A STUDY OF THE RELATIONSHIP BETWEEN ALCOHOL INTAKE AND GASTRIC LUMINAL ANTIOXIDANT CONCENTRATIONS. ZH Zheng, SE Patchett, D Perrett, MFG Farthing. Digestive Diseases Research Centre and Dept of Medicine, Medical College of St Bartholomew's Hospital, London, UK.

Epidemiological studies have suggested that there is a relationship between alcohol consumption and the development of gastric cancer. Adequate intake of anti-oxidants (vitamins C, E, and β-carotene) may be protective against gastric cancer and the levels in gastric juice may be particularly important. We therefore measured gastric luminal vitamins C, E, and β-carotene concentrations and examined whether they are influenced by alcohol intake.

Anti-oxidant concentrations were determined in gastric juice obtained at upper gastrointestinal endoscopy in consecutive patients (vitamin C n=63, vitamin E n=68, β-carotene n=59). All values were measured in duplicate using HPLC/elecrochemical detection and expressed as median [interquartile range]. Patients were interviewed with regard to their alcoholic and cigarette consumption prior to endoscopy. Levels of alcohol consumed was graded as none, 21-21-42 and > 42 units/week. Cigarette consumption was similarly recorded as none, <10, 10-20 and > 20 cigarettes/day.

The levels of each anti-oxidant in gastric juice were unaffected by the following endoscopic diagnosis. When controlled for age and sex, alcohol drinkers had significantly lower β-carotene in gastric juice than non-drinkers, 3.12nm (0.4-7.8) vs 3.92 (2.91-6.61), p<0.01. The β-carotene level was inversely related to the amount of alcohol consumed (r=0.32, p<0.02). No relationship between alcohol consumption and vitamin C or E level was evident. Furthermore there was no association between smoking and the levels of any of these anti-oxidants regardless of the number of cigarettes smoked.

Alcohol intake would appear to be a determinant of gastric juice β-carotene concentration but not of vitamin C or E. The adverse effects of alcohol consumption on β-carotene levels may have implications for gastric cancer development particularly in subjects with high alcohol intake.

IBD and AIDS

TRANSDERMAL NICOTINE COMPARED WITH ORAL PREDNISOLONE FOR ACTIVE ULCERATIVE COLITIS. GA Thomas, J Rhodes, K Ragunath, V Man, G Williams, R Newcombe, MAH Russell, C Feyerabend. Dept of Gastroenterology, UWH, Cardiff, Leigh Infirmary, Manchester, Institute of Psychiatry, Kings Hospital, London.

Ulcerative colitis (UC) is largely a disease of non-smokers. Controlled trials have shown benefit with transdermal nicotine (TN) given with 5-aminosalicylic acid (5-ASA) in active disease but not when given alone as maintenance therapy. We examined TN alone compared with prednisolone in active disease.

Methods: 61 patients with active UC were given either TN or 15 mg prednisolone for 6 weeks in a randomised, double-blind study. Incremental doses of TN were given for the first 9 days; patients tolerated 15 to 25 mg /16 hours. Most were taking 5-ASA at entry which was stopped at 9 days, a few taking topical steroids stopped these at the onset. Clinical, sigmoidoscopic and histological assessments were made at entry and at 6 weeks, or at premature withdrawal. Side-effects and serum nicotine and cotinine concentrations were monitored throughout.

Results: 43 completed the trial. Of these, 6 of 19 on TN achieved full sigmoidoscopic remission compared with 14 of 24 on prednisolone (p<0.08). In those who completed the study, there was significant improvement with both TN and prednisolone for the St Marks score (p<0.05 and p<0.001, respectively), Global Clinical Grade (p<0.01 for both), and sigmoidoscopic score (p=0.01 and p<0.001), differences between groups favour prednisolone, but none reach statistical significance. Those on TN had more withdrawals (11 versus 7 respectively), both for deterioration (6 vs 5) and for side-effects (5 vs 2) Side-effects were more frequent on TN than prednisolone (44 vs 19; p=0.03), the most common of which were nausea, lightheadedness and tremor.

Conclusions: Nicotine alone was of benefit in acute colitis, but 15 mg of prednisolone was more effective.
### BUTYRATE ENEMAS ARE LESS EFFECTIVE THAN PREDNISOLONE ENEMAS IN TREATING DISTAL OR LEFT SIDED ULCERATIVE COLITIS

Nightingale J MD, Barthose B J, Wert K F, Mayberry J F, Wicks A C W

Butyrate, a short chain fatty acid readily metabolised by colonocytes, has been proposed as treatment for diversion colitis and distal ulcerative colitis (UC) unresponsive to standard therapy. To compare butyrate enemas with prednisolone enemas and combined butyrate/prednisolone enemas, 21 patients with active distal or left sided UC were randomly allocated into 3 groups of 7. The enemas (all 100ml aqueous for 6 weeks) were 20mg prednisolone 21-phosphate, 100 mmol sodium butyrate or the same amount of prednisolone and butyrate mixed together as one enema. After two weeks treatment, median stool frequency fell significantly in the prednisolone group 9 stool/24hr to 3 stool/24 hr, p<0.05 but not in those given butyrate enemas 7 stool/24hr at 0 and 2 weeks. There was a resolution of urgency, blood loss, abdominal tenderness and sigmoidoscopic appearance in the prednisolone group, but not in the butyrate group. At 2 weeks 7/21 patients receiving butyrate showed no improvement in their colitis and withdrew from the trial. No steroid treated patients withdrew. At 6 weeks the improvement in those receiving prednisolone was maintained, only 3 patients receiving butyrate had a reduction in stool frequency. There was no additional benefit in combining prednisolone and butyrate into one enema. Prednisolone enemas were successful in treating all patients while butyrate enemas only improved 3/7 patients. There was no advantage in combining both butyrate and prednisolone into one enema.

### A RANDOMIZED CONTROLLED TRIAL OF ALBENDAZOLE FOR TREATMENT OF DIARRHOEA IN AFRICANS WITH AIDS

P Kelly, P Lunga, E Kanze, R Baggaley, P Kazembe, JOM Pohoe, MJ Parfion. University of Zambia School of Medicine, Lusaka; Digestive Diseases Research Centre, Medical College of St Bartholomew's Hospital, London.

AIDS in sub-Saharan Africa is a major problem for health care services, but there are few effective treatments for patients with diarrhoea. We have previously shown that intracellular enteropathogenic protozoa are found in the majority of HIV infected hospital patients with persistent diarrhoea in Zambia. We therefore carried out a randomised, double blind, placebo controlled trial of albendazole in the treatment of persistent diarrhoea in HIV infected individuals in urban Zambia. 174 patients were randomised to receive albendazole (800mg twice daily for 14 days) or placebo, and followed up for six months. Treatment and monitoring was carried out by community orientated AIDS care teams working in three urban settings. 105 patients completed treatment and at least the first month of follow up. Albendazole reduced the number of days on which patients experienced diarrhoea by 29% compared to placebo (p<0.0001). In patients with Karnofsky scores of 50-70, diarrhoea was reduced by 50% or sustained over six months of follow up. Minimal adverse effects were noted. No benefit was detectable in moribund patients or in those who were still able to work. On an intention-to-treat basis, complete remission was obtained in 22% of all patients who received albendazole (p=0.004 against placebo), failing to 13% at 6 months. Albendazole had no effect on mortality. Thus, for HIV infected Zambians with diarrhoea of more than three weeks duration, albendazole offers substantial relief from symptoms and may be used empirically, without prior investigation. This is the first agent shown to be effective in a controlled trial for treatment of this disease in this setting.

### Small bowel F164-F172

### INTRALESIONAL CHEMOTHERAPY IN THE TREATMENT OF GASTRIC KAPOSI'S SARCOMA IN AIDS

J A J Smithson, B G Gazzard (Introduced by B G Gazzard)
Dept of Gastroenterology, Royal Infirmary, Anlaby Road, Hull.

Introduction: Gastric Kaposi’s sarcoma is well described in patients with AIDS, as well a cause of mortality, it is an important cause of morbidity with symptoms of anaemia, abdominal pain and gastrointestinal haemorrhage. Gastric Kaposi’s sarcoma is conventionally treated by systemic chemotherapy or radiotherapy with all the associated side effects.

Patients: Five patients with previous AIDS diagnoses were found to have gastric Kaposi’s sarcoma, confirmed by histological samples taken at upper gastrointestinal endoscopy. All of the 5 patients had declined or been unable to have systemic treatment. The patient’s symptoms were noted, and their gastric lesions mapped at endoscopy and recorded photographically. The gastric lesions were then injected with 1ml of bleomycin (0.2mg/ml) into each lesion or a total of 2mls at different sites if the lesion was greater than 2cm. A repeat endoscopy was performed at two weeks and again at one month if they required further treatment or if their symptoms had returned.

Results: At repeat endoscopy the lesions had diminished in size and number in all 5 patients. In 3 patients all of the lesions had resolved. All patients noticed an improvement in their symptoms after the first 3 days post treatment. This symptomatic improvement was particularly marked for anaemia resulting in weight gain for 4 of the patients. Longer term follow up showed that patients tolerated the treatment well and that the response was sustained with no recurrence at the sites initially responding to the injections. One patient remains lesion free at 14 months. One patient had a pyloric ulcer lesion which was causing symptoms of obstruction this lesion resolved completely along with the symptoms.

### CHARACTERISATION OF GLUTEN PEPTIDE/HLA DQ BINDING IN COELIAC DISEASE

Gastroenterology Unit, UMDS, St Thomas’ Hospital, London, UK and *Georgetown University Medical Center, Washington.

Background: A peptide corresponding to amino acids 31-49 of A-gliadin, peptide A, has been shown to induce the histological features of coeliac disease (CD) both in vitro and in vivo (Sturgess, Lancet 1994; 343:758). Recent work has shown the binding affinity of this peptide to HLA DQ2 (a1*0501, b1*0201), the HLA restriction element of CD, correlates with its toxicity (Shidrawi et al., Gut 1995; 36: A53).

Aims: We wished to characterise the binding of peptide A to HLA DQ2 by identifying which residues within this peptide are important in peptide/HLA binding.

Methods: Truncations and alanine point-substitutions for proline residues of peptide A were made using fmoc chemistry that were tested for >95% purity and identity using reverse phase HPLC and mass spectrometry. Lymphoblastoid B cell lines from coeliac patients homozygous for HLA DR17(3) and HLA DQ2, determined by PCR-SSP genotyping, were used in peptide binding assays to compare the binding of these peptides with the binding of peptide A.

Results: Truncation of peptide 31-49 beyond residues 31-47 resulted in loss of binding. Alanine substitution for L31, Q33, P34, P41 and P42 also resulted in loss of binding, while alanine substitution for P34, P35, and P44 had no effect on binding. Alanine substitution for P39 improved binding affinity.

Conclusions: This data correlates with T cell proliferation work and identifies those residues in peptide 31-49 of A-gliadin that are important for binding to HLA DQ2 and therefore critical for coeliac toxicity.
Th2 CYTOKINES INTERLEUKIN-4 AND INTERLEUKIN-10 IN THE SMALL INTESTINE OF PATIENTS WITH COELIAC DISEASE.
Reckett C.G., Dell'Olio D., Neufler J.M., Premeistro R. and Cellerlira P.J. Gastroenterology Unit, UMDS, St.Thomas’ Hospital, London. SE1 7EH.

