngeal bar and a myotomy over approximately 3 cm.¹⁷

The results, however, have been less satisfactory, inasmuch as reoperation for recurrent dysphagia became necessary in two patients. The recurrent dysphagia apparently was the result of the formation of a ridge caused by fibrotic retraction toward the esophageal lumen at the staple line.

Motor disorders of the esophageal body

The most common motility disorder of the esophageal body is achalasia. Until the turn of the century, treatment consisted in some form of dilatation often performed in group sessions in an outpatient clinic setting. The introduction of the principle of myotomy according to Heller¹⁹ offered a more definitive perspective, and the results of this operation as published in the literature are excellent or good in up to 90% of the patients. The most important, still ongoing debate is whether to add an antireflux procedure to prevent complications of GE reflux by prolonged exposure to acid in an amotile esophageal body.

Analysis of 12 larger studies from the literature shows a 4% incidence of reflux if the myotomy is combined with an antireflux procedure and a 12%

incidence of reflux if no antireflux procedure is added. These results are confirmed by my own rather limited experience in which a long myotomy is combined with a Belsey Mark IV antireflux procedure.²⁰

The results of surgery have been challenged over the past three decades by the development of pneumatic balloon dilatation. In my own institution, Van Trappen and Hellemans²¹ performed pioneering work with this method, obtaining good results in approximately 80% in a series of over 700 patients and with minimal mortality and morbidity.

Pneumatic dilatation therefore remains the first therapeutic option in dealing with this condition. There is, however, no doubt that today minimally invasive surgery, in its turn, is challenging pneumatic dilatations. Sinanan and Pellegrini,²² using video-assisted thoracoscopic surgery, obtained good relief of dysphagia in 92%. They did not add an antireflux procedure, however, and noticed pathologic 24-hour pH tracings in 60% of the patients. As a result, they switched to a laparoscopic Heller procedure, combining it with a Dor fundoplication, and had no further pathologic pH studies. Similar excellent results were reported by Ancona and coworkers.²³ The results from both surgery and pneumatic dilatation seem to be superior and much longer lasting than the results obtained by the recent introduction of botulism toxin injection via endoluminal endoscopy.

Diverticula of the esophageal body are uncommon. They mostly appear as epiphrenic diverticula, and a variety of underlying motor disorders is diagnosed in the vast majority of the cases. As a result, the principles of treatment are the same as in Zenker's diverticulum, that is, diverticulectomy or diverticulopexy associated with a myotomy at the opposite side of the esophageal wall. Long-term results from my own experience with 16 diverticula

Fig. 3. Hematoxylin-and-eosin coloration in control specimen (A) and Zenker's diverticulum specimen (B). Irregular shaped patterns, inflammation, increased fibrotic tissue, size variation, and necrosis in Zenker's diverticulum are in contrast to the regular shaped organization of the muscle fibers without necrosis or inflammation in the control specimen.

of the esophageal body showed an excellent to very good outcome in 91% of the cases. Today, as for achalasia, these diverticula can be treated through a video-assisted thoracoscopic approach, reducing the access-related morbidity and therefore resulting in a shorter hospital stay and earlier socioeconomic re-integration.²⁴

Gastroesophageal reflux disease (GERD)

The first attempts to treat GE reflux as a functional disorder, rather than as an anatomic defect, were made by Allison²⁵ in the early fifties. Nissen²⁶ developed his technique from a rather incidental observation of a continent valve after partial esophagectomy, and Belsey developed his Mark IV oper-

Fig. 4. Adenosine triphosphate, pH 4.3. Control (A) and diverticulum specimen (B). The control specimen shows a predominance of type II (pale colored) fibers, whereas in Zenker's diverticulum, type I (dark stained) fibers dominate.

ation as a result of different trials designed to control reflux.

He put the Mark IV operation to the test of time in his follow-up clinic, meticulously recording the results before bringing them to public attention through his publications with Hiebert²⁷ and Skinner.²⁸ The Belsey school later played a major role in

the development and understanding of reflux disease and its surgical management.

The Mark IV operation had been my standard technique in the surgical treatment of GE reflux disease (GERD) until the advent of laparoscopic surgery. The objective and subjective results of medium long-term follow-up of a group of 147

Fig. 5. Acetylcholinesterase coloration. Diverticulum specimen. Only 50% of the fibers are surrounded by the dark-stained acetylcholinesterase coloration.

