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-II 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 45 replied (22 male).

**Results:** Forty-five patients (mean age 56.9 yrs, range 28 to 81 yrs) 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. Healing 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%) had antacids alone at least weekly. Only 2 patients were not on any anti-reflux medication. No patient had undergone anti-reflux surgery or 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 Pepsin: Role of Nitric Oxide, Prostaglandins and EGF**

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Mucosal adaptation to sequential irritants is a fundamental mechanism 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 model of sequential irritations in rabbits by perfusing a recirculating 50 ml solution of acidified pepsin (AP) (saline at pH 2 + 2000 U of pepsin/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 uninformed observers from 0 = Normal to 3 = Confluent haemorrhage and/or erosions. Mucosal barrier function was measured by %H2O, K+ 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 t-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 damage when compared to control experiments (direct exposure to AP). Concomitant treatment with either parental aspirin (100 mg/kg, i.v.) or the nitric oxide inhibitor, L-NNAME (10 mg/kg, i.v.) or an antibody against EGF receptors (1: 1000 dilution; i.v.) decreased the pre-exposure period completely reversed all the indices of damage and mucosal adaptation.

<table>
<thead>
<tr>
<th>Pre-exposure</th>
<th>Muc. Damage</th>
<th>K+</th>
<th>K+</th>
<th>Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.7 ± 0.2</td>
<td>153 ± 37</td>
<td>239 ± 9</td>
<td>256 ± 11</td>
</tr>
<tr>
<td>Saline pH2</td>
<td>0.5 ± 0.2*</td>
<td>32 ± 9</td>
<td>4.2 ± 2*</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>LNAME</td>
<td>1.7 ± 0.4*</td>
<td>277 ± 94</td>
<td>59 ± 19</td>
<td>50 ± 30</td>
</tr>
<tr>
<td>+ ASA</td>
<td>1.9 ± 0.3*</td>
<td>504 ± 78</td>
<td>15 ± 2.3</td>
<td>46 ± 25</td>
</tr>
<tr>
<td>+ AbEGF.R</td>
<td>1.7 ± 0.1</td>
<td>451 ± 146</td>
<td>22 ± 8.3</td>
<td>213 ± 80</td>
</tr>
</tbody>
</table>

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

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


Nitric oxide (NO) is formed from L-arginine (L-Arg) by constitutive NO synthase in epithelial and endothelial cells and nitro oxidergic 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 N2-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 Ebrotidine**

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The interaction of gastric epithelial cell base surface integrin receptors with distinct adhesive proteins of the extracellular matrix is of considerable significance to a variety of processes associated with tissue repair. Hence, the expression of integrin receptors in gastric mucosa is of importance in successful ulcer healing. The purpose of this study was to investigate the effect of antilucer agent, ebrotidine, 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 ebrotidine at 100 mg/kg or placebo, and then at different stages used for the quantitation of gastric mucosal laminin receptor. The binding essays 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 ebrotidine 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 ebrotidine treatment, and a 1.7-fold increase was still observed at the 14th day of treatment. The results suggest that ebrotidine, 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**


Earlier (GE 1991; 101, 935) we have shown that beer and fermented glucose are powerful stimulants of GAS in humans, and that gastrin 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 and 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 (autocatalyzed fermented glucose). III. Gel filtration on Sephadex G-25. Two fractions were separated: (a) molecules with a molecular weight (MW) >1000; (b) molecules with a MW <1000. IV Anion exchange of the fraction ib (MW <1000) on ambersite IRA-400 (pH10). (a) Cations: fraction non-bounded 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
<10000 on Sephadex G-10: (a) anions with a MW 1000-7000, and (b) with a MW < 700. Furthermore the last fraction was split in 3 subgroups with MW between 700-1000, 1000-4000, and <400. Vi. Cation exchange of the anions with a MW < 700 on anionite IRA-PLUS (pH 1.0): (a) fraction not bound at the column, (b) fraction eluted with 1.0 M NaCl. On different days 2 x 500 ml (within one hour) of one of the above mentioned liquid test meals was given; 5.8% (w/v) glucose and distilled water were used as controls. Plasma gastrin was measured using a specific radioimmunoassay.