Aims: Our aim was to compare the level of production of IL-4 and IL-10 mRNA and inflammatory infiltrate in jejunal biopsies from patients with untreated (CD/ND) and treated coeliac disease (CD/GFD) as well as disease controls (DC).

Methods: 28 patients with CD (treated n=7, untreated n=21) and seven disease controls were studied. Cytokine mRNA from jejunal biopsies were identified by in-situ hybridization and quantified by eye-piece graticule. Histology was scored according to the degree of inflammation present. The fall in Th2 cytokine/CD45 ratio between CD/ND and CD/GFD along with the increase in inflammatory infiltrate in CD/ND confirm that the immunoreactive response in CD is predominantly Th1 driven.

Results: IL-4 or IL-10 positive cells were noted in the epithelium. In the lamina propria, the cytokine staining is expressed per 0.02mm²:

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>CD/ND</th>
<th>CD/GFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>0.8</td>
<td>4.1</td>
</tr>
<tr>
<td>IL-10</td>
<td>1.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

There was a significant increase in CD45 staining between both CD/ND and CD/GFD (p=0.003) compared to DC, as well as between CD/ND and CD/GFD (p=0.004). There was no significant differences in IL-4 or IL-10 staining between the groups. When cytokine staining is expressed as a percentage of CD45 staining, the maximum reduction was noted in both IL-4 (p=0.014) and IL-10 (p=0.038) staining between CD/ND and CD/GFD.

Conclusions: These results demonstrate that in CD, there is no primary deficiency of the Th2 cytokines IL-4 and IL-10, and that the lamina propria is the site of production. The fall in Th2 cytokine/CD45 ratio between CD/ND and CD/GFD along with the increase in inflammatory infiltrate in CD/ND confirm that the immunoreactive response in CD is predominantly Th1 driven.

NITRIC OXIDE IN THE SMALL INTESTINAL MUCOSA OF PATIENTS WITH COELIAC DISEASE.
Reckett C.G., Dell'Olio D., Neufler J.M., and Cellerlira P.J. Gastroenterology Unit, UMDS, St.Thomas’ Hospital, London. SE1 7EH.

Introduction: Increased expression and production of proinflammatory cytokines such as interferon-gamma and tumour necrosis factor-alpha have been found in the lamina propria of patients with untreated coeliac disease (CD). However, their precise role in the development of the mucosal lesion remains to be determined. It has been demonstrated in other disease states that these cytokines can mediate their effects via nitric oxide (NO).

Aims: Our aim was to use the NADPH-diaphorase activity of nitric oxide synthase (NOS), the enzyme that catalyses the production of NO, to indicate whether there is increased NOS in jejunal biopsies from patients with CD compared to disease controls.

Methods: Fifteen patients with CD (treated n=8, untreated n=7) and disease controls (n=8) were studied. Cytostat sections from jejunal biopsies were fixed in 4% paraformaldehyde, which inhibits all NADPH dependent enzyme systems except NOS. The sections were incubated in a solution of 100mMol Tris pH7.6 containing 0.3% Trition X1, 1.2mmol/l NADPH and 0.24mMol/l nitro blue tetrazolium (NBT) at 37°C for 3.5 hours to allow the insoluble blue reaction product to form. After a final wash, the sections were mounted in glycerol. Two independent observers assessed the sections and counted a 0.1mm² area of lamina propria on two sections from each patient using an eye-piece graticule.

Results: In the lamina propria, there was significantly more NADPH-diaphorase staining of untreated CD (median:50.75, range:43-65.5) compared to treated CD (median:32.88, range:7.95-48.75) (p=0.003 and controls (median:14.38, range:3.75-22.25) (p=0.001) as well as between treated CD and controls (p=0.046). The staining appeared to be almost entirely cellular in origin. In the epithelium, no staining was observed.

Conclusion: We have demonstrated, using NADPH-diaphorase as an indicator of NOS, significantly greater staining in the lamina propria of patients with untreated CD compared to treated patients and controls, thus for the first time implicating nitric oxide in the pathogenesis of the mucosal lesion in CD.

BONE MINERAL DENSITY AND BONE TURNOVER IN TREATED COELIAC DISEASE. NA McFarlane, J Dixey, J Dumpy, AK Bhalla, DAF Robertson, Dept of Gastroenterology, Royal United Hospital, Bath, BA1 3NG, Bath Institute of Rheumatism Diseases, BA1 1RL.

AIMS: To determine both bone mineral density [BMD] and bone turnover (bone formation and resorption) in patients with treated coeliac disease compared with healthy adults.

METHODS: 75 adults (60 females with coeliac disease (average age 52 years), median duration on gluten free diet (GFD) 3.4 years) had BMD measured at the lumbar spine and femoral neck using Hologic QDR dual energy X ray absorptiometry. 55 (45 females) of the above 75 patients underwent further detailed study of biochemical bone turnover markers. Bone formation was assessed by measuring two products of osteoblast activity, serum osteocalcin (Bone GlA protein) and procollagen I terminal propeptide (PINP), and resorption assessed with the urinary collagen crosslinks, pyridinoline (PINP) and deoxypyridinoline (DPyr).

RESULTS: BMD in patients was significantly lower than in paired healthy controls matched for age and sex, at both spine (0.886 c 1.000 g cm², p<0.001, Student’s t test) and hip (0.72c 0.76, g cm², p<0.04) Compared with controls, patients had higher serum PINP (111.16 c 80.8 11 mmol/mmol creatinine, p<0.02) and DPyr (5.4 c 2.3 mmol/mmol, p<0.001). There was no difference in serum osteocalcin compared with controls (5.9 c 6.1 mmol/L). There was a strong correlation between the bone turnover markers and BMD or rate of loss of BMD, however in the subgroup of postmenopausal coeliac patients (n=23) there was a significant negative correlation between %/year change in BMD and both Pyr (r=-0.72, p<0.001, Spearman’s rank correlation) and Dpyr (r=-0.69, p<0.005).

CONCLUSIONS: Reduced BMD is an important complication of coeliac disease, and increased bone turnover may be an important underlying pathophysiological mechanism. In particular, in postmenopausal patients high urinary collagen crosslinks, which indicate increased resorption, may be a marker of future bone loss, and in conjunction with a low initial BMD would indicate those patients most in need of intervention to preserve bone mass.
TWO-PHASE RANDOMISED CONTROLLED CLINICAL TRIAL OF ORAL DIETARY SUPPLEMENTS IN SURGICAL PATIENTS.

A.M. Keevil1, M.J. Bray2, P.W. Emery1 and D.B.A. Silk1

1Department of Gastroenterology and Nutrition, Central Middlesex Hospital NHS Trust, London NW10 7NS and 2Department of Nutrition and Dietetics, King’s College, London W8 7AH.

It has previously been shown that the administration of oral dietary supplements (ODS) results in clinically significant short-term benefits in surgical patients. The aims of this study were (1) to re-evaluate the short-term clinical efficacy of ODS administered postoperatively to in-patients undergoing gastrointestinal surgery (phase 1), and (2) to investigate the clinical efficacy of ODS given during the first 4 months following hospital discharge (phase 2). 100 patients who were scheduled to undergo moderate to major gastrointestinal surgery entered the study. They were randomly assigned to receive a normal ward diet postoperatively, or the same diet supplemented ad libitum with ODS (Fortiaid, Nutricia, 6.3 kJ/ml, 8 mg N/ml). The study period was from the day the patients started ingesting free fluids postoperatively (mean 5.3 days after surgery) until the day of hospital discharge. On discharge patients were further randomised to their usual home diet, or taking ODS in addition to their usual diets for 4 months, resulting in the formation of 4 treatment groups in phase 2.

In phase 1, the mean daily energy and protein intakes were significantly higher in the treatment group than in the control group at study days 1, 2, 3 and 4 (by an average 1473±SEM 122 kJ, 13±1.3 g protein). Patients in the treatment group lost significantly less weight than control patients by discharge: 2.2±0.5 kg vs 4.2±0.4 kg (p<0.001). Control patients showed a significant reduction in hand grip strength over their hospital stay, (p<0.02), whereas treatment patients maintained their hand grip strength. Significantly more patients in the control group (12) developed serious complications (wound infection 7, avoidance dehiscence 1, gastrointestinal perforation 1, hepatic abscess 1, multiple complications 1) than in the treatment group (4; wound infection 2, wound dehiscence 1, multiple complications 1; p<0.05). In phase 2, supplemented patients had significantly higher energy and protein intake one month after discharge and significantly higher hand grip strength and discharge, compared with control patients. There were no significant differences in indices of nutritional status and wellbeing between the groups.

We conclude that the prescription of oral dietary supplements postoperatively to patients undergoing moderate to major gastrointestinal surgery results in clinically significant benefits. These benefits, however, are restricted to the in-patient phase.

SUPPLEMENTAL ENTRAL NUTRITION IN PATIENTS UNDERGOING MAJOR RESECTIONAL SURGERY.

PM Murtagh1, BD Palmer1, S Townsend1, CJ Mitchell1, J Macfee1

Combined Gastroenterology Unit, Scarborough Hospital, UK.

We investigated the impact of supplemental enteral nutrition given in pre- and post-operative period on nutritional status and outcome of patients undergoing major surgical excision.

Patients were randomised to receive normal diet or diet supplemented by a commercially available nutritional sip feed (20g protein, 600 kcal/400 ml per day), for a minimum period of 14 days preoperatively and further randomised postoperatively. Parameters analysed: weight, hospital stay, POSSUM score, morbidity, serum proteins, anthropometric measurements and serial dynamometric assessment of muscle function. Group A, Pre- and postoperative supplements (n=12), Group B Pre-operative supplement only, (n=14), Group C Post-operative supplements only (n=11), Group D No supplemental nutrition (controls) (n=13). Patients were well matched for age, sex and type of operation as well as standard home and in hospital diet. Patients receiving pre-operative nutritional support (groups A & B) showed a mean weight gain (0.14±0.09 kg) from randomisation to day of surgery differing significantly with a weight loss of 1.25±0.74 kg (p<0.05) in those not receiving supplements. ANOVA While patients in all groups sustained some weight loss following surgery, control patients had a significantly greater weight loss than patients in any of the treatment groups (D of A, P<0.01; D of B P<0.05; D of C, P<0.05). Duration of hospital stay was longer in patients not receiving any sip feeds (15±2 days) compared to patients receiving both pre and post-operative nutrition (25±3 days) P<0.05. No differences were recorded in complication rates, POSSUM scores or biochemical indices of nutritional status.

Pre- and postoperative supplemental nutrition reduces the inevitable weight loss associated with major excisional surgery and results in earlier hospital discharge.
**Helicobacter pylori** F173-F176

**F173**

**H. Pylori Infection is Associated with Decreased Gastric Juice β-Carotene Concentration.**

ZW Zhang, SE Patchett, D Perrett, P Domizio, MJA Farthing. Digestive Diseases Research Centre, Depts of Medicine & Histopathology, Medical College of St Bartholomew's Hospital, London, UK.