Table V. Biochemical studies

	No.	ATP ($\mu\text{mol/gm}$ dry weight)	No.	NAD ($\mu\text{mol/gm}$ dry weight)	No.	CK (units/ μg dry weight)
Cricopharyngeus muscle						
Zenker	14	5.8 (± 2.9)	9	0.54	3	1.9 (± 1)
		($p = 0.033$)		($p = 0.011$)		
Control	6	10.4 (± 2.2)	6	0.903	3	2 (± 1.6)
Sternocleidomastoid muscle						
Zenker	10	12.1 (± 4.8)				
Control	6	17 (± 1.7)				

ATP, Adenosine triphosphate; NAD, nicotinamide adenine dinucleotide; CK, creatine kinase. Numbers in parentheses are standard deviations.

patients followed up for a mean of 4.5 years showed an objective and subjective reflux control of 87% when two or more pathologic examinations were used as an indicator of objective reflux (Table VII).

The final score, including undesirable side effects, showed excellent or good results in 77.7% of the patients, 11% having a bad result.²⁹

The more recent introduction of potent acid secretion inhibitors, as well as the introduction of laparoscopic techniques, have been reviving hot debates about medical versus surgical treatment. There is no doubt that proton pump inhibitors can cure a great number of patients with esophagitis. However, maintaining these results on a long-term scale seems to be more problematic, recurrent

esophagitis occurring in up to 50% after 5 years of follow up or more, unless high maintenance doses are used.³⁰

The advantages claimed by laparoscopic surgery are shorter hospital stay, earlier social and professional reintegration, less consumption of pain medication, and cost benefit. Dallemagne,³¹ Weerts,³² and their colleagues pioneered the laparoscopic antireflux technique, showing excellent subjective short-term outcome in more than 90% of the patients. Their experience resulted in a rapid and widespread use of the laparoscopic Nissen as the standard procedure in antireflux surgery. Thus it is no surprise to notice from the literature a great variation in reported complications and recurrences

Fig. 6. Zenker's diverticulum. Before (A) and after (B) extramucosal myotomy and diverticulopexy. Arrow, Contrast line at the base of the up-ended diverticulum.

of up to 20% in some series, all this still at short-term follow-up.³³

Peters and associates³⁴ prospectively compared open and laparoscopic approaches using a short floppy Nissen technique. From this study it can be concluded that in experienced centers the results of both approaches are the same in the short term, therefore justifying the use of minimally invasive surgery provided the indications are correct.

In my opinion, the current indications for surgery are persistent or recurrent esophagitis and/or symptoms despite optimal medical treatment, persistent regurgitation, noncompliance with the medical management of the patient, drug-related side effects, and biliary reflux.

From my own experience with 107 laparoscopic Nissen operations, a complete subjective and objective reevaluation was performed in 39 consecutive patients operated on for at least 1 year. Objective evaluation consisted in barium swallow endoscopy, manometry, and 24-hour pH study (Table VIII).

Thirty-seven patients were symptom-free (94.9%).

Five patients (12.8%) had a pathologic 24-hour pH study. Two patients had an intrathoracic migration of the fundoplication (4.8%) but had no subjective nor objective reflux, and one patient showed grade II esophagitis on endoscopy.

Overall complete subjective and objective reflux control was seen in 84.7% of this group. Including anatomic appearance, 32 patients (82%) had a totally successful correction. In the same time period, however, another 113 patients were treated by open surgery mostly because of redo surgery or previous major surgery in the upper part of the abdomen. In this group of patients a variety of as many as ten different techniques had to be used to remedy the reflux problem, including resection and coloplasty in three patients. This experience clearly illustrates that one single laparoscopic Nissen-type of operation does not suit all patients, and attempting to treat all patients by the same technique is therefore the wrong attitude. GERD is a complex disease necessitating an in-depth understanding of the pathogenesis. A whole battery of sometimes

Table VI. Results of surgical treatment of Zenker's diverticulum

	No. of patients
Diverticulectomy (1953-1974)	36
Patients followed up	7
Asymptomatic	5
Barium swallow recurrence of spastic ring-like indentation at level of cricopharyngeal muscle	
Symptomatic	2
Substenosis	1
Recurrence 16 yr postop.	1
Diverticulectomy + myotomy (1975-1996)	174
Mean follow-up 72 mo	
Excellent or very good: 96.6%	
Bad: 3.4%	
Swallowing and/or respiratory symptoms	6
Reintervention (primary muscle disease?)	1
Follow-up 10-19 yr	28
Totally asymptomatic	28
Videoscopic diverticuloesophagostomy	11
Reoperation	2
Excellent	4
Good	5
Fair	2

