Barrett's Esophagus May Still Progress

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Introduction: Barrett's Esophagus (BE) has been assumed to be an abnormal mode of healing of erosive or ulcerative reflux esophagitis. Assuming that erosive or ulcerative esophagitis can relapse to the same grade or progress to a more severe grade after an inefficient treatment, it is conceivable that some BE may progress.

Patients and methods: Between January 1963 and December 1992, 428 BE without adenocarcinoma were diagnosed at the University Hospital of Lausanne. 145 out of 428 adults with BE (columnar epithelium extending at least 3 cm upwards the gastric mucosa) were endoscopically followed-up and biopsied one year or more after the initial diagnosis. 25% of 145 adults with BE were excluded from the final prospective study because of incomplete data. Each patient underwent at least 2 endoscopical examinations (mean: 5, extremes: 2-28). Required for inclusion into this study were BE progression or regression of at least 2 cm, in order to avoid possible errors of estimation. Regression in form of squamous epithelium islands amongst BE and progression in form of isolated columnar epithelium tongues located above BE were excluded.

Results:

<table>
<thead>
<tr>
<th>Regression (%)</th>
<th>Stabilization (%)</th>
<th>Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9</td>
<td>82</td>
</tr>
<tr>
<td>Mean age</td>
<td>53.8 years</td>
<td>62.2 years</td>
</tr>
<tr>
<td>Follow-up</td>
<td>64 months (12-156)</td>
<td>60.8 months (12-238)</td>
</tr>
<tr>
<td>Initial length (cm)</td>
<td>5.9 (3.5-11)</td>
<td>5.7 (3-15)</td>
</tr>
<tr>
<td>Final length (cm)</td>
<td>2.1 (0-8)</td>
<td>5.7 (3-15)</td>
</tr>
</tbody>
</table>

Conclusions: This study demonstrate that BE can have 3 evolutive profiles: (1) Regression or disappearance; (2) Stabilization; (3) Progression. BE has the same evolutive characteristics than reflux esophagitis by which it is preceded.

Incidence of Adenocarcinoma in Barrett's Esophagus. An Italian Multicentric Study

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These data are part of a multicentric survey aimed at studying the biologic characteristics and the natural history of Barrett's Esophagus (BE). From November 1987, 591 patients had multiple biopsies from the lower third of the esophagus because of moderate or severe GERD. Those aged up to 75, free from invasive cancer at any site and from life-threatening diseases were eligible for a yearly endoscopic and histologic follow-up. Until November 1993, 213 of 396 eligible pts (53.8%), 149 with histologic proven BE (68 gastric type and 81 Specialized columnar epithelium, SCE, alone or mixed with gastric type) and 64 with esophagitis had one or more endoscopic and histologic follow-up examinations (range 1-6) during a period ranging from 1 months and 5.5 years. BE was confirmed in 134 out of 149 pts (98.9%); during the follow-up 30 pts who, at the first examination did not show BE at histology developed metaplasia (19 gastric type and 11 SCE, alone or mixed). Dysplasia was observed in BE in all cases.

Endoscopic examinations

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Basal</th>
<th>1st Fup</th>
<th>2nd Fup</th>
<th>3rd Fup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ind.</td>
<td>7</td>
<td>21 (2)</td>
<td>10 (5)</td>
<td>4 (-)</td>
</tr>
<tr>
<td>L.G.</td>
<td>5</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>1 (-)</td>
</tr>
<tr>
<td>H.G.</td>
<td>0</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

In brackets cases with dysplasia detected at the previous examination.

In two pts H.G. dysplasia was associated to adenocarcinoma. Overall pts with BE provided 336 py of follow-up and the incidence of adenocarcinoma was 1/198 py; if dysplasia examination was confined to pts with SCE, 172 py of observation were provided and the incidence was 1/86 py.

Clinic and Pathologic Characteristics of Barrett's Esophagus

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A multicentric survey aimed at studying the natural history of Barrett's Esophagus (BE) started in Italy in 1987.