Previous studies suggest that β-carotene may be protective against gastric cancer. This is thought to be related to its ability to inhibit lipid peroxidation especially at low oxygen partial pressures. Factors reducing gastric β-carotene concentration maybe increase the risk of gastric cancer. This study aimed to investigate effect of H. pylori infection on gastric luminal β-carotene concentration and relate this to the severity of histological changes in the stomach.

β-carotene concentrations were determined in gastric juice of 59 consecutive patients attending for upper endoscopy. H. pylori status was determined by rapid urease test, histology and culture. All specimens were examined ‘blind’ by the same histopathologist and both density of organisms and severity of histological changes were graded (0-3) according to the Sydney system. Measurements were performed in duplicate using HPLC/electrochemical detection and expressed in µM (median [interquartile range]). There was no association between β-carotene levels and patient age or sex. H. pylori infected patients (27/59) had significantly lower β-carotene in gastric juice than uninfected patients, 3.12 [0.4-8.1] vs 4.33 [3.41-7.39], (p<0.02) and levels were inversely related to the density of organisms (r=0.28, p=0.03). Intestinal metaplasia was associated with significantly lower β-carotene level than histologically normal mucosa 2.82 [2.0-3.96] vs 4.76 [3.53-6.88] (p<0.05). Increasing severity of inflammation and degree of atrophy were also associated with decreasing β-carotene levels though this failed to reach statistical significance.

H. pylori infection and its related histological changes are associated with decreased gastric luminal β-carotene concentrations. This may be relevant to the development of gastric neoplasia perhaps through impaired prevention of lipid peroxidation at low oxygen tensions found in the stomach.

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**Circulating Iga Antibodies to 60Kda But Not 32Kda Heat Shock Proteins Are Raised in Patients with Helicobacter Pylori-Related Gastrointestinal Atrophy.**

SGRG Barton, ILP Beales*, VR Winrow, DS Rapmton, J Calam*, London Hospital Medical College and *Hammersmith Hospital, London.

Heat shock proteins (HSP’s) are ubiquitous, highly immunogenic intracellular molecules induced in vitro by inflammatory mediators and oxygen free radicals. It has been suggested that they may induce autoimmune phenomena in vivo. Helicobacter pylori (HP) causes varying gastroduodenal pathologies and itself produces a 60KDa HSP and induces free radical stress. We have now assayed sera of patients with either gastritis (G), gastric atrophy (A), duodenal ulcer (DU) or gastric ulcer (GU), all with HP infection, as well as sera of HP-negative controls (N), for antibodies to the 60KDa and 32KDa HSP’s.

**Methods:**

All sera were tested for IgA, IgG and IgM antibodies against both 60KDa and 32KDa HSP antigens using established ELISA’s. Results are expressed as optical density ratios using a standard control.

**Results:**

32 kDa HSP serology showed no differences between patient groups. 60 KDa HSP serology results are shown below (mean (SEM)).

<table>
<thead>
<tr>
<th>HSP</th>
<th>Normal</th>
<th>Atrophy</th>
<th>Gastritis</th>
<th>DU</th>
<th>GU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hp</td>
<td>No.</td>
<td>IgA</td>
<td>IgM</td>
<td>IgG</td>
<td>IgG</td>
</tr>
<tr>
<td>Normal</td>
<td>45</td>
<td>1.82 (0.32)</td>
<td>1.03 (0.09)</td>
<td>2.24 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>+ 43</td>
<td>2.97 (0.46)*</td>
<td>1.13 (0.12)</td>
<td>2.95 (0.50)</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>45</td>
<td>2.17 (0.30)</td>
<td>1.09 (0.10)</td>
<td>2.10 (0.20)</td>
<td></td>
</tr>
<tr>
<td>DU</td>
<td>15</td>
<td>2.05 (0.21)</td>
<td>1.75 (0.36)</td>
<td>2.81 (0.72)</td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>15</td>
<td>2.18 (0.49)</td>
<td>1.72 (0.43)</td>
<td>2.34 (0.70)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.005 from normal*; *p<0.05 from gastritis (Mann-Whitney U).

**Conclusions:** Elevated IgA antibody levels to the 60KDa HSP in patients with HP-related gastric atrophy compared with HP-negative normal patients may reflect (a) a response to increased release of HSP from damaged gastric epithelial cells, and (b) generation of antibody cross-reacting with HP-derived or -induced HSP. Elevated IgA antibody levels in atrophy patients compared to gastritis patients may (1) indicate more HP shedding and (2) contribute to gastric atrophy through an adverse effect on epithelial cell protection by HP’s.

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**Somatostatin Receptor 1 (SSTR1) mRNA is Reduced in Helicobacter Pylori (Hp) Infection.**

Gibbons AJ, Legon S. and Calam J. Depts of Medicine and Metabolic Medicine, Hammersmith Hospital, Du Cane Road, London, W12 ONN.

Introduction. 5 subtypes of somatostatin (SST) receptor have been identified so far. Northern blotting of SSTR mRNAs suggests that SSTR1 is the most abundant in human gastric mucosa. SSTR1 has not been studied extensively but is thought to mediate the inhibitory effect of SST on cell proliferation. As gastroepithelial proliferation and the risk of gastric carcinoma are increased in Hp infection we studied the abundance of SSTR1 mRNA in patients with and without this infection.

**Method.** Biopsies were taken from the gastric antrum of 6 Hp+ and 4 Hp- dyspeptic patients for total RNA extraction and Northern blotting. A 32P labelled cDNA probe for SSTR1 was used to detect the mRNA, the signals being quantified by phosphor imaging. GAPDH mRNA levels were measured to correct for loading and transfer variations.

**Results.** The expression of SSTR1 mRNA in the gastric antrum was significantly reduced in Hp positive patients (p=0.005). The median antral SSTR1 mRNA in Hp+ mucosa was 0.3 (0.2-0.4) versus 0.6 (0.4-0.8) in Hp- mucosa.

**Conclusions.** Antral SSTR1 mRNA is reduced in Hp infection. A recent study showed that chronic exposure to SST increased the expression of SSTR subtypes in pituitary cells. We and others have previously shown that SST peptide and mRNA are reduced in Hp+ patients. Therefore the lack of peptide may account for the reduced expression of the receptor in antral mucosa.

**Deficiency** of this receptor may further decrease the restraint of cell proliferation by somatostatin and thus predispose to carcinoma.

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**H. pylori Positive Patients with Duodenal Ulcer Have Increased D Cell Counts in the Duodenal Bulb.**

AW Harris, PH Le Roux, J Miświeca, JH Baron, MM Walker Parks.' Helicobacter Study Group, Central Middlesex and St Mary's Hospitals, London, UK.

It has been reported that antral D cell density and somatostatin concentration are low in H. pylori (Hp)-ve patients with duodenal ulcer (DU), and that they increase to normal after eradication of Hp. The relationship between HP and D cells in the duodenal bulb is unknown. We have investigated duodenal bulb D cell numbers in Hp+ve DU before and 6 months after Hp eradication, and compared them with Hp-ve patients with recurrent, non-NSAID DU and Hp-ve controls.

We studied 10 Hp+ve DU (7 men, mean age 37, range 22-58) before and 6 months after Hp eradication (n=6, 6 men, mean age 39, range 24-58), and compared them with 6 Hp-ve recurrent DU (6 months, mean 18) after Hp eradication (5 men, mean age 39, range 28-53), and with 10 Hp+ve controls with normal endoscopy (4 men, mean age 33, range 24-40). Hp status was determined by antral and body histology and culture and by the *1C-UBT*, and classified as Hp-ve on any +ve result and Hp-ve on all three tests. Four biopsies (one from each quadrant) were taken from the duodenal bulb, stained with polyclonal antibodies raised against human somatostatin using a peroxidase-antiperoxidase technique. A single blinded observer used a computer enhanced image intensifier to count the D cells in 3 low power (×20) fields in each biopsy. Results were expressed as cell counts/mm².

Duodenal D cell counts were significantly (p<0.005, Mann Whitney test) higher in Hp+ve DU than in Hp-ve recurrent DU and in Hp-ve controls, with median (range) 30.5 (20-44), 11 (4-21) and 13 (3-24), respectively. Six months after Hp eradication, duodenal D cell counts fall significantly (p<0.05, Wilcoxon signed rank test) to 15 (3-40), which was not significantly different from Hp-ve recurrent DU or Hp-ve controls.

In contrast with the reported effect of Hp on antral D cell counts, duodenal D cell counts are significantly higher in Hp+ve DU than Hp-ve recurrent DU and Hp-ve controls, and fall significantly after Hp eradication. The pathophysiological significance of these observations is unclear. Further studies are needed.
Oesophagus and motility

A COMPARISON OF OMEPRAZOLE 10MG AND 20MG OM WITH RANITIDINE 150MG BD FOR THE TREATMENT OF GORD IN PRIMARY CARE.

Nine hundred and ninety four patients with heartburn as the predominant symptom were endoscoped (only ulcerative oesophagitis excluded), then randomised double blind to omeprazole 10mg, omeprazole 20mg, or ranitidine 150mg bd for 4 weeks. The three groups were well matched at entry. The primary efficacy variable of relief of heartburn (no more than 1 day of mild symptoms in the last 7 days) after 4 weeks treatment, was compared between treatment groups for all patients treated and for the subgroup with erosive oesophagitis. The costs of individual treatment success were also calculated.

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Patients</th>
<th>Relief</th>
<th>Cost per treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omepr 20mg om</td>
<td>330</td>
<td>61%</td>
<td>£58 (CI 54-63)</td>
</tr>
<tr>
<td>omepr 10mg om</td>
<td>338</td>
<td>49%</td>
<td>£41 (CI 37-45)</td>
</tr>
<tr>
<td>ranit 150mg bd</td>
<td>326</td>
<td>40%</td>
<td>£65 (CI 57-74)</td>
</tr>
<tr>
<td>Erosive oesopha</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omepr 20mg om</td>
<td>101</td>
<td>79%</td>
<td>£45 (CI 41-50)</td>
</tr>
<tr>
<td>Omepr 10mg om</td>
<td>102</td>
<td>48%</td>
<td>£42 (CI 34-52)</td>
</tr>
<tr>
<td>Ranit 150 mg bd</td>
<td>113</td>
<td>33%</td>
<td>£79 (CI 62-108)</td>
</tr>
</tbody>
</table>

Both 10mg and 20mg doses of omeprazole provided relief of heartburn in significantly more patients than ranitidine 150mg bd (p < 0.05, p < 0.001, respectively). The omeprazole groups also showed greater symptom relief compared to ranitidine in those patients with erosive (grade 2 and above) oesophagitis (p < 0.05, p < 0.001 respectively). In all cases the costs of treatment success are lower with omeprazole.

Within a General Practice setting where the GP is primarily treating symptomatic heartburn, it is important to initiate therapy which can achieve adequate symptom relief across the spectrum of GORD. This study demonstrates that both omeprazole 10mg and 20mg om are superior, both in terms of clinical efficacy and costs, to ranitidine 150mg bd for the relief of heartburn associated with GORD.