Results: Thermostable and polar substances, substances with a MW < 1000, anions with a MW <1000 and <700, resp., and the fraction not bound at the cation exchange resin caused a significantly (p < 0.05) higher increase in GAS (82%, 111% 98%, 93%, 77% and 76%, respectively, of fermented glucose) and GR (95%, 112%, 89%, 76%, 67% and 53% of fermented glucose) than water and glucose. The increase in GAS was 15.4 ± 2.0, 19.7 ± 2.2, 17.5 ± 2.1, 16.5 ± 1.5, 13.6 ± 1.4 and 13.4 ± 2.4 mmol/H (± SEM), resp., and the increase in GR was 3390, 4019, 2485, 2732, 2360 and 1906 compared to control. All the other tested liquid test meals had no effect.

In vitro experiments showed that gastrin and fermented glucose are thermostable and polar stimulants with a number of anionic substances with a similar structure but different MW, all <700; (2) the effect of effect on GAS and GR of these small substances after separating them by their MW indicates that there is an additive or potentiating interaction between the constituents of fermented glucose is the main agent on GAS; (3) gastrin is the mediator of gastric acid response to the purified ingredients of beer and fermented glucose; (4) the potent stimulatory action of the non-bound phase of the cation exchange suggests that substances like organic acids, phenols or polyphenols but not peptides, amino acids and nucleotides are the active ingredients of fermented glucose and beer.

### 127 Gastric Mucosal Repair and Release of Bicarbonate After Damage by 2 M NaCl in the Cat: Role of Systemic Acid Base Status

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This study examines gastric mucosal repair and gastric luminal release of bicarbonate in cats made acidotic by infusion of NaHCO3 or alkaliotic by infusion of NaHCO3 after mucosal damage by 2 mol NaCl. Saline at pH 5 or 1 was perfused through the stomach lumen and a chamber with pH and PCO2 electrodes. Bicarbonate was calculated by the Henderson-Hasselbalch equation. Mucosal blood flow was measured with microspheres. Release of bicarbonate to the gastric lumen increased immediately after damage in alkaliotic animals from 0.8 to 3.4 µmol/min (PHum = 5) and from 1.0 to 2.5 µmol/min (PHum = 1), and in acidotic animals from 0.8 to 1.3 µmol/min (PHum = 5) and from 1.0 to 2.5 µmol/min (PHum = 1). Luminal bicarbonate thereafter turned towards predamage level at 90 min except in alkaliotic animals (PHum = 5). Availability of bicarbonates is defined as: Arterial HCO3−/mucosal blood flow (GMBF), µmol/min × g. At luminal pH = 5:

<table>
<thead>
<tr>
<th>Art HCO3− mmol/l</th>
<th>GMBF (ml/min × g)</th>
<th>HCO3− availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After damage</td>
<td>After damage</td>
</tr>
<tr>
<td>37±1</td>
<td>0.37±0.07</td>
<td>0.79±0.15</td>
</tr>
<tr>
<td>13±1</td>
<td>0.40±0.08</td>
<td>0.43±0.03</td>
</tr>
<tr>
<td>With luminal pH 1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33±2</td>
<td>0.77±0.14</td>
<td>1.33±0.10</td>
</tr>
<tr>
<td>11±1</td>
<td>0.48±0.07</td>
<td>0.89±0.11</td>
</tr>
</tbody>
</table>

Mean values ± SEM, n = 8 in each group. A denotes significant differences between groups. B denotes significant differences between conditions. Bicarbonate release was measured to availability of bicarbonate in alkaliotic animals (PHum = 5). Histologic evaluation on coded sections at 90 min revealed that mucosal surface length judged as normal or restored at PHum = 5 were 74 ± 25% in alkaliotic compared to 35 ± 20% in acidotic animals (p < 0.025), and at PHum = 1; 44 + 40% in alkaliotic compared to 9 + 11% in acidotic animals (p < 0.001).

Conclusions: (1) Systemic acidosis abolish or hamper the immediate hyperemic response caused by 2 M NaCl at high and low luminal pH. (2) Leak of bicarbonate to the gastric lumen increases after mucosal damage, but depends on availability by blood and consumption within the mucosa. (3) Blood borne bicarbonate has a major influence on gastric mucosal repair.

