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 acidic by infusion of NaHCO₃ or alkalotic 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 alkalotic animals from 0.8 to 3.4 μmol/min (pH₇₅ = 5) and from 1.0 to 2.5 μmol/min (pH₇₅ = 1), and in acidic animals from 0.8 to 1.3 μmol/min (pH₇₅ = 5) and from 1.0 to 2.5 μmol/min (pH₇₅ = 1). Luminal bicarbonate thereafter turned towards predamage level at 90 min except in alkalotic animals (pH₇₅ = 5). Availability was defined as: Arterial HCO₃⁻/mucosal blood flow (GMBF) μmol/min × g. At luminal pH 5:

<table>
<thead>
<tr>
<th>Art.</th>
<th>HCO₃⁻</th>
<th>GMBF (μmol/min × g)</th>
<th>HCO₃⁻ availability</th>
</tr>
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<tbody>
<tr>
<td>Before</td>
<td>After damage</td>
<td>After damage</td>
<td>After damage</td>
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<tr>
<td>HCO₃⁻</td>
<td>15 min</td>
<td>90 min</td>
<td>15 min</td>
</tr>
<tr>
<td>37±1</td>
<td>0.37±0.07</td>
<td>0.79±0.15</td>
<td>A</td>
</tr>
<tr>
<td>13±1</td>
<td>0.40±0.08</td>
<td>0.43±0.12</td>
<td>0.65±0.13</td>
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<tr>
<td>With luminal pH 1:</td>
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<tr>
<td>332±2</td>
<td>0.77±0.14</td>
<td>1.33±0.19</td>
<td>AB</td>
</tr>
<tr>
<td>11±1</td>
<td>0.48±0.07</td>
<td>0.89±0.11</td>
<td>1.16±0.18AB</td>
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Mean values ± SEM, n = 8 in each group. A denotes significant differences between groups, B denotes significant differences between bicarbonate and control group. Histologic evaluation on coded sections at 90 min revealed that mucosal surface length judged as normal or restored at pH₇₅ = 5 were 74 ± 25% in alkalotic compared to 35 ± 20% in acidic animals (p < 0.025), and at pH₇₅ = 1; 44 ± 40% in alkalotic compared to 9 ± 11% in acidic animals (p < 0.001).

Conclusions: (1) Systemic acidosis abolishes 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 mucus. (3) Blood borne bicarbonate has a major influence on gastric mucosal repair.

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

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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 0.5, 50, 100 and 1000 ng/kg/h to study the effect on gastric lipase activity (trypsinin 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 Alpha-2A in Patients with Ulcerative Colitis

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The aim of this study was evaluated the effect of Interferon alpha 2a (Roferron-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 effect of a 6 to 12 month period therapy (as two groups) of Roferron-A (R) on the clinical and endoscopic findings in patients with UC. All of the patients (19 male, 9 female, mean age: 37.6) had 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 was affected. Endoscopic findings: Acute UC. Clinic and endoscopic activity was evaluated according to Schroed 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 12.2% 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 - 10⁶ IU in the first week and 3 x 3 - 10⁶ 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 ther-
apy had been stopped. All symptoms and laboratory findings improved and patients gained physical activity. A few patients suffered from short-period attacks of bloody diarrhea after therapy had been ended. Complaints disappeared in nearly 10 days under a dose scheme of 3 x 3.10^7 IU/week. Besides well-known side-effects, large ulcered and gross bleeding external hemorrhoids were observed in 4 patients.

**Conclusions:** The results of the study suggest that interferon alfa-2a may be beneficial to colonic mucosa in patient with Ulcerative Colitis and therapeutic effect of drug results probably from its immunomodulatory and/or antiviral properties.

### 131 Hepatobiliary Complications of Ulcerative Colitis. A Study on Estonian Patients

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The aim of the study was to determine the prevalence of hepatobiliary complications in patients with ulcerative colitis (UC) attending Tartu University Hospital during a 20-year period. A computer search to identify all patients with UC for the years 1973-1992 was performed. The case records were carefully reviewed, and patients fulfilling the criteria of UC were included in the study. The diagnosis of primary sclerosing cholangitis (PSC) was based on typical findings on endoscopic retrograde cholangiography and liver biopsy. For the diagnosis of chronic autoimmune hepatitis (CAH) a liver biopsy compatible with CAH, anti-nuclear antibodies, and negative tests for hepatitis B were required. The prevalence of UC was 31.0 per 10^5, the annual incidence was 1.5 per 10^5. At the time of diagnosis 59% of the patients had proctitis, 15% left-sided and 26% total colitis. Among 98 patients with UC, 18 were found to have elevated alkaline phosphatase (ALP) and/or transaminases values. In 15 patients ALP values did not exceed the upper normal limit more than two times, and transaminases elevation was mild. Abnormal liver tests normalized when the patients were in remission. These patients were diagnosed as having their liver abnormalities related to UC. Chronic liver disease was diagnosed in three patients. Among these patients, there were one female with CAH and two males with PSC. All of them had total colitis. The present study on Estonian UC patients leads us to two major findings: the prevalence of abnormal liver tests was about 18%, and the prevalence of CAH and PSC was 3%.

### 132 The Effect of Colectomy on Histological and Biochemical Liver Changes Associated with Ulcerative Colitis

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The effect of colectomy on the hepatobiliary changes associated with ulcerative colitis (UC) has been controversial. In the present follow-up study we included colectomized ulcerative colitis patients with even minor histological liver abnormalities found at preoperative liver biopsy in 1982-1987 to assess the effect of colectomy on histological and biochemical features of the liver in patients with UC.