SYMPTOM RELIEF WITH OMEPRAZOLE IN PATIENTS WITHOUT UNEQUIVOCAL OESOPHAGITIS.
CM Bate, SM Griffin, PWN Keeling, ATX Azon, MW Driffield, RWG Chapman, D O'Donoghue, J Calam, J Crowe, RA Mountford, DA Watts, MD Taylor, PDI Richardson and the HARMONY Investigator Group Gastroenterology units in Wigan, Newcastle, Dublin, Leeds, Peterborough, Oxford, Hammersmith, Bristol and Astra Pharmaceuticals Ltd, Kings Langley

As many as 40% of patients with typical symptoms of gastro-oesophageal reflux disease (GORD) do not have oesophagitis. This study was designed to evaluate omeprazole as therapy in such patients, in who as yet, the role of antisecretory drugs has not been established.

Two hundred and nine patients (125 female, 84 male) aged 18-79 years with normal oesophageal mucosa (60%) or non-erosive oesophagitis (40%) presenting with moderate or severe symptoms of GORD (predominantly heartburn) were randomised, double-blind, to receive either omeprazole 20mg om (n=98) or placebo (n=111) for 4 weeks. Symptoms were assessed at clinic visit and by diary card, a series of patient questionnaires gave further details of symptoms, impact of symptoms on lifestyle, and anxiety/depression score.

A greater proportion of patients in the omeprazole group compared with those receiving placebo were free of heartburn (57% vs 19%) and regurgitation (75% vs 47%) after 4 weeks' treatment (both p<0.001). Diary card analysis showed that patients in the omeprazole group took less relief medication; p<0.05. The lifestyle and gastrointestinal symptom questionnaires both gave evidence in favour of treatment with omeprazole with improvements seen during the study. The reduction in anxiety over the treatment period was greater in omeprazole patients than in the placebo group (reduction in mean score = 1.81 (mean baseline score = 4.94) vs 1.09 (4.5) p<0.05). There was no difference in the improvement in depression over the same period. The frequency of adverse events recorded during the study was the same for omeprazole and placebo groups. 6 patients in each group stopped treatment due to adverse events.

Analysis of all patients identified low initial bowel score and treatment with omeprazole (p<0.05) as significantly increasing the probability of successful symptom relief. In conclusion omeprazole 20mg om was more effective than placebo in providing relief of typical GORD symptoms in patients with essentially normal oesophageal mucosa.

THE EFFECT OF OMEPRAZOLE ON QUALITY OF LIFE IN PATIENTS WITH THE "SENSITIVE OESOPHAGUS": A DOUBLE BLIND CROSS-OVER PLACEBO CONTROLLED STUDY.
R Gwatkin, NI McDougall, TCK Tham, BT Johnston. Department of Medicine, The Queen’s University of Belfast, Northern Ireland.

The term "sensitive oesophagus" has been proposed to describe patients with gastro-oesophageal reflux disease (GORD) symptoms whose total distal oesophageal acid exposure is within normal limits (pH>4 for 16% of the time) on ambulatory pH monitoring, and yet in whom at least 50% of symptom events coincide with reflux events. We have previously shown that treatment of erosive oesophagitis patients with omeprazole (OME) significantly improves several parameters of quality of life (QOL). The aim of this study was to determine if treating OGD/pH negative GORD patients could improve QOL, particularly in those with a symptom index (SD) ≥ 50.

Method: Subjects were patients with typical GORD symptoms (heartburn and/or reflux), normal OGD and total distal oesophageal acid exposure on ambulatory pH monitoring of less than 5%. Eleven patients had a positive symptom index (≥ 50%) and 6 had a negative SD. All patients were given in random order omeprazole 20mg BD and placebo, each for 4 weeks, in a double blind, cross-over design. Quality of life was assessed at the end of treatment with each regimen using the OMEPQ (Derived from a previously validated OMEPQ, between 0 and 100), and results compared using the Wilcoxon signed rank test.

Results: The table shows the overall QOL results for OME and placebo with statistically significant differences (p<0.05) marked by *.

<table>
<thead>
<tr>
<th>OME</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>76.8</td>
</tr>
<tr>
<td>Role</td>
<td>55.1</td>
</tr>
<tr>
<td>Pain</td>
<td>68.9</td>
</tr>
<tr>
<td>Health</td>
<td>66.3</td>
</tr>
<tr>
<td>Vitality</td>
<td>62.8</td>
</tr>
<tr>
<td>Mental</td>
<td>78.1</td>
</tr>
</tbody>
</table>

Both vitality (p=0.049) and bodily pain (p=0.029) were significantly better while on OME for the overall group. When patients were divided into those with and without a positive symptom index, both groups had a significantly better score for bodily pain on OME.

Conclusion: Treatment of OGD/pH monitoring negative GORD patients with OME improves both the bodily pain and vitality parameters of QOL measured by the SF-36. This supports the use of OME in GORD patients with normal investigations, but larger numbers are necessary to determine if a greater improvement is seen in those with a "sensitive oesophagus".

MONITORING THE LOWER OESOPHAGEAL SPHINCTER: SPHINCTOMETER OR SLEEVES?
Nigel Trudgill, Faz Hussain, Stuart Riley. Northern General Hospital, Herries Road, Sheffield, S5 7AU.

Lower oesophageal sphincter (LOS) function has been extensively studied in healthy volunteers. Recently a solid state sphinctometer has become available, permitting ambulatory studies of LOS function. Studies using the two devices in patients with reflux disease have yielded conflicting results. We have therefore compared the Dent sleeve and sphinctometer in a controlled laboratory setting.

Following a four hour fast, six healthy volunteers (4F, 21-37 years) were intubated with a solid state catheter containing a sphinctometer and a perfused catheter, which measured gastric, oesophageal and LOS (via a Dent sleeve) pressures. Submental EMG monitored swallowing and a pH probe was positioned 5 cm above the LOS. Following 20 minute accomodation and 30 minute basal recording periods, 200 kcal of long chain triglyceride (calogen) was infused into the stomach. Manometric and pH data was then recorded for a further 60 minutes. The Dent sleeve and sphinctometer readings correlated well within individuals. Using the criteria proposed by Holloway (Gastroenterology 1993: A-225 16 patients with oesophagitis (CLOS) were detected with the Dent sleeve and six were associated with reflux. The sphinctometer readily detected CLOS in volunteers with high basal LOS pressures, but performed less well in those with low pressures. The overall sensitivity was 69%, with nine false positive relaxations.

The sphinctometer may be of limited value in studying patients with reflux disease, particularly when basal LOS pressure is low.
OESOPHAGEAL MOTOR RESPONSES TO GASTRO-OESOPHAGEAL REFLUX IN HEALTHY CONTROLS AND REFLUX PATIENTS.

A Sargias, G Taylor, A Simpson, NF Bright, JW Wang, WA Owen, AR Jones, WJ Owen, Dept of Surgery, Radiological Science and Public Health Medicine, Guy's and St Thomas Hospital, London.

This study compared oesophageal motor responses to gastro-oesophageal reflux in 16 healthy controls (Group 1) and 25 reflux patients, of whom 15 were without (Group 2) and 10 with oesophagitis (Group 3).

All subjects had 24-hour ambulatory oesophageal pH measurements (5 cm above the lower oesophageal sphincter (LOS)) combined with pressure monitoring (5, 10 and 15 cm above the LOS). Motor activities occurring during reflux episodes (pH<4) were analysed semi-automatically. Contractions pattern (peristaltic, simultaneous, segmental and mixed-type including reverse peristaltic) and also the peristaltic contraction characteristics (amplitude, duration and velocity) were compared between the 3 groups. The total reflux episodes (RE), associated total motor activities (MA), total reflux duration (RD), average motor activities per minute (AMA), and medians of the total percentage of reflux (PR) in the 3 groups were:

<table>
<thead>
<tr>
<th>Group</th>
<th>RE (min)</th>
<th>MA</th>
<th>RD (min)</th>
<th>AMA</th>
<th>PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>459</td>
<td>706</td>
<td>465.6</td>
<td>2.1*</td>
<td>1.35*</td>
</tr>
<tr>
<td>Group 2</td>
<td>794</td>
<td>1923</td>
<td>2623</td>
<td>0.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Group 3</td>
<td>579</td>
<td>1263</td>
<td>1482.6</td>
<td>1.0</td>
<td>9.1</td>
</tr>
</tbody>
</table>

AMA was significantly higher in Group 1 (*p<0.05) but no differences were found in other groups. In all groups, the most common contraction patterns of motor activities was peristaltic. The 4% of peristaltic activity per subject was significantly higher in Group 1 (p<0.05). There were no significant differences between the other patterns of contraction in the 3 groups (p>0.05). Of the peristaltic contraction characteristics there were no significant differences for any parameters (amplitude, duration and velocity) in the 3 groups (p>0.05).

Motor responses to reflux were more frequent in controls than in reflux patients. Contractions in response to reflux was found to be predominantly peristaltic. The motor activities were similar in all groups except that the peristaltic activity was stronger in healthy controls.

CHARACTERISTIC OF REFLUX IN RELATION WITH SYMPTOM EVENT IN PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX RESISTANT TO OMEPRAZOLE THERAPY. S D Singh, J Wang, A Anggiasah, W A Owen, A R Jones, W J Owen, Dept of Surgery, Guy's Hospital, London.

Omeprazole is successful in producing relief from symptoms of gastro-oesophageal reflux (GORD) but it has been suggested between 10-20% fail to get symptomatic relief.

We investigated thirty-four patients (18 males, 16 females), age range 29-73 years (mean 40.3) with GORD with persistent heartburn and chest pain, who did not respond to omeprazole therapy. Mean duration of symptoms was three years and period of treatment was between 1-5 months with omeprazole 40-80 mg daily. Omeprazole was stopped seven days prior to the study.

All patients underwent 24 hour simultaneous oesophageal and gastric pH monitoring. Oesophageal pH was recorded 5 cm above the lower oesophageal sphincter determined manometrically and gastric pH was monitored at 15 cm below the oesophageal sensor.

A symptom event was defined as secondary to an acid reflux episode when oesophageal pH<4 or alkaline reflux when oesophageal pH>7 with associated rise in gastric pH>4 for longer than 20 seconds (2 minutes before and after the onset of symptom). The latter was analysed during inter-prandial periods only.

A total of 147 symptom events occurred during 24 hour pH monitoring in 34 patients.

Pathological acid reflux: 49/147 = 33.33%
Pathological alkaline reflux: 28/147 = 19.01%
Symptoms but no reflux: 70/147 = 47.61%

This study shows 33.3% symptoms were associated with acid reflux and 19.01% symptoms were associated with alkaline reflux whereas 47.6% symptoms were not associated with reflux. This suggests acid sensitive oesophagus and alkaline reflux are important factors which may contribute to failure of omeprazole therapy in this group of patients. Symptoms without reflux suggests these patients may have altered perception of pain or may have anxiety.

DOES INTOLERANCE OF pH MONITORING CAUSE FALSE NEGATIVE RESULTS?

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Several centres report that among patients undergoing diagnostic oesophageal pH monitoring, a small proportion show a positive symptom index (SI) with normal acid exposure time (AET). There is still doubt about whether these patients represent a distinct group within the GORD clinical spectrum or whether these findings are false negative results, perhaps related to intolerance of the test.

We invited 207 consecutive patients undergoing pH monitoring to record their deviation from normal eating patterns and degree of distress on visual analogue scales (VAS) on completion of the test. Regression analyses and Chi square tests were used to compare VAS results with demographic and clinical features, looking particularly for associations with distress or failure to eat normally during the test.