Table VII. Belsey Mark IV: Results of follow-up of patients (N = 147) operated on with at least 1 year's follow-up*

	No.
Objective findings at 1 year	
Endoscopy	121
Hiatus hernia	1 (0.8%)
Esophagitis	16 (13.2%)
Radiography	113
Hernia or patulous cardia	4 (3.6%)
Reflux	16 (14.2%)
24-hour pH study	81
Pathologic	11 (13.5%)
Subjective and objective recurrence	19/147 (13%)

*Mean follow-up was 4.4 years (range 1 to 13 years).

sophisticated investigations may be necessary before a patient's particular problem can be correctly appreciated. Inasmuch as diagnosis precedes treatment, no surgery, even so-called minimally invasive procedures, should be undertaken before the underlying cause of the patient's condition has been clarified. The further decision-making and eventually surgical treatment has to follow an algorithm, a tailored approach. Within this algorithm, laparo-

Table VIII. Laparoscopic Nissen fundoplication: Results of follow-up of 39 patients operated on with at least 1 year's follow-up*

	No.
Objective findings at 1 year	
Endoscopy	39
Esophagitis grade I	1 (5.1%)
Esophagitis grade II	1 (5.1%)
Radiography	39
Hernia	2 (5.1%)
24-hour pH study	39
Pathologic	5 (12.8%)
Subjective and objective recurrence	6 (15.3%)

*Mean follow-up was 25 months (range 1 to 3 years).

scopic surgery is indicated in patients with a normal esophageal body length, as judged by the reducibility of the GE junction on barium swallow and with a normal esophageal body motility.³⁵ In the case of clear motility disorders, a Belsey Mark IV operation is to be preferred, whereas in the case of shortening, a lengthening gastropasty—Collis-Belsey or Collis-Nissen—is the technique of choice.³⁶

Barrett metaplasia is now recognized as a more complex form, an end stage of GERD with more profound motor disorders of the esophageal body and a more profound mechanically deficient sphincter mechanism with prolonged exposure to acid and bile as well.^{37, 38}

This raises the question whether the results of surgery are comparable with those obtained in the non-Barrett reflux population. In this respect, I³⁹ analyzed a group of 25 patients with symptomatic Barrett reflux treated by a Belsey Mark IV operation and with a follow-up of at least 10 years and up to 17 years. From this study an increase of symptoms was seen over the years, from 12% at evaluation between 1 to 5 years up to 26% at evaluation after 10 to 17 years. The same trend was noticed in patients who agreed to undergo objective investigation, with an increase in pathologic 24-hour pH study from 15.8% up to 50% (six of 12 studies), although in two of the six studies the pathologic tracings were only marginally pathologic (Table IX).

The final outcome combining subjective and objective evaluation showed a satisfactory control of reflux in 65.3% of these patients. There are very few studies dealing specifically with long-term follow-up results after antireflux surgery in patients with Barrett metaplasia.

Sagar and coworkers⁴⁰ studied the effect of Nissen fundoplication in 56 patients with proven Barrett

Table IX. Belsey Mark IV antireflux operation in patients with Barrett's metaplasia: Results of subjective and objective evaluation after 10 to 17 years of follow-up (n = 25)

	Subjective symptoms	Objective		Subjective + objective
		Endoscopy	24-hour pH	
Evaluation at 1-5 yr	3/25 (12%)	4/20 (20%)	3/19 (15.8%)	5/25 (20%)
Evaluation at 10-17 yr	6/23 (26%)	2/14 (14%)	6/12 (50%)	8/23 (34.7%)
2 patients < 5% reflux				

n, Number of patients volunteering to undergo different time intervals.

Table X. Belsey Mark IV antireflux operation in patients with Barrett's metaplasia: Changes in length of Barrett mucosa at different endoscopic intervals*

Regression		
Complete (n = 4)	Major (n = 3)	Progression (n = 4)
4 -> 2 -> 2 -> 0	8 -> 8 -> 5 -> 4 (--> 6)	4 -> 7 -> 7 -> 2 (-->3)
3 -> 2 (-->4) -> 2 -> 0	8 -> 0 -> 2 -> 1	3 -> 5
6 -> 1 -> 0	10 -> 9 -> 2 (-> 2)	3 -> 2 (--> 6) -> 2 (-->6) ->4 (-->6)
3 ->0 -> 0		3 -> 7 (-> 9) -> 5 (-->8) ->6

-> Circumferential metaplasia; --> length of scattered islands of metaplasia.