### 128 Effect of Low-Dose Pentagastrin on the Gastric Lipase Secretion in Man

Morten Weidemann 1, Peter Narregaard 2, Berit Sternby 2, Helge Warming 3, Ole Olsen 1. 1) The Surgical Department C, Rigshospitalet, University of Copenhagen, Denmark; 2) Medical Department F, Glostrup Hospital, University of Copenhagen, Denmark; 3) Center of Experimental Research, Cellbiology Department, University of Lund, Sweden

Pentagastrin given in low-doses which may be identical with gastrin levels under physiological circumstances is associated with a significant and dose-dependent increase in the secretion of gastric lipase activity in gastric contents in man.

Five healthy volunteers (3 female 2 male, age: range 22-28 years) were examined after an overnight fast. Gastric contents were aspirated by intermittent suction 50-100 mmHg. Pentagastrin was infused intravenously in doses from 0, 50, 100, 500 and 1000 ng/kg/h to study the effect on gastric lipase activity (tributyrin kinetic assay) and concentration (ELISA titration).

Pentagastrin increased the lipolytic activity and at a dose of 50 ng/kg/h the lipase secretion was significantly increased above basal values. The lipase secretion measured quantitatively also showed a graded increase in the response to the same pentagastrin doses. In contrast to the quantitative concentration, the concentration of lipase activity decreased in response to the increasing pentagastrin doses. This decrease in lipolytic activity was significantly correlated to the pH of gastric contents.

Gastric lipase has previously been demonstrated to hydrolyze 17.5% of triglyceride acyl chains after a liquid meal. Several conditions, including chronic pancreatitis and cystic fibrosis, are associated with pancreatic insufficiency and the gastric lipase secretion might compensate for this defect. Therefore, the understanding of the release mechanisms for gastric lipase may lead to clinical improvements.

### 129 Nicotine Patches Can Prevent Steroid Use in Relapsing Ulcerative Colitis

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Ulcerative colitis is known to be more common in former smokers and nicotine, either in gum or in transdermal patches is reportedly more effective than placebo in the treatment of the disease.

To further investigate the matter, five outpatients in maintenance treatment with high-dose (1 g bid) mesalazine, experiencing a clinical relapse, were studied.

All patients, who in the past had received corticosteroids during the acute phases of their disease, consented to try transdermal nicotine instead of a further course of steroid therapy.

After a six-day run-in period during which nicotine patches were kept on the skin for six to twelve hours to improve subsequent tolerability, transdermal nicotine 15 mg was applied and maintained in situ for 24 hours per day for four weeks.

A substantial improvement of clinical symptoms (number of daily stools, presence of blood etc.) was obtained in three of the five patients, thus preventing the use of systemic corticosteroids in those subjects.

Our preliminary results suggest that transdermal nicotine can be an effective alternative to steroids during relapse of mild to moderate forms of ulcerative colitis.

### 130 Treatment of Interferon Alfa-2A in Patients with Ulcerative Colitis

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The aim of this study was the evaluation of the effect of Interferon alfa-2a (Roferon-A) on the clinic and endoscopic findings in patients with Chronic Active Ulcerative Colitis (UC).

Patients and Methods: In this study, from September 1991 to March 1993, we have investigated the effects of a 6 to 12 month-period therapy (as two groups) of Roferon-A (R) on the clinical and endoscopic findings in patients with UC. All of the patients (19 male, 9 male, mean age: 37.6) have had bloody diarrhea, abdominal pain, fever and weight loss for 12-24 months as well as a bloody defecation rate of 10-15 per day. Patients had a disease period of 1-16 years. In 6 patients the whole colon, in the remaining left descending colon were affected. Endoscopic findings: Acute UC. Clinic and endoscopic activity was evaluated according to Schroeder et al. Clinically 71.42% of the patients had score 3 whereas 28.5% had score 2 and 85.7% of patients had score 3 and 12% had score 2 endoscopically. All the individuals were unresponsive to classical therapy without having complete remission. The patients were started only R at a dose 3 x 9-10^6 IU in the first week and 3 x 3 -10^6 IU every week for 6 or 12 months.

Results: 25 patients (62.8%) received therapy for 6 months, in 11/26 patients (43.9%) it was prolonged up to 12 months whereas 5/28 patients (17.8%) didn't respond to therapy in 2 months and 2 of them (7.1%) underwent colectomy; the other 3 (10.7%) achieved late remission. 26 patients, under R therapy, were followed-up in order for 2 years and nearly 90% achieved remission during the first month and stayed in remission. The patients were also observed during a remission period of 6 to 18 months after the-