Only 27% of patients recorded a degree of distress in the upper half of the VAS. In patients with positive SI, no associations were found between eating pattern or distress during the test and symptoms of heartburn or dysphagia, presence or absence of oesophagitis or AET. However tolerance of the test was less good in young patients.

Patients showing a positive SI and normal AET have not been especially intolerant of the test. This suggests that the results cannot be categorised simply as "false negatives" and that the patients represent a distinct group with symptomatic reflux disease.


Previous studies have shown that various regions of the gut, in particular the colon and rectum, are abnormally sensitive to balloon distension in patients with IBS. However, these studies have only examined up to two anatomical regions in the same patient at any one time and thus is it not known whether all or just specific areas of the gut are abnormally sensitive. Sensory and motility responses to balloon distension of the oesophagus (O), duodenum (D), jejunum (J), ileum (I), colon (C) and rectum (R) were therefore evaluated in random order in 20 patients with diarrhoea predominant IBS (aged 22-57, 11 females) and compared with 20 matched healthy volunteers (aged 20-57, 10 females). All patients had loose stools (>3 bowel movements per day) and fulfilled the Rome criteria for IBS. In addition, patient anxiety scores were evaluated using the Hospital Anxiety and Depression questionnaire (abnormal > 10). RESULTS In accordance with previous studies, IBS patients had significantly lower sensory thresholds in the O [vol to discomfort (mL); IBS 109(60,225) geometric mean (range) v controls 175(80,325); p<0.001] and C [100(50,180) v 166(60,500); p=0.005] compared with controls. Furthermore, IBS patients exhibited significantly lower thresholds for discomfort, provoked by distension of the O [106(20) v 208(110); p<0.002], D [45(15,70) v 83(20,150); p=0.02], J [45(15,70) v 73(20,170); p<0.001] and I [38(15,120) v 55(30,150); p=0.03]. However, these sensory changes were not associated with any change in blood pressure or heart rate with calorie load.

Patients with IBS had significantly higher anxiety scores [92(19), median (range)] than controls [4.5(7,2); p<0.001], there was no correlation between their anxiety score and sensory threshold in the D (r = 0.21; p=0.39), J (r = 0.23; p=0.28), I (r = 0.38; p=0.38) and R (r = 0.41; p=0.08), with the exception of the O (r = 0.54; p=0.027). Conclusion This is the first study to confirm the suspicion that IBS represents a generalized disorder of visceral sensation. Furthermore, although these results do not exclude a sensory defect at a local level within the gut, they lend some support to the concept of there being an abnormality of the visceral afferent nervous system or its central modulation.
GUT 1995; 37 (suppl F186)

ANXIETY, DEPRESSION AND INTESTINAL TRANSIT.
DA Gorard, JE Gomborone, GW Libby, MJG Farthing. Digestive Diseases Research Centre, Medical College of St. Bartholomew's Hospital, London.

Patients with anxiety and depression often have bowel symptoms, but there have been no objective measurements of intestinal transit in patients with psychiatric illness. This study measured intestinal transit times in 21 psychiatric outpatients (5 M, median age 27y, range 17-45y) fulfilling DSM-III-R criteria for major depression and/or generalised anxiety disorder. These patients were taking no drugs and bowel symptoms were not necessary for study entry. 21 healthy controls, 6 M, 24 (19-45y) were also studied. All subjects had a structured clinical interview and completed the Beck Depression Inventory (BDI), and Hospital Anxiety (HAD-A) and Depression (HAD-D) scale. Orocecal transit time (OCTT) was measured by lactulose hydrogen breath test.

Whole gut transit time (WGTT) was measured by abdominal radiography after ingestion of radio-opaque markers on 3 consecutive days.

Results: median (range)

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th>Depression</th>
<th>Anx. &amp; depression</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>11.5 (7-19)</td>
<td>25 (10-41)</td>
<td>19.5 (18-22)</td>
<td>1 (0-7)</td>
</tr>
<tr>
<td>HAD-A</td>
<td>15 (11-17)</td>
<td>12 (7-18)</td>
<td>15 (11-16)</td>
<td>4 (1-5)</td>
</tr>
<tr>
<td>HAD-D</td>
<td>5.5 (2-10)</td>
<td>11 (9-18)</td>
<td>13 (10-15)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>OCTT (min)</td>
<td>60 (10-70)</td>
<td>110 (60-180)</td>
<td>70 (60-90)</td>
<td>75 (50-135)</td>
</tr>
<tr>
<td>WGTT (h)</td>
<td>14 (6-29)</td>
<td>49 (35-71)</td>
<td>14 (18-43)</td>
<td>42 (10-68)</td>
</tr>
</tbody>
</table>

The anxiety group had shorter transit times than both the depressed group (OCTT, p<0.01; WGTT, p<0.001) and the controls (OCTT, p<0.05; WGTT, p<0.001). Prolongation of transit time in depression compared to controls did not reach statistical significance (OCTT, p = 0.08; WGTT, p = 0.09). However in the total patient group, WGTT correlated positively with BDI (r = 0.59, p<0.01) and HAD-D (r = 0.66, p<0.001).

These measurements of transit in affective disorders are consistent with clinical impressions that anxiety is associated with increased bowel frequency, and depressed patients tend to be constipated. The findings demonstrate that mood does have a direct effect on the enteric nervous system.

GUT 1995; 37 (suppl F187)

COLONIC DISTRIBUTION OF DAILY DOSED, RADIO-LABELLED RESIN : RIGHT-SIDED RESERVOIR & LEFT-SIDED COLOSTOMY.
Hebdon JM, Gilchrist PJ, Blackshaw PE, Perkins AC, Wilson CG, Spiller RC. Dept of Medicine, University Hospital, Nottingham; Dept of Pharmacology, Strathclyde University

Early radiological studies of regional colonic residence used radio-opaque pellets which give a poor colonic image especially for regions containing few pellets. We have used repeated dosing with radio-labeled resin to provide a clear colonic outline allowing accurate assessment of regional distribution of resin.

Methods: On 4 consecutive mornings 10 healthy female volunteers ingested a Eudragit-coated gelatin capsule containing In-label labelled amebrel resin. All capsules were manufactured together so that each dose decayed at the same rate. Subjects were scanned on the morning immediately prior to dosing, and at 4, 8 and 12 h later. The distribution of label in ascending (AC), transverse (TC), descending colon (DC), and rectosigmoid region (RS) was expressed as % total colonic activity. Results (mean±SEM, n=10).

- Similar activity distributions were obtained in each of the 4 scans. Averaging the 4 scans activity was distributed as follows: AC 30±8, TC 36±6, DC 15±4, RS 19±5. The mean % in the distal colon (DC+RS) was 34, the 95% Confidence Interval 45±23 did not overlap 50%, p<0.05.

Conclusions: During the day 2/3rds of a daily dosed, enteric coated formulation lies within the proximal colon with only 1/3rd in the distal colon and only 15% in the DC. Compared with the proximal colon's reservoir function the distal colon appears to behave more like a conduit.

The descending colon appears to be the most difficult area of the colon to target with locally acting drugs.

GUT 1995; 37 (suppl F188)

DO AMBULATORY POUCH AND ANAL MOTILITY PATTERNS IN COLON POUCHES EXPLAIN POOR FUNCTIONAL OUTCOMES?
J Romanos, S Humphreys, N J McC Mortensen
Department of Colorectal Surgery, John Radcliffe Hospital, Oxford

Colonic anastomosis with a J-colon pouch formed from the descending colon is a relatively new operative approach to tumours of the middle and lower third of the rectum. This may resolve the functional problems of increased frequency, urgency, incontinence and nocturnal seepage associated with rectal excision. The aim of this study was to record the motility pattern of the neorectum, its coordination with anal canal motor activity and its relationship to functional outcome.

Fourteen patients (9 male, 5 female; median age 62, range 43-71) were assessed clinically and studied using ambulatory manometry (Gaeltec; 4 transducer system) for a median duration of 6 hours (range 6-24). Twelve patients had a functional pouch for a median period of 32 months (range 11-55) and two patients with a pouch formed 7 and 12 months previously still had their ileostomies. Seven healthy controls (5 male, 2 female; median age 40, range 33-50) were studied for a similar period.

Median day and night time stool frequency in 12 patients with a functioning pouch, was 3.3 (1-4) and 0.3 (0.2-5) respectively. Four patients complained of minor fecal leakage and 7 of incomplete evacuation. Compared with the controls the pouch group had lower resting anal pressures, median 73 (44-118) vs 100 (45-200) cmH2O and higher pressure pressures, median 4 (1.4-7) vs 15 (5-29) cmH2O. Pouchocanal pressure gradient was as high as 60 (4-114) cmH2O in pouch patients and 85 (32-100) cmH2O in the control group (NS). Incontinent patients had a even lower pressure gradient 39 vs 63 cmH2O than continent patients (p<0.01). Slow wave activity in the anal sphincter (median frequency 7 cpp; controls 16 cpp, p<0.001) was present in 12 patients (85%). "Sampling episodes" were seen in 7 patients (50%). Two incontinent patients (14%) showed spontaneous anal relaxation with a reversed pressure gradient. Large isolated contractions (>30 cmH2O and >20 sec) were seen in 10 patients (63%). Rhytmic contractions were seen in 7 (50%) patients.

These motility patterns tended to be more prominent in poor function (incomplete emptying, incontinence) pouches. Apart from a few rhythmic low amplitude contractions, no other activity was observed in non functioning pouches.

Colonic pouches represent a very promising alternative to the excised rectum, acting as reservoirs which preserve a high pressure gradient against the already compromised anal canal. In poor function pouches a lower pressure gradient and more prominent motility pattern was noted.
Liver perfusion  F189-F192

Indocyanine Green Clearance reflects the degree of reperfusion injury and accurately predicts graft function following orthotopic liver transplantation.

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Scottish Liver Transplant Unit, The Royal Infirmary Edinburgh, Scotland.

Introduction: Primary graft dysfunction remains difficult to predict. We have previously shown that indocyanine green clearance (ICG) measured at 24hrs following orthotopic liver transplantation (OLT) accurately predicts graft survival and outcome.

Aims and Materials: We evaluated the use of ICGC as a marker of graft function following OLT in 46 liver transplants (41 patients; 16 males, 25 females) and investigated its relationship with the markers of reperfusion injury during OLT. In all patients ICG clearance was measured at 24hrs; in 4 patients ICG was measured at the end of operation and 4-8 hours for 48hrs. In 24 patients repeated blood samples were taken before, during the anhepatic and reperfusion phase and up to 12 hrs following OLT to measure the levels of neutrophil elastase and reactive oxygen intermediates (ROI). All patients had normal hepatic artery DQPP-post-OLT.

Results: a)All patients with ICGC>200 ml/min (N=38) recovered following OLT and remained well. Eight patients had an ICGC<200 ml/min, four were retransplanted for graft failure, 2 died and 2 survived after prolonged hospitalisation. b) ICGC significantly correlated with ROI production and neutrophil elastase during OLT (R=0.74, p<0.01 and R=0.70, p<0.01 respectively) c) Repeated ICGC’s did not change during the first 48 hrs post-OLT. Conclusion: ICGC at 24hrs post OLT reflects the degree of reperfusion injury and accurately predicts primary graft function and outcome.