*Figures indicate length (in centimeters) at each endoscopic evaluation during follow-up.

metaplasia and documented postoperative pathologic acid exposure in 30 patients (53.5%). Most other available but scarce studies are dealing with a mixture of Barrett and non-Barrett populations but are indicative of what to expect on a long-term basis. Ackerman and coworkers⁴¹ reported a 21.5% incidence of persistent or recurrent reflux disease 10 to 20 years after Nissen fundoplication. The incidence of heartburn was 27%. Luostarinen⁴² noticed in his series a wrap dehiscence of 31% and a 26% incidence of recurrent endoscopic esophagitis after 7 to 10 years of follow-up. DeMeester⁴³ documented an 18% incidence of pathologic 24-hour pH studies in 36 patients who volunteered to have this examination 1 to 10 years after the Nissen fundoplication. These patients were a subset of a group of 100 consecutive patients treated with a short floppy Nissen fundoplication and in whom an overall subjective reflux control of 91% was found. Hiebert and O'Mara⁴⁴ reported a 75% incidence of good results up to 25 years after the Belsey Mark IV repair.

All these studies, including ours, seem to be comparable, showing in general a stabilization after 20 years' follow-up with a subjective reflux control around 75%. However, objective evaluation shows a higher incidence of recurrence on endoscopy and 24-hour pH study⁴⁵ whereby obviously a number of patients are remaining subjectively free of symptoms. This of course questions the value of antireflux surgery in preventing degeneration in Barrett's

esophagus, a risk that is now widely accepted and considered as the main contributing factor in the sharp rise of adenocarcinoma of the esophagus and GE junction in the Western world.

From the available data it seems that surgery is scoring better than medical treatment. McCallum and colleagues⁴⁶ noted that only 3.4% of the patients progressed toward dysplasia after surgery versus 19.7% of the patients receiving medical treatment; this observation was confirmed by another, randomized study by Ortiz and associates.⁴⁷

The ultimate question, of course, is whether adenocarcinoma is occurring after successful antireflux surgery. The data in this respect are scarce. From most studies it is not clear whether in case of degeneration the antireflux procedure was indeed successful or whether, as for example in the study by McDonald and coworkers,⁴⁸ occult invasive carcinoma or carcinoma-in-situ was already present at the time of the operation; in all three reported cases in their series of 108 patients the carcinoma developed within 30 months. Nevertheless, adenocarcinoma occurring after successful antireflux surgery has been reported.*

In my aforementioned group of 25 patients, no malignant disease occurred. Complete or major

* Hölscher HA. Classification des cancers de l'oesophage. Eighteenth J Chir Dig. Rennes. March 1996. Personal communication.

Table XI. *Microscopic Barrett's esophagus: Relationship to acid and bile reflux in symptomatic patients*

	No Barrett (n = 44)	Microscopic Barrett (n = 12)	Macroscopic Barrett (n = 15)
Acid exposure (% of time)	5.2 ± 0.9	6.8 ± 2.9	14.1 ± 4.1*
Bile exposure (% of time)	3.9 ± 1.9	9.4 ± 5.7	22.1 ± 6.7*

**p* < 0.005 compared with No Barrett.

regression was documented in seven patients (28%), but surprisingly progression was noticed in as many as four patients (16%), only one of them having a documented recurrence of reflux (Table X). This puzzling and troublesome phenomenon has also been described by Sagar and colleagues,⁴⁰ who noticed a 16% progression, over half of their patients having symptoms. Eventually, adenocarcinoma developed in one patient 9 years after an unsuccessful antireflux procedure.

This uncertainty about the potential risk of degeneration and the rather occasional complete regression,⁴⁹⁻⁵¹ as well as the reported progression, recently generated intensive research in ablation of the mucosa using photocoagulation or laser.⁵²

Especially when combined with subsequent antireflux surgery, laser ablation seems to result in a regeneration by squamous cell epithelium of the destroyed metaplastic area.⁵³ Although the procedure looks very attractive, the side effects of ablation caused by thermal effects may result in fibrosis and stricture, jeopardizing the feasibility of this method as well as the results of subsequent antireflux operations.

Follow-up and surveillance will be much more difficult, and at this point it is not known in how much laser ablation of Barrett's mucosa effectively will prevent malignant degeneration, a process that is believed to be related to a progressive acquisition of multiple genetic abnormalities over a time lapse spanning several years.⁵⁴ The more recent interest in ablation of the Barrett mucosa by using ultrasound, thus avoiding the thermal side effects, may open some interesting perspectives.