From November 1987 to October 1993, 591 patients (418 males and 173 females, median age 59 yrs, range 13-85 yrs) had multiple biopsies from the lower third of the esophagus because of moderate or severe GERD (esophagitis grade 2-4 and/or BE). Endoscopic appearance of BE (at least 3 cm of metaplastic epithelium at the distal esophagus) was observed in 269 pts (45.5%): 240 (89.2%) of them showed metaplastic epithelium at histology/123 cardiac and/or fundic and 117 specialized columnar epithelium, SCE, alone or mixed with gastric types). In 134 cases, who did not show BE at endoscopy, metaplastic tissue was identified at histology (56 gastric type and 78 SCE, alone or mixed). Males had a significantly higher rate of histologic BE than females (272 vs 102, p = 0.047) but the distribution of the subtypes was similar in the two genders. No relationship was observed between age at diagnosis and severity of GERD or histologic detection of BE. However, as age increased an increasing rate of SCE was observed while the frequency of gastric types decreased (chi-square test = 18.44, p < 0.0001). Dysplasia was detected in 28 pts (16 indefinite, 10 low grade and 2 high grade); in all cases dysplasia was confined to specialized columnar epithelium.

Conclusions: as dysplasia is confined to SCE it seems that only pts with SCE are at increased risk of developing adenocarcinoma of the esophagus and need for a periodic surveillance. However the observed difference in the age between pts with gastric types BE and those with SCE could suggest that the persistence of gastroesophageal reflux can cause a shift from gastric types to SCE.

Regression of Barrett's Mucoza with Long-Term Omeprazole Treatment


Barrett's oesophagus is a severe complication of gastro-oesophageal reflux disease. This prospective trial was aimed at evaluating the effect of long-term omeprazole treatment on the length of Barrett's metaplasia (BM) in patients with reflux oesophagitis.

Methods. From July 1989 to July 1991, 26 patients with at least 3 cm of histologically proven BM (mean age 63.5 years, 20 M, 6 F) were enrolled in the trial after erosive lesions of the squamous mucosa had been healed by an 8-week omeprazole treatment. All, except two, had abnormal acid exposure at 24-hour pHiometry (before treatment). Omeprazole was given orally at a 20 mg once daily dosage for 2 years (except in two patients treated subsequently with 40 mg). Endoscopic and histologic controls were performed at 6 months interval. Three patients were lost to follow-up and 3 were excluded during the first year because of high grade dysplasia. One patient died of an intercurrent disease between 18 and 24 months. Data of the 19 patients who completed the 2 years of treatment were analysed using non parametric variance analysis (Friedman) and Dunnett test.

Results. The length of BM remained unchanged in 9 patients and decreased (>1 cm) in 6 other subjects. In the last 4 patients BM regressed to values <3 cm. Statistical analysis showed a significant regression of BM length with time (p < 0.01) starting at 12 month (p < 0.05). The exact values (cm. m ± SD) were: 5.8 ± 2.1 at entry; 5.1 ± 2.4 at 6 months; 4.8 ± 2.4 at 12 months; 4.6 ± 2.9 at 18 months and 4.3 ± 2.8 at 24 months. Treatment was well tolerated and proved very effective in relieving symptoms of reflux.

Conclusions. In patients with Barrett's oesophagus, omeprazole treatment is able to induce a slow and partial regression of metaplasia. Although these results have probably little clinical relevance, they provide a good rationale for the use of omeprazole in addition to other therapeutic approaches (e.g. laser therapy). Such combined treatments should be evaluated in further studies.


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Changes in the pattern of cancer development in the esophagus and cardia have been reported recently. In Norway complete data are available from 1957 in the Norwegian Cancer Registry.

2971 male and 1097 female patients with esophageal cancer are registered, i.e. 116 patients per year. There was no change in total incidence during the period. The frequency of cancer in the lower third increased by 1.7% and 1.3% for men and women. The proportion of adenocarcinomas increased from 5% to 23%. Spinningcell carcinomas were reduced from 85% to 71%. The change of pattern started in the early 1970-thies and accelerated in the early 1980-thies. It was most pronounced for men. The stage distribution for spinningcell carcinoma was unchanged during the period. About 50% had localized cancer. Age adjusted mortality rate was unchanged. 5 years survival was for men 2% for adenocarcinomas and 5% for spinningcell carcinoma. Women with spinningcell cancer had 11% 5 years survival.