ROLE OF GMP ON HAEMODYNAMIC CHANGES DURING LIVER TRANSPLANTATION.

K. Bastia, N. Henderson, J. Dillon, A. Lee, P. Hayes
Scottish Liver Transplant Unit, Edinburgh Royal Infirmary.

During liver transplantation haemodynamic instability particularly upon reperfusion often occurs. Profound pulmonary hypertension, systemic hypotension and cardiac arrest have been reported. Changes in vascular tone due to humoral factors released upon reperfusion of the graft has been suggested as a possible mechanism. In this study we looked at the changes in cGMP, a marker of nitric oxide (NO) activity before and upon reperfusion, and investigated its possible role in the haemodynamic changes.

Methods: Measurements of cGMP by radioimmunoassay were performed on blood samples taken through a right atrial catheter from 14 patients at pre-anhepatic, anhepatic phase and post reperfusion at 30 minutes, one and two hours. Haemodynamic data recorded were mean systemic and pulmonary arterial pressures(MAP, &MPAP), cardiac output(CO), pulmonary and systemic vascular resistances (PVR,&SVR).

Results: cGMP decreased to 3.19±0.88 nmL (Mean ± SEM) upon reperfusion from a baseline level of 5.3±0.73 nmL (p<0.01). It decreased further to 1.63±0.90 nmL two hours post-reperfusion. MAP decreased on reperfusion to 74±9.8 from 88±5.4 mmHg (p<0.05), MPAP increased to 23±7 mmHg, from 17±4 mmHg (p<0.02), and PVR decreased to 8.72±0.84 L/min, from 10.3±1.67 L/min (NS), and SVR to 571±76.2 from 632±105 dyn-s cm⁻¹ (NS). The changes in cGMP correlated with MPAP (p<0.01), and PVR (p<0.01) when compared at equivalent time points.

Conclusion: The haemodynamic alterations seen in this study were comparable to those reported in literature. The significant increase in pulmonary pressure and vascular resistance correlated with the reduction in NO activity following reperfusion. This could be the initiating mechanism of further potential haemodynamic deterioration.


HAEMODYNAMIC CHANGES IN TOXIC HEPATIC INJURY.

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The hyperdynamic circulatory changes induced by acute hepatic failure are associated with multiple organ failure and a high mortality. Aim: To determine to what extent the changes in systemic haemodynamics affected hepatic haemodynamics. Methods: Experiments were performed at different times over the course of severe toxic liver injury induced in rats by galactosamine (1.1 g/kg, i.p.). Liver injury was confirmed by a prolonged INR and elevated AST. The animals (n=6-10) were anaesthetised with pentobarbitone. Mean arterial pressure (MAP) was monitored throughout. Cardiac output, hepatic arterial (HABF) and portal venous blood flow (PVBF) blood flow were measured using the radioactive microsphere technique. Hepatic arterial (DhaO₂) and portal venous (DvpO₂) oxygen delivery were calculated from blood flow values and direct measurements of arterial and portal venous blood oxygen content. Results: MAP fell from a baseline value of 115±6 mmHg (± SEM) to 99±1.3 mmHg at 12 hours and 84±1.5 mmHg at 24 hours (p<0.05), recovering to 90±3.5 mmHg by 48 hours. Cardiac output did not alter from a baseline value of 240±13 ml/min until after 12 hours and peaked at 404±18 ml/min (p<0.05) by 48 hours. Within 12 hours of galactosamine administration total hepatic blood flow increased by 60% from 3.3±0.3 ml/min to 5.3±0.8 ml/min (p<0.05), mainly due to increased PVBF. Over the next 12 hours HABF increased by 450% from 1.0±0.2 ml/min to 4.5±0.7 ml/min (p<0.01). Between 24 and 48 hours PVBF increased by a further 100%, from 2.9±0.9 ml/min to 10.5±2.2 ml/min (p<0.05). At 48 hours total hepatic blood flow had increased by 500% from baseline with 44% of the cardiac output passing via the hepatic circulation to a control value of only 21%. In control animals DvpO₂ was twice DhaO₂ (3.4±0.1 and 1.5±0.1 ml O₂/min/g respectively) but within 24 hours the hepatic artery became the dominant source of delivered oxygen (5.7±1.6 vs 9.2±1.0 ml O₂/min/g). By 48 hours oxygen delivery to the liver was split equally between the portal venous and arterial circulations (9.7±1.2 and 9.9±1.3 ml O₂/min/g). Systemic and hepatic haemodynamics returned to control values by 72 hours. Conclusion: These changes in the hepatic circulation may have important implications for the management of fulminated hepatic failure. The isotropic agents used to maintain the MAP are vasoconstrictors and may thus impair arterial blood flow and oxygen delivery at a stage when the artery is the main source of delivered oxygen further compromising cellular function and exacerbating the hepatic injury.

Clinical vs haemodynamic response to drugs in portal hypertension

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Introduction: Up to now success of drug therapy in individual patients has been based on the occurrence or non-occurrence of variceal bleeding. Recently it has been suggested that drug induced changes in the hepatic venous pressure gradients (HVPG) may reliably predict rebleeding, and that an absolute value of ≤12 mmHg or a reduction of ≥20% from baseline should be used as haemodynamic indices to target drug therapy. This approach has been reported to be successful for both primary and secondary prophylaxis.

Method: We investigated this prospectively in 62 patients with cirrhosis and variceal bleeding who were treated with a combination of propranolol and isosorbide mononitrate. Mean age was 52 years (range 20-80), 46 male, 62% alcoholic. We used the same haemodynamic criteria as above. Drug doses were increased if the haemodynamic criteria of response were not fulfilled. 9 patients had three measurements of HVPG 19 patients were excluded from the analysis because initial measurements were not available. 11 because repeat measurements were not performed (including some who bled) and 1 because of very low initial HVPG, leaving 43 patients for analysis.

Results: There were 27 haemodynamic responders, 10 non-responders. Rebleeding occurred in 9/27 (33%) responders as a mean of 226±59 days and in 4/16 (25%) non-responders at a mean of 575±154 days. Two patients bled shortly after stopping drug therapy, one in the responder and one in the non-responder group.

Conclusion: In this cohort, measurement of portal venous pressure did not predict likelihood of rebleeding. Therefore, further prospective studies need to be done to establish the predictive value of repeated HVPG measurement.
Clinical practice  F193–F199

F193

BISMUTH CARBOMER ENEMAS IN TREATMENT OF CHRONIC UNREMITTING POUCHITIS.


Antibacterial drugs are the mainstay of treatment of pouchitis, especially metronidazole which is the only drug with efficacy shown in a controlled study. However 15% of patients have chronic unremitting pouchitis despite medical treatment, with high incidence of side-effects, and recurrence within one week after discontinuation of therapy.

We report the results of an open trial of bismuth retention enemas in patients with chronic unremitting pouchitis. 12 patients (4 females, 8 males; median age 36 years, range 21-47) were studied. All of them discontinued chronic antibacterial or anti-inflammatory therapy on entry to the study. The median follow-up time after pouch surgery was 48 months (range 6-104). Diagnosis of pouchitis and its response to treatment were evaluated with the Pouchitis Disease Activity Index (PDAI), which includes clinical, endoscopic and histological criteria. Patients were treated with enemas of bismuth citrate complexed with a polycarboxylate carborner (Tillot Pharma AG Ziefen, Switzerland) for 45 days, and they were monitored for evidence of relapse at monthly intervals for 1-6 months. The median PDAI score decreased from 12 (range 9-15) to 6 (range 4-15) (p<0.002) with decreases in either the clinical symptoms and endoscopic and histologic PDAI scores (p=0.002 for all variables). Of the 10 patients who responded to the treatment (83%), only two experienced an early relapse after discontinuation of therapy (within 2 months). No side-effects were reported. Our findings suggest that a randomized, double blind trial of bismuth citrate/carborner enemas is warranted in patients with pouchitis.

F194

Treatment of Corticosteroid Resistant Ulcerative Colitis with Heparin - A report of 9 cases

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Heparin, a sulphated proteoglycan, inhibits thrombin formation and neutrophil elastase and binds chemokines. It has potential as an anti-inflammatory agent by inhibition of neutrophil activation, adhesion and endothelial penetration through these mechanisms. The long half-life of endothelial bound heparin may permit intermittent treatment. Previous reports have shown a beneficial anti-inflammatory effect of heparin in Ulcerative Colitis (Goffrey et al Lancet 1987;337:238-239).

Aims: To assess the role of heparin as a therapeutic agent in Ulcerative Colitis in an open study.

Methods: Hospitalised patients in relapse from Ulcerative Colitis and unresponsive to high dose corticosteroid therapy were treated with intravenous heparin, the dose adjusted to provide standard anticoagulant activity. This continued as subcutaneous injections on discharge, with a gradual reduction in the frequency of doses.

Results: Within one week of starting heparin 6/9 patients had shown a considerable reduction in stool frequency. After two weeks of heparin therapy stool frequency had improved from 7/day (3-11) [median(range),pre treatment] to 3/day (1-5) and by 4 weeks 7/9 were in clinical remission although one subsequently relapsed at 8 weeks while still receiving heparin. Three of the patients required elective colectomy but six remain well. Apart from bruising at s/c injection sites no complications were seen due to the anticoagulant activity.

Conclusion: The response to heparin in patients with UC resistant to standard therapy is encouraging and supports the previous uncontrolled evidence for a therapeutic effect. A controlled trial of heparin in UC is clearly indicated.

F195

LONG TERM SEQUELAE AFTER SPHINCTEROTOMY FOR ANAL FISSURE.

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Internal sphincterotomy is the standard treatment for anal fissure. It has recently been reported that this procedure may have long term sequelae such as impaired continence in up to 30% of patients.

This study investigated the long term outcome following internal sphincterotomy for anal fissure in one Hospital. Outcome was assessed by postal questionnaire, followed by consultation where requested by respondents.

Questionnaires were sent to 128 patients, Ninety nine (78%) were returned. Thirty five patients (33%) had experienced anal pain for more than 1 month post-operatively. Twenty eight (28%) complained of persistent mucus discharge, 18% had ongoing difficulty in controlling flatus, 19% had difficulty holding liquid stool.

Ten (10%) patients who replied to the questionnaire wished to be reviewed to discuss ongoing symptoms. Five of these had a recurrent fissure, all of whom were successfully treated with topical GTN cream.

Although sphincterotomy is standard treatment for fissure, a large proportion of these patients will experience either a recurrence of their fissure or a disturbance in their continence mechanism. In view of these findings, non-surgical treatment of anal fissure should be investigated.

F196

CURRENT PRACTICE - USE AND ABUSE OF CHEMICAL FAECAL OCCULT BLOOD TESTS

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INTRODUCTION. Chemical faecal occult blood (FOB) tests are liable to interference by dietary porcylases and fecal bld deg, but are routinely used by many clinicians. The aim of this audit was to assess which FOB tests were being used, the laboratory recommendations on use, and the perceived clinical indications and diagnostic value.