Another topic of intense research is so-called short Barrett's esophagus, often represented by short tongues of metaplasia and in which up to 18% of intestinal type metaplasia was found.⁵⁵ In a study by Clark and coworkers,⁵⁶ dysplasia was found in 17% of their cases, suggesting an association be-

tween short Barrett's esophagus and ultrashort (i.e., intestinal metaplasia in the cardia) Barrett's esophagus and adenocarcinoma of the gastroesophageal junction; they found up to a 43% incidence of intestinal metaplasia and a 77% incidence of dysplasia in their resected GE junction tumors. In my own series of adenocarcinoma of the GE junction, an incidence of 12% dysplasia was recorded.⁵⁷

As a result, Spechler and colleagues⁵⁸ concluded that the classic definition of a 3 cm metaplastic zone as the true Barrett esophagus is too restrictive. They proposed columnar-lined esophagus with intestinal metaplasia irrespective of its length as a more accurate definition. How often the short and ultrashort Barrett esophagus is associated with reflux is not clear. In our institution a study was performed by Van Vaerenbergh and colleagues⁵⁹ to assess the association of microscopic Barrett's esophagus and reflux of acid and bile. The prevalence of microscopic Barrett's esophagus was evaluated in a group of 56 consecutive patients who were evaluated for suspected reflux and without apparent Barrett's metaplasia at endoscopy. Multiple biopsy specimens were taken including the cardia in retroversion. In all patients, 24-hour ambulatory pH and Bilitec spectrophotometer (Medtronic Synectics, Stockholm, Sweden) monitoring was performed. Fifteen patients with known "classic" Barrett's esophagus served as controls (Table XI).

Intestinal microscopic metaplasia at the GE junction was present in 12 patients (21%). In patients without microscopic Barrett's esophagus, esophageal acid exposure was 5.2% ± 0.9% compared with 6.8% ± 2.9% in those with microscopic Barrett's esophagus and 14.1% ± 4.1% in those with "classic" Barrett's esophagus. The values for bile exposure were 3.9% ± 1.9%, 9.4% ± 5.7%, and 22.1% ± 6.7%, respectively. From this study, it was concluded that microscopic Barrett, like classic Barrett but to a lesser extent, is associated with both acid and bile reflux. Whether this is linked with a higher risk for degeneration remains to be studied, but if this is not the case our concepts about the interrelation between reflux, Barrett, and degeneration might well change in the near future.^{60, 61}

Obviously the whole field of antireflux therapy remains a fascinating subject, and it is likely that further refinement in instrumentation used for minimal invasive surgery and endoluminal manipulation, as well as the further insights into the pathogenesis of reflux and the development of more effective drugs (e.g., against bile reflux) will dramat-

ically change the scenery of antireflux therapy in the next MILLENNIUM. The actual minimally invasive antireflux operation seems nothing more than a transitional phase in this rapidly changing evolution.⁶²

Esophageal carcinoma and carcinoma of the GE junction

Attempts to treat carcinoma of the esophagus surgically emerged at the beginning of the century. Torek⁶³ successfully resected the thoracic esophagus in 1913. Turner⁶⁴ in 1931 in the United Kingdom and Denk⁶⁵ in 1929 in Germany were the first to perform transhiatal esophagectomy. Oshawa⁶⁶ in Japan in 1933 reported resection of the thoracic esophagus and immediate esophagogastrostomy, and a similar operation was independently reported by Adams and Phemister⁶⁷ in 1938.

Further progress was obtained through the developments of thoracic surgery largely based on the experiences gained during World War II. Most often the main goal was good palliation; according to a statement by Belsey, "cure is an accident." The reasons for the bad reputation concerning esophageal carcinoma are multiple. Poor general condition, advanced stage at diagnosis, chaotic lymphatic spread, and multicentric localization are only some well-proven factors.

Lymph node status seems to be the most important single prognostic factor, with involvement in 30% to 80% of reported series.⁶⁸ In more than 40% of the recurrences, lymph nodes are involved⁶⁹. As a result, mainly two attitudes toward extent of resection and lymphadenectomy evolved. There are those who believe that lymph node involvement equals by definition systemic disease, thus claiming that it is useless to make efforts to perform wide peritumoral resections and lymphadenectomy to improve survival. The standard technique typical for this approach is transhiatal stripping and use of gastric tube for reconstruction, as advocated by Orringer, Marshall, and Stirling.⁷⁰ Others, like Skinner,⁷¹ believed that radical en bloc esophagectomy had a beneficial effect on cure rate, even in cases of lymph node involvement. Mainly in Japan, much attention has been paid to meticulous extended lymphadenectomy.⁶⁸ All these efforts are made to obtain a so-called R₀ situation (i.e., no residual microscopic tumor), because either microscopic or macroscopic residual tumor leaves the patient with virtually no chance for cure.

