DOMICILIARY ENEMAS FOR OUTPATIENT SIGMOIDOSCOPY
Asha Senapaty, M.K. Thompson
St Mary's Hospital, Portsmouth.

Flexible sigmoidoscopy examines 40 cm more colon than a rigid sigmoidoscope. Its universal acceptance has been hindered by the lack of facilities available in clinics to give enemas. As a result we have performed outpatient flexible sigmoidoscopy on the unprepared bowel for many years. Although views are sometimes excellent they may be poor. This randomised controlled trial compares the effect of an enema administered at home to no preparation on the views obtained at flexible sigmoidoscopy.

Patients 118 patients were entered. There were 52 men and 66 women with a mean age of 53 years. 58 patients were sent an enema with instructions on its use and an explanatory letter prior to attending out patients. 60 patients received an explanatory letter only. 10 patients sent letters and/or enemas did not attend the clinic.

Results 94% of patients sent enemas used them. The overall percentage view of mucosa seen on flexible sigmoidoscopy after an enema was 74% and without an enema was 74% (p<0.02). The mean length of colon examined both with and without an enema was 52 cm. In the enema group the full distance could not be reached due to faeces in 15% and without an enema in 35% (p<0.02). 74% of patients found the enema easy to use. There were no complications and 4 patients had minimal soiling. In those who were not sent an enema 82% said they would have been willing to use one at home had it been sent.

Use of an enema at home prior to attending an outpatient clinic is both acceptable to the patients and safe. The views obtained are more satisfactory than without preparation and therefore is likely to enhance the diagnostic yield of the examination. We recommend that this be the normal practice prior to outpatient flexible sigmoidoscopy.

FDP109

FORMALIN TREATMENT FOR HAEMORRHAGIC RADIATION PROCTITIS
Seow-Choen F, Eu KW, Ho YH, Tay SK, Koh HS
Department of Colorectal Surgery, Singapore General Hospital.

Eight patients (7 females, 1 male) with haemorrhagic radiation proctitis were treated with endoluminal formalin. The technique used ensured minimal contact with formalin. Median age was 68 years (range 62-73 years). Seven patients had had cancer of the uterine cervix and one patient cancer of the prostate treated with radiotherapy at a median time of 30 months (range 9-46 months) previously. The median duration of time of symptomatic rectal haemorrhage before formalin therapy was 8 months (range 1-12 months). The median number of units of blood transused previously per patient was 6 (range 2-32).

Results: Time taken for formalin therapy was 20 minutes (range 10-70 minutes). One patient required repeat formalin application at two weeks. Bleeding ceased immediately in seven patients after formalin treatment. No further bleeding was noted nor was any blood transfusion needed at follow up at 4 months (range 1-6 months).

Conclusion: Formalin therapy is a simple, cheap and effective treatment for haemorrhagic radiation proctitis.

CD3 AND γδ Lymphocyte Responses to Short-Term Rectal Challenge in Gluten-Sensitive (GS) Subjects
A. Issani, A. Morgan, K.J. Merritts, M.N. Marsh
University Department of Medicine, Hope Hospital, Salford M6 8HD, U.K.

In previous studies, it has been shown that rectal mucosa in GS responds to antigen (gluten)-specific challenge with a biphasic inflammatory response, and a 6-12h peak in CD8+ intra-epithelial (IEL) lymphocytes. In GS jejunum, chronic gluten exposure also seems to evoke a rise in TCR γδ IEL. We therefore asked whether a similar phenomenon occurs in GS rectum, and attempted to evaluate its diagnostic potential. Methods: 8 untreated and 10 treated GS subjects, and 5 disease-control (DC) subjects were challenged locally with 6g gliadin. Mucosa were obtained before and 4h post-challenge and snap frozen in liquid N2-cooled isopentane, sectioned at ~5µm in a cryostat: an indirect, paired immunoperoxidase technique was employed to demonstrate CD3+, γδ+, CD19+, IL-2RA+ and HLA-DR+ cells, which were quantified in absolute terms with respect to a test area of 10µm2 muscularis mucosa. Sera were analysed for anti-gliadin antibodies (IgA and IgG) and soluble IL-2R by ELISA at 0, 2 and 4h post-challenge. Results: There was a significant rise in CD3+ IEL (but not CD8+ CD3- lymphocytes) 4h post-challenge (p<0.005): γδ+ IEL in untreated GS subjects also rose, although the increase was only just significant (p<0.05). No significant changes in neutrophils (CD15+): IL-2-R or HLA-DR-expressing cells were observed during the time-course of the challenge. ELAM-1, and especially VCAM-1, expression on microvascular endothelia within GS lamina propria became upregulated by 4h post-challenge. In sera, although anti-gliadin antibodies (A&G) were elevated in untreated GS vs DC, 4h challenge did not yield further rises in their titre, nor in further increased levels of soluble IL-2R material. Conclusions: 1. Rectal mucosal of GS subjects responds to gliadin challenge with a rise in CD3+, and to a much lesser extent, in γδ+ IEL. 2. Expression of ELAM-1 and VCAM-1 are upregulated during challenge. 3. The marked rise in CD3+ lymphocytes 4h post-challenge therefore has useful potential in the diagnosis of gluten-sensitivity: changes in γδ+ lymphocytes appear to be far less discriminating, however, in this respect.
**F213**

**y6+ T CELLS IN THE RECTAL MUCOSA FOLLOWING LOCAL GLUTEN CHALLENGE IN COELIAC DISEASE.**


The Rayne Institute, St. Thomas' Hospital and University Lambeth Palace Road, London SE1 9NH, U.K. and Department of Medicine, Hope Hospital, Manchester, UK.