DESIGN. Questionnaires were posted to laboratories and consultant physicians and surgeons in an interest in gastroenterology in the West Midlands, and also to GPs in a local hospital catchment area.

RESULTS. Sixteen of the laboratories replied (80%), using a total of >20,000 tests in 1993. Seven different FOB tests were being used, and all but one were gastric tests, with the most commonly used test being Peroheme 40C (BDH) (38%). Three-quarters requested 3 faecal samples, 38% advised dietary restriction, 25% advised avoidance of oral iron supplements, and 25% reported grades of positivity. Twenty-two GPs and 32 of the consultants replied (42%). The clinical indications for routine use of FOB tests favoured by the highest proportion of GPs were (a) men with iron deficiency anaemia (IDA) (81%), (b) post-menopausal women with IDA (62%) and (c) altered bowel habit in patients >50 years (62%). The majority of the consultants requesting FOB tests for the above indications stated that a negative test result would not influence decisions on arranging further investigations. The clinical indications for routine use of FOBs favoured by the highest proportion of consultants were (a) men with IDA (46%), (b) post-menopausal women with IDA (43%) and (c) post-menopausal women with IDA (42%). The majority of the consultants requesting FOB tests for the above indications stated that a negative result would not influence decisions on arranging further investigations. FOB tests were never requested by 42% of the consultants.

CONCLUSION. The wide discrepancies in the routine use of FOB tests indicates that these tests are often used inappropriately. The optimum use of each FOB test requires evidence-based definition.
F197

CLINICAL PATTERNS OF FAMILIAL INFLAMMATORY BOWEL DISEASE: EVIDENCE FOR GENETIC ANTICIPATION?

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Introduction About 15-20% of patients with ulcerative colitis or Crohn's disease will have another family member affected, usually a first-degree relative. Both genetic and environmental factors may be pertinent. Clinical patterns of disease within families remain poorly documented, but may be valuable in understanding disease heterogeneity, and inheritance of susceptibility.

Subjects Over 200 multiply-affected families resident in the United Kingdom have identified. Clinical details were obtained from the family members and from their physicians. 54 families in whom 1 parent and at least one child were affected (a total of 27 parent-child pairs), and 155 families in which at least 2 siblings were affected (a total of 190 affected sibling pairs) were involved. Clinical characteristics were compared in these pairs of affected relatives - disease type (CD, UC or indeterminate), extent, age of onset, need for surgery and presence of extra-intestinal manifestations.

Results Parent-child pairs Parent and child were concordant for disease type in 58 of 77 pairs (75.3%), for extent in 63.6%, extra-intestinal manifestations in 70.1%, and smoking history in 85%. However the median age of onset in parents was significantly higher than in offspring (p<0.01). In 40 pairs, 60.6%, the parent was at least 10 years older than the child at diagnosis.

Sibling pairs Siblings were concordant for disease type in 81.6% of pairs, extent in 76.0%, extra-intestinal manifestations in 83.8% and smoking history in 81.3%. In contrast to the parent-child pairs, in 68.1% (111 sibling pairs), siblings were diagnosed within 10 years of each other. The median age of onset was 24.0 years.

Conclusions Consistent clinical patterns are evident in many families with familial inflammatory bowel disease. The differences in age of onset between parents and children are not readily explained by a simple cohort effect or reporting bias, and may reflect the effect of genetic factors, producing anticipation between generations.

F199

CROHN'S DISEASE: A NATIONAL STUDY OF PREVALENCE AND INCIDENCE

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Aim: To produce nationally representative data of prevalence and incidence for Crohn's disease (CD) using a primary care based survey

Introduction: There are few sources of data from which the prevalence or incidence of CD can be estimated. Previous UK measures of CD prevalence were obtained from the British General Practice Research Group and showed aged adjusted prevalence rates of 0.00036 to 0.00046 per 100,000, respectively. These previous studies of prevalence have not differentiated between those with active and inactive disease. The fourth Morbidity Statistics in General Practice (MSGP-4) represents a study of why patients in England or Wales visit their GP, it covered 60 practices in 1991-92 and a population 486,042. Methods: All GPs who reported a patient with CD were sent a questionnaire to confirm the diagnosis, and to determine when and by whom the diagnosis had been made. Supportive details of the diagnosis were sought from the notes. Those GP practices sending to the questionnaire were contacted by telephone. Results: 515 patients were reported in MSGP-4 to have CD. The episodes were obvious (80%), in 44 cases details were not available patient had moved (n=12), died (n=11) or was not identified (n=1). The diagnosis of CD was confirmed in 148 cases (88%) and refuted in 24 cases (12%), half of which were reported by one doctor. The patients in 5 cases there were no medical details (excluded from analysis), in 11 there were medical details only and in 17 there were supportive details (medical, radiological, pathological, and/or endoscopic). The mean age of patients was 44 years (SD 18) and mean duration of CD was 8 years (SD 9). There was a male female ratio of 1.15. 108 (59%) patients had required surgery for CD. 22.9% of all patients were diagnosed within the period of 1991-92 (incident cases). Conclusions: This study suggests a prevalence for CD of 18/100,000 and an incidence of 13/100,000 in England & Wales (the highest recorded)

Motility F200–F205

F200

COMPURERISED RECORDING AND DISPLAY OF OESOPHAGEAL MANOMETRY WITH VIDEO BARIUM SWALLOW

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Aim: To develop a technique, using ambulatory pressure monitoring and digital video recording equipment such that combined oesophageal manometry and barium fluoroscopy can be performed as a one step investigation in patients with suspected swallow disorders. Method: The technique uses a computerised synchronous ‘WINDOS’ display of the results. The manometry recording was made using a Gaetel EFR2 ambulatory pressure recorder while the barium swallow was recorded from a Phillips Diagnostic 66 X-Ray system connected to a personal computer (PC) with a digital acquisition system. The PC controlled both the ambulatory recorder and the digital video system enabling a synchronous review of the combined test. The examination involved intubating the patient with a 4 sensor catheter tip pressure transducer. The profile of the lower oesophageal sphincter was determined and the transducers located in the oesophagus. This was followed by the combined oesophageal manometry and barium swallow test. The ‘WINDOS’ display of the two sets of data allowed accurate step forward/ backward analysis of the relationship between bolus transit and pressure contractions. Results: The instrument system developed proved able to synchronously display the recorded digital video and manometric recordings; the ambulatory recorder and catheter tip transducer were well tolerated by the patient; the test was not difficult to incorporate into the standard barium swallow examination and the transducer did not interfere with visualisation of bolus transit. Conclusion: Those patients with combined test have one less hospital visit than normal and benefit from having the two related investigations performed at the same stage of medical treatment. The integrated review is providing new insight into the relationship between oesophageal bolus transit and synchronous pressure contractions. It also helps clarify previously poorly understood motility data and enables more appropriate therapeutic measures initiated.

Nitric oxide may influence gallbladder motility. 


The nitric oxide (NO) pathway may influence gallbladder function. Postprandial gallbladder emptying (GBE) was measured on separate occasions in 6 healthy volunteers during infusions of normal saline (P;3ml/minute), NO donors nitroglycerine (NG;mediated dose 0.05mg/kg/min) and sodium nitroprusside (SNP; 1mg/kg/min); hydralazine (H;200mg/min) as a control hypertensive agent and the NO synthase inhibitor L-NAME (L; 3mg/kg over 2 minutes). NG, SNP and H were infused in doses sufficient to reduce systolic blood pressure by 10%; L significantly increased blood pressure. Infusions were started before and maintained for 90 minutes after ingestion of a fatty meal (two egg omelette). Gallbladder volume was measured by ultrasonography.

Results: Fasting volumes were similar with all infusions. Both N and S caused significant impairment of GBE.

<table>
<thead>
<tr>
<th>Time/min</th>
<th>% fasting GB volumes±SD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>P</td>
</tr>
<tr>
<td>0</td>
<td>100±0</td>
</tr>
<tr>
<td>15</td>
<td>81±5</td>
</tr>
<tr>
<td>30</td>
<td>57±7</td>
</tr>
<tr>
<td>60</td>
<td>25±14</td>
</tr>
<tr>
<td>90</td>
<td>15±5</td>
</tr>
</tbody>
</table>

*p<0.05 (ANOVA)

Conclusion: Pharmacological doses of NO donors impair postprandial GBE.

THE INFLUENCE OF INTESTINAL TRANSIT TIME ON FAECAL PH

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Normally, short chain fatty acids (SCFAs), derived chiefly from bacterial fermentation of unabsorbed carbohydrates, keep colonic and hence faecal pH below 7. Which limits the bacterial formation of putative co-carcinogens like deoxycholic acid. The determinants of faecal pH are unknown except for high intake of undigested carbohydrates. Theoretically, speeding up colonic transit could lower pH by limiting the absorption of SCFAs or raise it by limiting their formation.

We have measured faecal pH, stool form (Bristol scale), whole gut transit time (WGTT) (using radiopaque pellets), stool weight and defecations per week on 77 occasions over 7-day periods in healthy women eating their normal diets, with monitoring of fibre intake. These measurements were repeated in 57 subjects after taking either wheat bran, senna or imodium for 8 weeks in triplets to sample this effect and volume intake. A total of 90 women were included in this study.

Results: Median value before and after senna, imodium and wheat bran supplements

<table>
<thead>
<tr>
<th>Senna (n=19)</th>
<th>Imodium (n=20)</th>
<th>Wheat bran (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Active</td>
<td>Baseline Active</td>
<td>Baseline Active</td>
</tr>
<tr>
<td>WGTT (h)</td>
<td>86±92</td>
<td>53±89</td>
</tr>
<tr>
<td>Stool weight (g/wk)</td>
<td>745±97</td>
<td>1146±90</td>
</tr>
<tr>
<td>Stool form</td>
<td>3.8 ± 4.5</td>
<td>3.5 ± 2.6</td>
</tr>
<tr>
<td>Defecations / wk</td>
<td>7 ± 8</td>
<td>7 ± 5</td>
</tr>
</tbody>
</table>

Faecal pH 7.08 ± 6.92 b 6.86 ± 0.75 6.93 ± 6.86

*p<0.001, *p<0.002, *p<0.003, *p<0.007, *p<0.016, *p<0.028, *p<0.031, *p<0.049

Intestinal transit time is a determinant of distal colonic pH, independent of diet. This finding may be relevant to the aetiology of cancer of the distal colon since the latter is more common in populations with lower stool weight, and stool weight is determined by transit time and of course dietary fibre intake. The results also confirm the relationships between intestinal transit time, stool weight and stool form.

FAT INDUCED CCK RELEASE AND EFFECTS ON ANTRAL AND GALLBLADDER MOTILITY ARE DEPENDENT ON MEAL COMPOSITION

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Background: Long chain fatty acids (FA) releases CCK but the physiological mechanisms are poorly understood. Aim: to examine the effect of nutritional and gastrointestinal responses to a FA given alone or added to a physiological meal.

Methods: After an overnight fast healthy volunteers were given a test meal on 2 separate occasions. Realtime ultrasound was performed from baseline until 60 minutes after meal to measure antral and GB circumference, antral excursion ratio (ER) was calculated as released minus contracted divided by released excursion circumference. Blood samples were taken at intervals 0-60 minutes for CCK immunoradiometric assays. Meals were Protocol 1: either vehicle (3.75 ml Tween 80 in 250 ml buffered saline, V) or fatty acid (0.034 ml oleic acid in vehicle solution, OA). Protocol 2: (OA) either chicken soup alone (360 ml, 200kcal, low (0.2%) fat, CS) or with oleic acid (quantity as protocol 1: CS+OA).