We were able to carry out a follow-up liver biopsy on 24 (71%) of the 34 patients with liver abnormalities together with 8 patients with initially normal liver biopsy. Liver function values, i.e. alkaline phosphatase, alanine aminotransferase and bilirubin were analysed before the initial liver biopsy at colectomy and before the follow-up biopsy. The mean follow-up period was 46 months.

In five out of 7 patients whose initial liver biopsy showed PSC-like cholangitis, the stage of the disease had remained unchanged or progressed. There were no statistically significant improvements in the liver function values. All but one of the eight patients with nonspecific reactive hepatitis (NRH) at initial biopsy showed normal liver histology at the follow-up biopsy. Seven of the nine patients with steatosis initially showed normal liver histology at follow-up. Two of the eight patients with normal liver biopsy initially showed abnormalities at follow-up, one moderate steatosis and the other lymphoid cholangitis.

There seems now to be convincing evidence that colectomy has no beneficial effects on PSC-like cholangitis in patients with UC. On the other hand, NRH and steatosis seem to disappear or be subdued after colectomy. Since, however, in nearly 10 days under a dose scheme of 3 x 3.10^7 IU/week. Besides well-known side-effects, large ulcered and gross bleeding external hemorrhoids were observed in 4 patients.

**Conclusions:** The results of the study suggest that interferon alfa-2a may be beneficial to colonic mucosa in patient with Ulcerative Colitis and therapeutic effect of drug results probably from its immunomodulatory and/or antiviral properties.

### 133 Serum Anti-Neutrophil Cytoplasmic Antibodies in Ulcerative Colitis: Clinical Utility

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Antineutrophil cytoplasmic antibodies (ANCA) are useful for diagnosis and follow-up of patients with systemic vasculitis. These antibodies have also been detected in the serum of patients with inflammatory bowel disease (IBD), especially in cases of ulcerative colitis (UC). The aim of the present study is to determine the presence of ANCA using indirect immunofluorescence (IF) in patients with IBD and some other illnesses that give rise to diarrhea to evaluate their possible use as a serological marker and their relation to other clinical parameters, both analytical and therapeutic.

**Methods:** Using IF, the serum of 91 consecutive patients with IBD was evaluated, 46 ulcerous colitis (UC) and 45 Crohn's disease (CD), together with that from 10 patients with other diseases giving rise to diarrhea (3 cases of salmonella enteritis, 1 shigella, 4 of unknown etiology and 2 cases of irritable bowel syndrome).

**Results:** ANCA was detected in 28 of the 46 patients with UC (60.8%) but in only 3 of the 45 patients with CD (6.6%) (p< 0.01) and in no other illnesses that cause diarrhea. The pattern of predominant staining was perinuclear in 62% of cases of UC (23/28), and in 3 cases of CD. Thus, the sensitivity of the test for IF of perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) in the diagnosis of UC attained 50%, with a 93% rate of specificity. In patients with UC no correlation was found between a positive test result and age, sex, stage of development, location, extraintestinal manifestations or the treatment that followed. A certain relation between the presence of ANCA and the activity of UC was found, although this did not attain statistical significance (p = 0.05).

**Conclusions:** (1) The presence of ANCA as detected by IF is associated mainly with UC. (2) In patients with UC the predominant staining pattern is perinuclear (p-ANCA). (3) No correlation has been found between a positive test result and clinical features or treatment in patients with UC. (4) Screening IBD patients for ANCA can be helpful in distinguishing UC from CD patients as well as for other diseases which cause diarrhea.

### 134 Bone Mineral Density in Children with Inflammatory Bowel Disease

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Bone mineral density (BMD) was measured by Lunar DPX densitometer in 27 children (M-14, F-13) aged 7.8-18.3 yrs with Inflammatory Bowel Disease (IBD). Crohn disease (CD) was diagnosed in 8 pts, Ulcerative Colitis (UC) in 15 pts and Nonspecific Colitis (CNS) in 4 pts. The reference BMD was calculated for age, height and body weight of 318 healthy children (M-164, F-154) aged 5-18 yrs.

The height of 7 (26%) pts and body weight of 8 (30%) was below 10 percentile. No differences between CD and UC was noted.

Z-score of BMD was calculated for age, height and body weight. Z-score for control was below -2 in 3 (37%) pts with CD (mean -1.82), 2 (13%) pts with UC (mean -0.78) and in none with CNS. Z-score for height below -2 was found in 2 (25%) pts with CD (mean -0.37). 1 (7%) pts with UC (mean -0.22) and none with CNS. Z-score for body weight below -2 was found in 3 (37%) pts with CD (mean -0.54). 2 (13%) pts with UC (mean -0.35) and none with CNS.

The duration of disease in children with CD and z-score for age below -1 was 5.9 yrs and in children with CD and z-score above -1 was 1.9 yrs. The duration of disease in children with UC and CNS had no significant meaning for BMD. The previous steroid treatment didn't significantly influence BMD. The correlation (1) BMD in CD and UC. In children with CNS BMD doesn't differ from BMD of healthy population.

(2) The duration of CD is an important factor influencing BMD.

(3) The steroid treatment didn't significantly influence BMD of children with CD and UC.

### 135 NADPH Diaphorase Activity in Ulcerative Colitis

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Evidence has been presented that there is increased nitric oxide (NO) production in ulcerative colitis (UC) and that the enzyme NO synthase (NOS) is induced. Neuronal NADPH diaphorase (NADPHD) activity and NOS co-localize and are homogenous on purification. NADPH diaphorase was investigated in colonic biopsies from patients with acute UC. 24 snap frozen mucosal biopsies stored before analysis at -80°C were incubated with 2.5 mM NADPH, 1 mM nitro blue tetrazolium and 10% dimethyl sulphoxide for 30 minutes at 37°C. L-monomethylamine (LMNMA) 300 μM was used as an inhibitor of