During the period gastric cancer was reduced by 60% from 1450 to 840 per year. In contrast the frequency of cancer of the cardia increased in men from 2 in the early 1970-thies. Cancer in the gastric remnant after resection for benign ulcer also increased. Distant metastases were present in 1/3 of the patients with cancer of the cardia/hafus and in 1/6 of the antral cancers. Five years survival was 10% for both sexes in cancer of the cardia.

The reason for the change of pattern is unknown. It has been claimed that
the increase of adenocarcinomas are due to gastro-esophageal reflux.

122 The Natural History of Reflux Oesophagitis: A 10 Year Follow-Up

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Aims: To study the long term effects of oesophagitis and its cost to the community.

Methods: Eighty-eight patients in whom grade I–III oesophagitis (modified Savary-Miller class.) was diagnosed in one centre 10 to 12 years ago were traced and invited to complete a detailed questionnaire on symptoms and drug therapy. Eleven patients had died (none due to oesophageal disease), 32 did not respond and 46 replied (22 male).

Results: Forty-five patients (mean age 56.9 years, range 28 to 81 years) were followed-up after a mean of 138 months (121–153 months). Thirteen (29%) had grade I oesophagitis at initial endoscopy and 32 (71%) had grade II–III. Heartburn occurred at least monthly in 30 (67%) patients of which 15 (33%) had daily symptoms. Severity of symptoms was considered minor in 21 (47%), moderate/major in 22 (49%) or unbearable in 2 (4%). Twenty-one (47%) said their condition was better now than 10 years ago. Twenty-three (51%) were currently on maintenance acid suppression ± antacids, and a further 11 (24%) were on antacids alone at least weekly. Only 2 patients were not on any anti-reflux medication. No patient had undergone anti-reflux surgery nor had developed an endoscopically proven stricture, although 4 (9%) had daily dysphagia with liquids and solids. No significant differences were found on comparing the symptoms and drug consumption of those with grade I oesophagitis to those with grades II or III. A total of 8813 weeks of standard dosage of either H2-receptor antagonists or proton pump inhibitors had been taken over the review period – an average of 192 weeks of therapy per patient. Based on today’s prices this approximates to a total cost of £62,710, or £121 per patient per year for acid suppression therapy alone.

Conclusions: Oesophagitis contributes significantly to morbidity in the community 10 years after initial diagnosis. Grade of oesophagitis did not influence the degree of symptoms or amount of therapy taken.

123 Adaptation of the Esophageal Mucosa to Acid and Peptic: Role of Nitric Oxide, Prostaglandins and EGF

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Mucosal adaptation to sequential irritants is an important means of mucosal defence developed by the stomach and intestine. It is not known whether the esophageal mucosa is able to elicit mucosal adaptation and the potential mechanisms involved in this phenomenon. In this study we investigated esophageal mucosal adaptation to a "vivo" model of oesophagitis in rabbits by perfusing a recirculating 50 ml solution of acidified PEI (saline at pH 2 + 2000 U of papesin/ml) for 1 hour (Gut 1990; 39:11). Mucosal adaptation was induced by pre-exposing the esophageal mucosa to a mild irritant (acidified saline, pH 2) for 1 hour before being exposed to a stronger one with AP. The extent of both gross and microscopic mucosal damage were graded by 2 uninformmed observers from 0 = Normal to 3 = Confluent haemorrhage and/or erosions. Mucosal barrier function was measured by H+ (µEq), K+ (µEq) flux rates and total hemoglobin (Hb) content (mg). Each experimental group contained 6-8 animals and results (x ± ES) were analyzed using the Student’s unpaired two tailed test. Results: Pre-exposure of the esophageal mucosa to acidified saline (mild irritant) followed by AP significantly (P < 0.01) decreased all the indicators of EGFR receptors (1:1000 dilution); i) during the pre-exposure period completely reversed all the indices of damage and mucosal adapta- tion.

Conclusions: (1) the rabbit esophagus shows mucosal adaptation to acid and peptic, (2) this adaptation seems to be controlled by different and complementatory mechanisms that enable endogenous nitric oxide, epidermal growth factor and prostaglandin regulation.