Lymphocytes infiltrate the intestinal epithelium in response to gluten challenge in patients with coeliac disease. The proportion of intraepithelial lymphocytes (IEL) that utilise the y6 form of the T cell receptor is increased in coeliac disease, but their function remains unexplained.

The response of intraepithelial lymphocytes to rectal gluten challenge in coeliac (n=7) and control (n=4) subjects was studied. Rectal biopsies were taken before, 1, 2, 6, 12 and 48 hours after a challenge of 2g of Faerger's Fraction III and snap frozen in liquid nitrogen. Cryostat sections were cut, and streptavidin-biotin immune histochemistry performed using anti-y6 (Pan T-cell) and TCR61 (all y6 T-cells). Counts were expressed as IEL (mean ± 1 SD)/100 epithelial cells.

A marked rise in CD3+ IEL occurred after challenge, in the coeliac patients, peaking at 6 hr and returning to normal by 48hr (mean counts: 0hr-12.2 ± 3.4, 6hr-27.1 ± 9.4; P<0.01), with no significant changes in the y6TCR+ IEL (0hr-1 ± 0.6, 6hr-1.4 ± 0.5; NS). There were no significant changes following challenge in the controls.

Acute gluten challenge induces infiltration of the rectal mucosa by T cells in coeliac patients. This is not accompanied acutely by increased numbers of y6 TCR+ IEL, which implies that T cells utilising the y6 TCR are infiltrating the epithelium.

This study supports the hypothesis that y6 TCR+ T-cells are of importance in the early response of coeliac patients to local gluten.

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**F214**

**REDUCED BONE MINERAL DENSITY IN COELIAC DISEASE - THE NEED FOR BONE DENSITOMETRY ESTIMATIONS.**


Gastroenterology Unit and Department of Radiology, RPMS, Hammersmith Hospital, Du Cane Road, LONDON.

Coeliac disease may present with calcium malabsorption and osteomalacia, and could predispose patients to the development of osteoporosis. Women who obtain a poor peak bone mass prior to menopause are at risk of developing symmetric osteoporosis.

Our aims were to review by questionnaire our patients' understanding of these conditions and compare this with their bone mineral density (BMD) determined by dual energy X-Ray absorption (Lunar DPA).

20 women with coeliac disease were assessed, aged 36-85 years, duration of treatment 1-47 years. All but one graded their adherence to a gluten free diet (GFD) as "mostly" or "always". 5 were premenopausal and 7 of the postmenopausal group were on calcium, vitamin D or HRT. Only 5 were aware of concern about osteoporosis. 14 were members of the Coeliac Society.

BMD values were obtained in vertebral bodies (L2-L4), neck of femur and total body. There were good correlations between these three estimations (r=0.83, P<0.01) in patients 1-4, whereas tissue that expected, had BMD more than 1 standard deviation below control values matched for age/sex/weight and ethnic origin. There were no differences in this osteopoenic group compared to coeliac disease patients with normal BMD, nor any correlations overall between duration of disease, adherence to a GFD or body mass index.

We conclude that reduced BMD is prevalent in women with coeliac disease, and that its presence cannot be predicted clinically. This suggests that estimation of BMD is important in detecting those women with coeliac disease who are osteopoenic.

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**F215**

**Brain-gut axis**

TOPOGRAPHIC MAPPING AND CONDUCTION VELOCITY OF CORTICAL RESPONSES EVOKEO BY OESOPHAGEAL DISTENSION. Q. Ax, P. Fewell, J. Barlow, A. Hobson, D. Whittle, S. Alani, J. Banker, D. Thomas. Dept of Medicine, Surgery and Neurophysiology, University of Manchester and Aston University.

Background: Topographic mapping of visual and somatosensory evoked cortical responses is well described, but the topography of visceral evoked responses and their speeds of conduction remain unknown.

Aims: To identify the precise cortical topographic location and conduction velocity of afferent neural pathways from the human oesophagus to the sensory cortex.

Methods: Oesophageal stimulations were performed in six healthy volunteers using a 2cm length silicone balloon attached to a cuffed inflator capable of achieving a stimulation frequency of 1hz and balloon inflation time of 0.1ms. Cortical evoked potentials were recorded by placing 24 scalp electrodes referenced to linked ears using the international 10/20 system and topographically localised using a Concerto Brain Mapper (Dantec).