My experience deals with 1147 cases, and resection was possible in 80%. For tumors located below

Fig. 7. Overall 5-year survival after primary surgery in tumors of the esophagus, in Barrett's carcinoma, and in tumors of the paraesophageal junction (GEJ).

the carina, a left-sided transthoracic approach is used and the diaphragm is opened at its periphery, offering wide exposure in the chest and abdomen as well. Besides a wide peritumoral dissection, much attention is paid to a meticulous lymphadenectomy around the celiac axis, superior mesenteric artery and, for tumors of the GE junction, down to the renal artery, clearing out all tissues in the left upper abdominal quadrant. In the chest, the posterior mediastinum is cleaned out including subcarinal nodes, aortopulmonary window, and thoracic duct. In tumors of the upper half, a right-sided approach is used and attention is paid to a meticulous dissection of lymph nodes along the left recurrent nerve and brachiocephalic trunk. Reconstruction is performed by using a gastric tube after resecting the lesser curvature, again for oncologic reasons.

Overall 5-year survival for tumors of the esophagus is 30%,⁷² for GE junction tumors 33%, and for Barrett carcinoma 58%, the last figure being influenced by a higher number of early carcinomas (Fig. 7). The stage-by-stage survival in carcinoma of the esophagus is 90% and 56% for early stage I and II and 16% for stage III. Lymph node status appeared to be a most important prognostic factor, with a 63% 5-year survival for patients with node-negative disease versus 12% for those with node-positive disease.

In a retrospective study on a subset of patients in whom the surgeon had the impression of a curative intervention, we⁷² compared radical versus nonradi-

Fig. 8. Five-year survival comparing radical versus nonradical curative resections in tumors of the esophagus.

cal surgery, revealing a significant benefit in favor of the radical interventions (Fig. 8). Similar results have been reported by Altorki, Girardi, and Skinner⁷³ and Hagen, Peters, and DeMeester.⁷⁴ For the advanced stage, the survival figure confirms that only a complete R_0 resection offers a chance for cure, up to 20% in this subset of patients.⁷⁵

In Barrett carcinoma the overall 5-year survival was as high as 58%, and this relates to a high number of early-stage carcinomas, with a 100% and an 87% 5-year survival for stage I and II, respectively. Again, the lymph node status was the most important prognostic factor, but even in patients with node-positive disease a 38% 5-year survival was obtained. The high survival figures, especially in the early stages, relate to the value of surveillance in Barrett's esophagus.

Indeed, three fourths of patients under surveillance had node-negative disease, that is, the majority of those with stage I and II carcinomas, as opposed to patients who had carcinoma at their first medical contact and in whom only one fourth had negative nodes.⁷⁶

Today much attention is focused on the behavior of tumors of the GE junction, which we defined as tumors with the core of the tumor located at the Z line and within an area of maximum 5 cm orally or aborally from the anatomic junction between the esophageal and gastric wall on the resected speci-

men.⁷⁷ Overall 10-year survival was 31%, and again high survival figures of 90% and 70% were obtained in early stage I and II disease, with even a 28% survival in stage III and an 11% survival in stage IV, the latter being a rather unexpected finding.

We therefore analyzed separately patients with intrathoracic lymph node metastasis, that is, stage IV because of distant lymph node metastasis in the actual International Union Against Cancer (UICC) TNM classification.⁷⁸ Because we found in this group of patients a gratifying 13% cure rate, we believe that positive intrathoracic lymph nodes should not exclude patients from treatment modality aiming at cure.⁵⁸

Moreover, these findings raise the question whether GE junction tumors ought to be classified as esophageal carcinoma rather than as gastric carcinoma, as in the actual TNM classification system. This question gains validity because much of the debate is now focusing on Barrett metaplasia possibly being the common origin of all adenocarcinomas of the esophagus and GE junction, as discussed earlier.⁶⁰

Adding lymph node dissection in the neck, "the third field," as advocated by the Japanese authors, is believed to improve staging, disease-free survival, and cure rate.⁷⁹ In my experience with 37 patients in whom three-field lymphadenectomy was performed, no hospital mortality occurred and morbidity, in-

cluding recurrent nerve paralysis, was perfectly comparable with that of two-field lymphadenectomy. The impact on staging was impressive, as 30% of the patients appeared to have unforeseen positive nodes in the neck, causing a change in pTNM staging in 16% of the whole group as compared with only two-field lymphadenectomy. Most impressive was the high incidence of positive cervical nodes in patients with distal esophageal carcinoma, again 30%.