Results: Protocol 1: OA increased CCK (peak at 15 mins 6.12±1.2 pmol/l) vs V (2.4±0.2 pmol/l, p<0.05) but did not trigger fed state antral motility, sporadic antral contractions were the same after OA (mean ER 1.17±0.03) vs V (1.15±0.02). In contrast CCKbm (peak after OA 70±11 pmol/l) was not observed at any time after CCK+OA (94.3±12.6 pmol/l), 94±5 pmol/l). Significant: OA alone releases CCK and contracts the GB but does not trigger fed state antral motility, while CS alone triggers fed state antral activity without marked CCK release or GB contraction. However OA and CS in combination do not enhance CCK release or alter antral motility. We postulate that these differences of fat and CCK may be due to differences of fatty acid emulsification. This study emphasizes that the effects of fat on CCK and gastric motility depend on its mode of administration.

VISCERAL SENSATION AND EMOTION: A STUDY USING HYPNOSIS

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We have previously shown that hypnosis can be used to study the effect of different emotions on the physiology of the gastrointestinal tract. These studies showed that both anger and excitement increase colonic motility, whilst happiness led to its reduction (Lancet 1992; 340: 69-72). The purpose of this study was to investigate the effect of hypnosis on gut motility, specifically on the threshold of visceral sensation of the rectum. Both sensory and motility responses to balloon distension of the rectum were assessed in 12 patients with irritable bowel syndrome (aged 29-62 yrs, 10 females) on four separate occasions in random order during exposure to either hypnotic suggestions (H), hypnotic suggestions (H), general hypnotic relaxation (HR) or control wake conditions (C). All patients fulfilled the Rome criteria for IBS and completed a Hospital Anxiety and Depression questionnaire which allows a score to be calculated to detect the presence of abnormal anxiety or depression.

Results: Induction of HR tended to reduce rectal sensitivity [vol. to discomfort (ml): 175 (100-225), median (range)] compared with C (163 (100-200); p=0.09). This was not associated with any significant change in rectal compliance [ml/cmH, O: HR, 5.1(2.9-2.9) ml/cmH; p=0.131). In contrast, induction of H significantly increased rectal sensitivity (100 (20-200)) compared with both HR (p=0.008) and C (p=0.015). H had no significant effect on rectal sensitivity (150(100-225)). Again these changes in visceral sensation were not associated with any change in rectal compliance [ml/cmH, O: RA, 4.7(3.0-11.0), HR, 4.7(3.0-8.8)]. HA significantly increased pulse rate [beats per min: 80(64-92)] compared with H (72(60-80); p=0.003), HR (72(60-80); p=0.001) and C (68±8). HA significantly increased respiration [per/min: HA, 20(12-28)] compared with H (16(12-20); p=0.05), HR (16(12-20); p=0.008) and C (16(12-20); p=0.035). HA and HR had no consistent effect on either variable compared with control conditions. There was no correlation between the patients anxiety level and change in rectal sensitivity for any of the emotional states studied.

Conclusion: In addition to our previous observations on motility, this study now shows that emotion can also affect visceral sensitivity. These results may help with the further understanding of the interactions between the mind and the gut.
Oesophageal acidification does not affect salivary secretion, but stimulated salivary flow decreases

ACID CLEARANCE TIME

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Waterbrash is commonly experienced by patients with gastro-oesophageal reflux (GOR) and is generally attributed to an increase in salivary secretion, suggesting an oesophago-salivary reflex link. This study was designed to assess the effect of oesophageal acid on salivary secretion and the role of salivary acid clearance.

After oesophageal manometry, a pH probe was placed 5 cm above the lower oesophageal sphincter (LOS) in 10 healthy volunteers, aged 21-38 years. An additional paediatric feeding tube was placed 10 cm above the LOS to allow infusion of either 20 ml of water or 0.1 N hydrochloric acid. Acid clearance time was measured in the upright position with one swallow every 45 s, modifying the quality of the swallows (wet vs. dry), the quality of the material swallowed (saliva vs. water) and salivary flow (basal vs. stimulated by a chewing gum base). Volume, protein concentration and pH of the expectorated saliva were measured. A portable digital recorder was used for acquisition of oesophageal pH data at a sampling frequency of 0.15 Hz. (Mean ± SE).

Gum-stimulated salivary flow was higher than basal flow (26.0 ± 3.4 vs. 13.2 ± 2.0 ml/15 min; p=0.005). The presence of acid in the lower oesophagus did not affect salivary flow, its protein concentration or pH. This was true both for resting and acid-clearance stimulated secretion. Acid clearance depended on the quality of swallows and salivary flow.

Acid clearance time (min)

<table>
<thead>
<tr>
<th>quality of swallows</th>
<th>basal salivation</th>
<th>stimulated salivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>dry swallows</td>
<td>12.6±2.6</td>
<td>9.1±2.3</td>
</tr>
<tr>
<td>wet swallows (saliva)</td>
<td>6.9±1.9</td>
<td>2.3±0.2</td>
</tr>
<tr>
<td>wet swallows (water)</td>
<td>7.8±1.8</td>
<td></td>
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</tbody>
</table>

We conclude that acidification of the lower oesophagus does not affect salivary flow in healthy volunteers. The act of chewing, however, markedly decreases acid clearance time and this may be useful as a non-pharmacological treatment option in the relief of symptoms due to gastro-oesophageal reflux.

Oesophageal epithelial cells are known to express type I growth factor receptors (EGF receptors), and low levels of salivary Epidermal Growth Factor (EGF) have been found in patients with peptic ulcer disease. However, nothing is known about the levels of EGF receptor ligands in the gastric juice in gastro-oesophageal reflux disease (GORD).

Twenty four patients with proven gastro-oesophageal reflux, twelve with endoscopic oesophagitis and twelve with no oesophagitis, were studied. At initial diagnostic endoscopy, with all patients fasted for a minimum of four hours, a sample of gastric juice was aspirated and stored at 30°C. The levels of two EGF receptor ligands, EGF itself and Transforming Growth Factor Alpha (TGFα), were then measured using reverse phase HPLC.

There was no difference in the levels of EGF in the gastric juice of patients with oesophagitis and those with no oesophagitis. However, the mean level of TGFRα in the oesophagitis patients (153 ng/ml, sd 46.4) was significantly less than that in the patients with no oesophagitis (268 ng/ml, sd 75.6) (95% confidence interval for the difference between the means = 53.3 - 179).

It is concluded that patients with oesophagitis as a result of GORD tend to have low levels of TGFα in the gastric juice, and that this may contribute to the development of oesophageal ulceration.

Saliva contains several protease inhibitors, but the role played by these in protecting the normal oesophagus against damage by refluxed gastric pepsins has never been investigated. Such activity would be of particular importance if significant quantities of saliva were present in the lower oesophageal following reflux, but failed to raise the oesophageal pH above 4. The effect of saliva was studied over a range of ratios where such conditions could exist.

Whole and parotid saliva samples, from healthy volunteers were snap frozen in liquid nitrogen and stimulated gastric juice samples collected on ice following injection of pentagastrin 6 μg/kg. Proteolytic activity was assessed using a modified haemoglobin digestion assay. To assess its pH independent ability to inhibit gastric pepsins, saliva, buffered to pH 3 or 4, was added to a gastric juice, to which peptic digestion assay. Activity was assessed using a signed rank test (ranges), n=10.

**Antiproteases in control assays to which were not added, mediants and (ranges), n=10.

<table>
<thead>
<tr>
<th>ASSAY TYPE</th>
<th>RATIO OF SALIVA TO GASTRIC JUICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALIVA</td>
<td>pH 25:1</td>
</tr>
<tr>
<td>Whole</td>
<td>pH 4</td>
</tr>
<tr>
<td></td>
<td>(81-113)</td>
</tr>
<tr>
<td>Whole</td>
<td>pH 3</td>
</tr>
<tr>
<td></td>
<td>(94-106)</td>
</tr>
<tr>
<td>Parotid</td>
<td>pH 4</td>
</tr>
<tr>
<td></td>
<td>(76-119)</td>
</tr>
<tr>
<td>Parotid</td>
<td>pH 3</td>
</tr>
<tr>
<td></td>
<td>(93-113)</td>
</tr>
</tbody>
</table>

These results demonstrate that neither parotid nor whole saliva has a pH independent effect on proteolysis by gastric juice (Wilcoxon signed rank test p=0.5, p=0.2-0.5**, p=0.2-0.06***). We conclude that abnormalities of salivary antiproteases are unlikely to be important in the component of reflux oesophagitis caused by peptic digestion. However, a possible role in the control of damage caused by leukocytes remains.

MECHANISM OF GASTRO PROTECTION BY EPIDERMAL GROWTH FACTOR IN THE RAT: INFLUENCE OF CAPSAICIN DESENSITISATION AND CLOSE ARTERIAL INFUSION OF A CALCITONIN GENE-RELATED PEPTIDE ANTAGONIST ON GASTRIC MUCOSAL BLOOD FLOW

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The gastro protective effect of capsaicin occurs via stimulation of afferent neurones, release of calcitonin gene-related peptide (CGRP) and consequent gastric hyperaemia. How epidermal growth factor (EGF) protects the stomach is not entirely clear but a gastric hyperaemic effect has also been described. The present studies aim to clarify the underlying mechanism of gastro protection by EGF. Gastric mucosal injury was induced by 2 ml absolute ethanol 1/2 hour after intragastric administration of solvent, capsaicin 5 mg or EGF 25 μg in adult male Sprague Dawley rats, half of which have undergone sensory ablation. Damage was assessed macroscopically and microscopically. In an ex vivo gastric chamber preparation the effects of subcutaneous capsaicin and topical EGF on gastric mucosal blood flow was examined with or without close arterial infusion with hCGRP8-37, a CGRP antagonist. Both capsaicin and EGF reduced ethanol-induced damage in animals with intact innervation, macroscopic damage being 26.7±5.6%, 0.2±0.2%* and 8.4±1.6%* in the solvent, capsaicin and EGF groups. In capsaicin desensitised animals macroscopic damage scores were 22.2±3.2%, 19.6±3.2% and 33.6±8.7%. Microscopic evaluation showed a similar trend. Both capsaicin and EGF induced gastric hyperaemia provided sensory nerves were intact (areas under the curve were 594.8±20.9, 829.8±64.5* and 760.2±33.6* for the solvent, capsaicin and EGF groups but 608.1±29.8, 610±29.8 and 751.4±22.7 in capsaicin desensitised animals). hCGRP8-37 abolished the hyperemic effect of both capsaicin and EGF. The areas under the curve were 863.2±67.3* and 829.8±64.5* for the solvent, capsaicin and EGF groups in the control experiment but were 565.3±25.1, 549.2±22.7 and 556.7±23.3 when hCGRP8-37 was infused. Conclusion: EGF may exert its effect via capsaicin sensitive afferent neurones leading to release of CGRP and gastric hyperaemia.

*p<0.05 versus control