124 Nitric Oxide in the Control of Gastric Acid Secretion, Gastrin Release and Blood Flow in Conscious Dogs

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Nitric oxide (NO) is formed from L-arginine (L-Arg) by constitutive NO synthase in epithelial and endothelial cells and nitrooxidergic nerves in the gastric mucosa but the role of NO in the control of gastric secretion is unknown. The aim of this study was to evaluate the role of NO in the control of gastric acid secretion, gastrin release and gastric blood flow in response to sham-feeding (SF), meat feeding (F) and i.v. infusion of bombesin (0.5 µg/kg-h), p-gastrin (4 µg/kg-h) or histamine (40 µg/kg-h) in conscious dogs with chronic gastric fistula (GF), Heidenhain pouch and esophageal fistula.

Infusion of N0-nitro-L-arginine (L-NNA), a potent inhibitor of nitric oxide synthase, in doses 0.3-2.5 mg/kg i.v. failed to affect basal gastric secretion or plasma gastrin but suppressed an increase of this secretion by F, SF or exogenous stimulants. Inhibition of gastric secretion by L-NNA was dose-dependent, the smallest dose that significantly reduced gastric acid secretion but not gastric blood flow was 0.6 mg/kg i.v. In tests with F, SF and bombesin infusion, L-NNA caused a significant and dose-dependent reduction (30–70%) in plasma gastrin levels. The inhibition of secretory response to p-gastrin, bombesin, histamine or feeding was accompanied by the decline in blood flow as measured in the gastric corpus via GF using laser Doppler flowmeter. L-arginine (50 mg/kg) infused i.v. significantly attenuated the L-NNA induced inhibition of gastric secretion, the reduction in plasma gastrin and the fall in gastric blood flow. We conclude that endogenous NO is involved in the regulation of stimulated gastric acid secretion and this effect is mediated, at least in part, by the alterations in gastrin release and gastric blood flow.

125 Expression of Gastric Mucosal Laminin Receptor with Ulcer Healing: Effect of Ebatrodone

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The interaction of gastric epithelial cell base surface integrin receptors with distinct adhesive proteins of the extracellular matrix is considered of significance to a variety of processes associated with tissue repair. Hence, the expression of integrin receptors important in gastric mucosa is of importance to successful ulcer healing. The purpose of this study was to investigate the effect of antilucor agent, ebatrodone, on the expression of mucosal laminin receptor during ulcer healing. Groups of rats with acetic acid-induced chronic gastric ulcers were treated twice daily for 14 consecutive days either with ebatrodone at 100 mg/kg or placebo, and then at different stages used for the quantitation of gastric mucosal laminin receptor. The binding assays revealed that the ulcer healing was accompanied by an increase in mucosal expression of laminin receptor. A 2.7-fold increase in the receptor expression occurred by 4th day following the development of ulcer and reached a maximum of 8.6- fold increase by the 14th day when the ulcer was essentially healed. Treatment with ebatrodone caused accelerated ulcer healing (7 days), accompanied by a remarkable enhancement in the laminin receptor expression. A 2.5-fold increase in the receptor expression occurred by the 4th day of ebatrodone treatment and a 1.7-fold increase was still observed at the 14th day of treatment. The results suggest that ebatrodone, by evoking enhanced mucosal cell laminin receptor expression, promotes re-epithelization and, thus, hastens the ulcer healing.

126 Comparison of the Effects of Some Purified Ingredients of Beer and Fermented Glucose on Gastric Acid Secretion (GAS) and Release of Gastrin (GR) in Humans

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Earlier (GE 1991; 101, 935) we have shown that beer and fermented glucose are powerful stimulants of GAS in humans, and that gastri is the most likely mediator of gastric acid response to both of them. To further identify the chemical structure of these stimulants we fractionated fermented glucose (11.5% v/v) by liquid chromatography of the different fractions on GAS and GR in 6 healthy human volunteers with the method of intragastric (ig) titration (pH 5.5). I. Polar substances. II. Thermostable substances (autoclaved fermented glucose). III. Gel filtration on Sephadex G-25. Two fractions were separated: from molecules with a molecular weight (MW) >1000; (b) molecules with a MW <1000. IV Anion exchange of the fraction lb (MW <1000) on amberlite IRA-400 (pH10). (a) Cations: fraction non-bound at the column (contains molecules with a positive or neutral electric charge by pH 10); (b) Anions: substances eluted with 0.25 M NaCl (molecules with different numbers of negative charges). V Gel filtration of the anions (MW