As a result, more recently an analysis was made of the pattern of lymph node involvement in patients with adenocarcinoma of the GE junction. This pattern was compared with that of patients with adenocarcinoma of the distal esophagus. To obtain comparable groups, the study was restricted to the T3 N+ subset of patients (Table XII). As many as 16% positive cervical nodes were found with GE junction carcinoma, whereas 30% were positive with adenocarcinoma of the distal esophagus. Also, the intrathoracic and intraabdominal pattern of lymph node involvement was very similar in both groups. As expected, differences in percentages were related to the location of the tumor, but surprising was the high figure, 50%, of thoracic duct involvement in distal esophageal carcinoma and the high percentage of involved subcarinal and aortopulmonary window lymph nodes in tumors of the GE junction. These findings again seem to indicate that tumors of the GE junction behave more like esophageal carcinomas, rather than like gastric carcinomas.

Besides improving staging, three-field lymphadenectomy is believed to have a beneficial effect on lymph node recurrence as first site of recurrence not only in the neck but also in the mediastinum and abdomen. In the initial group of 37 patients treated with three-field lymphadenectomy, six patients (16%) had local or regional lymph node metastasis—two in the neck, one in the mediastinum, and in three patients both in the mediastinum and in the abdomen.

All patients had stage IV disease because of lymph node metastasis, with more than five positive nodes in all. Nevertheless, in three of these patients lymph node metastasis occurred only 3 years or more after the operation, which seems to endorse the statement that three-field lymphadenectomy is indeed improving disease-free survival.

The final and most important question is whether three-field lymphadenectomy results in an increased cure rate. At this time it is too early to answer this question from our own experience. From 1992 until 1993, 100 consecutive patients with carcinoma of the

Table XII. Pattern of lymph node involvement in adenocarcinoma T3N+

	Distal esophagus (n = 11)	GE junction (n = 16)
Neck, paratracheal	36.3%	16.6%
Carina, main-stem bronchus	20%	22.2%
Aortopulmonary window		5%
Thoracic duct	50%	8.3%
Splenic artery, hilum	14%	61%
Celiac axis	10%	38%
Hepatic artery, portal vein	0%	0%

esophagus and GE junction underwent resection. There was no hospital mortality.

Disease-specific overall actuarial 5-year survival is 37%. Comparing the radical approach versus the nonradical approach shows no difference between stage I and II, but there seems to be a trend in favor of three-field dissection for the more advanced stages, that is, 21% versus 12% survival at 4 years (Fig. 9).

From the Japanese data an advantage favoring three-field lymphadenectomy has been reported, whether comparing N status, T status, or different stages.⁸⁰⁻⁸⁶ However, almost all reported series are dealing with retrospective studies underlining the need for prospective randomized studies.

Because of the relatively poor outcome after primary surgery, much attention has been focused on multimodality regimens, especially the combination of chemoradiotherapy in the neoadjuvant setting. A well-documented overview of the available literature is given by Fink and coworkers.⁸⁷ A large number of prospective studies or randomized trials have been reported mainly from the United States and to a lesser extent from Europe. It is impossible to give a detailed analysis of all these studies, and the following paragraphs are a compilation of the results from the most relevant studies. In potentially resectable tumors, four prospective randomized studies were analyzed⁸⁸⁻⁹¹ comparing preoperative chemotherapy followed by surgery with primary surgery. Resection rate varies from 81% to 92% for chemotherapy plus surgery versus 70% to 82% for primary surgery, R₀ resection from 35% to 45% versus 21% to 46%, postoperative mortality from 0% to 19% versus 0% to 10%, and median survival from 9 to 15 months versus 9 to 12 months. Median survival for responders varied between 13 and 43 months. These results indicate that, compared with surgery alone, neither resec-

Fig. 9. Actuarial survival comparing radical versus nonradical surgery in advanced (stage II_b to IV) tumors of the esophagus and GE junction. One hundred transthoracic resections were performed from 1992 to July 1993.

Fig. 10. Actuarial 3-year survival after chemoradiotherapy plus surgery: Outcome in complete pathologic response versus partial or no response in patients with clinical T4 disease. A total of 26 patients underwent exploration.

tion rate nor survival are significantly influenced by these regimens.

In locally advanced disease, however, the potential benefit becomes more evident with a substantial number of cases being downstaged and converted into complete resectability especially when using a combination of chemotherapy and radiotherapy. In three reported phase III trials⁹²⁻⁹⁴ mean R₀ resection rate

was 66.4%. Mean postoperative mortality was 10.5% and median survival 15.3 months and up to 28.2 months after R₀ resection. In 15% to 20% of these patients complete tumor “sterilization” was found on pathologic examination of the resected specimen. There is, however, no evidence that these neoadjuvant regimens are influencing overall cure rates even from the more recent data from the literature.

In the prospective randomized trials reported by Law,⁹⁵ Kelsen,⁹⁶ and their associates (intergroup study 113), chemotherapy plus surgery was compared with surgery. In the first trial, median survival was 16.8 months versus 13 months for surgery alone, but in the chemotherapy plus surgery group responders did significantly better than the nonresponders, with 42.2 months' median survival versus 13.8 months.

In the intergroup 113 study, resectability (65% vs 66%), median survival (16.1 vs 16.8 months), 1-year survival (62% vs 62%), and 2-year survival (38% vs 40%) were almost identical. Urba and coworkers,⁹⁷ comparing surgery versus chemoradiation plus surgery, noticed a median survival of 1.46 years after surgery versus 1.41 years for chemoradiation plus surgery. However, at 3 years, survival was 15% versus 32% for the multimodality regimen. In a European multicentric trial published by Bosset and colleagues,⁹⁸ chemoradiation plus surgery was compared with primary surgery in clinical early stage I and II squamous cell carcinoma. Median survival was 18.6 months in both groups, although induction therapy did prolong disease-free survival.

More recently, as a result of the increasing incidence of adenocarcinomas, attention has been focused on multimodality regimens specifically in patients with adenocarcinoma of the distal esophagus and GE junction.

Walsh and colleagues⁹⁹ reported a significant benefit in patients receiving chemoradiation before surgery, with a 3-year survival of 32% versus 6% for surgery alone. However, the trial was criticized because of the lack of precision in clinical staging methods, the great variation in surgical approaches, and the fact that in the authors' earlier experience a 5-year survival of 20% was obtained with surgery alone. It seems from the available experience that neoadjuvant therapy is rather having a locoregional effect, the chemotherapy component failing to control distant systemic metastasis. As far as adjuvant, that is, postoperative modalities are concerned, little data are available, but a recent multicentric trial by the Japanese Clinical Oncology Group¹⁰⁰ could not show any survival benefit when adding a cisplatin- and vindesine-based regimen, obtaining a 48.1% 5-year survival versus 44.1% 5-year survival for surgery alone.

At our own institution a chemoradiotherapy neoadjuvant therapy protocol before surgery was started for patients with clinical T4 disease. These tumors are mostly located in the upper half of the

esophagus. Twenty-six of 33 patients underwent exploration. Twenty-three patients underwent esophagectomy. Hospital mortality was 9%. In 19% an R₀ resection was achieved and in six patients a complete sterilization was seen on pathologic examination. The overall actuarial survival at 3 years is 32%, being 53% for the R₀ resections and as much as 83% for the six patients with complete sterilization. These figures are definitely superior to those obtained in our historical controls.

From all these data it becomes clear that surgery is still the gold standard. Surgeons therefore must play a major role in setting the future trends in the treatment of esophageal carcinoma. Multicentric trials are, in this respect, recommended.

In the future, randomized trials should focus on three points: (1) Squamous cell carcinoma and adenocarcinoma should be assessed separately. The sharp rise in incidence of adenocarcinoma noticed in the Western world over recent years requires urgent evaluation of the value of chemotherapy and/or radiotherapy before surgery. (2) It is important to optimize TN staging by using clinical endosonography¹⁰¹; minimal invasive surgery and positron emission tomographic scan may become important tools in staging the disease.^{102, 103} (3) Standardization of surgical techniques, pathologic examination, therapeutic protocols, and survival curves is crucial.

It is clear, however, that further research has to focus on pretherapeutic identification of potential responders, and this is a field in which molecular biology technology is most likely to play a major role in the future.¹⁰⁴⁻¹⁰⁶ This research needs to be combined with further efforts to develop less toxic regimens, and more prospective studies are needed to assess the role, extent, and timing of these different therapeutic regimens.

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