Protocol: 1) Test stimulation: Proximal and distal oesophageal stimulations were performed at two sites 10±2cm apart, 3cm below the upper oesophageal sphincter (UOS) and 5cm above lower oesophageal sphincter (LOS) respectively. 300 stimulations were averaged at each site.

2) Sham stimulations: The above procedure was then repeated with the catheter disconnected from the inflator.

Results: In the upper oesophagus, the cortical responses was clearly distinguishable from sham stimulation as a triphasic wave with its first negative peak (N1) having a mean latency of 58ms±6ms. This was followed by a delayed more general response with a mean latency of 310ms±7ms. Maximal amplitudes were localized to the vertex and 2-3cm lateral to it on each side over the sensory cortex. Responses from the lower oesophageal stimulations were identical in character and location but the onset of the early wave showed a mean conduction delay of 12.5ms (58ms vs 70.5ms p=0.03) indicating a conduction velocity of 8ms between the two stimulation sites.

Conclusion: These studies indicate for the first time that oesophageal sensation is localized bilaterally in the sensory cortex and conduction occurs via pathways whose velocit indicates transmission via myelinated fibers.

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**F216**

**THE EFFECT OF LIPID AND VISCOUS POLYSACCHARIDE ON GASTRIC EMPTYING AND FEELINGS OF HUNGER.**

S.J. French and N.W. Read, Centre for Human Nutrition, National General Hospital, Sheffield, S3 7AL.

The aim of this experiment was to investigate how the addition of lipid and/or viscous polysaccharide to a fat rich liquid meal influences the gastric emptying and hunger scored on visual analogue scaled questionnaires. Four different meals were fed in random order to 8 healthy male volunteers on separate test days separated by at least a week. The four meals were 400ml low fat (28 kcal) and high fat (+ 30g margarine, 249 kcal) beef consomme with and without the addition of guar gum (3% w/v) labelled with 1.85 MBq Technetium Tcm-99m. The addition of guar gum to the low fat soup delayed gastric emptying (17.1±1.6 vs 19.6±2.4 min; p<0.01) but only had a small effect on the time for hunger to return (31.9±1.1 vs 56.3±1.8 min; p<0.05). Nevertheless, there was a direct correlation between the delay in gastric emptying and the return of hunger (r=0.78, p<0.05) suggesting a role for gastric mechanoreceptors.

Increasing the fat content of the soup also delayed gastric emptying (17.1±1.6 vs 63.6±5.5 min; p<0.001) but had no effect on the return of hunger (31.9±1.1 vs 33.8±3.4 min; p>0.1). Significantly more of the high fat soup was present in the stomach when hunger returned (76.6±6.9 vs 40.8±6.7%; p<0.02). Addition of guar to the high fat soup produced a small delay in the gastric emptying (63.6±5.5 vs 78.3±7.4 min; p=0.053) but an pronounced delay in the return of hunger (33.8±3.4 vs 100±28.3 min; p<0.05) and a pronounced reduction in the amount of the meal left in the stomach when hunger returned (76.6±6.9 vs 54.9±9.4%; p<0.02).

In conclusion, our results show that the addition of guar gum produces the most dramatic effect on the time for hunger to return when added to a fatty soup and 2. Hunger is not just related to the amount of meal in the stomach but markedly modulated by the nutrient content of a meal.
GASTRIC EMPTYING IN AND SYMPTOMS OF ILLUSORY SELF MOTION
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Dept. of Biomedical Science and Centre for Human Nutrition, The University, Sheffield S10 2TN

Illusory self-motion (vection) induced by an optokinetic stimulus has been shown to elicit symptoms of motion sickness in susceptible subjects. These symptoms have been related to the presence of gastric mucosal electrical disturbances. We sought to investigate: (i) the effect of vection on gastric emptying; (ii) the relationship between symptomatic and gastric emptying.

Methods: Healthy male volunteers were studied, each on two occasions. After a 6 hour fast, four subjects ingested 300ml150mM saline labelled with 2Mbq 99mTc Tm Sulfur colloid. Gastric emptying was measured continuously for 120 minutes using a gamma scintillation camera. Vection was induced by viewing a rotating drum with black and white stripes around the seated stationary subject. During the test the drum was rotated about subjects for the first 30 min then removed (drum remained static during control studies). Subjects reported symptoms throughout the study; severity was assessed against an established motion sickness scale (Graybiel).

Results: Vection delayed gastric emptying, as shown in the table (figures represent mean values [n=8]):

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Control</th>
<th>Vection</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>40</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>60</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>80</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>100</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

7/8 subjects experienced symptoms which ranged from mild symptoms of motion sickness (headache, sweating) with or without epigastric sensations, through to severe nausea. No correlation was found between severity of symptoms and delay in emptying; no consistent temporal relationship existed between the occurrence of any symptoms and changes in the rate of emptying.

Conclusions: Vection delays gastric emptying and causes symptoms of motion sickness in susceptible individuals; the effect on gastric emptying occurs independently of the provocation of symptoms.


Background: Direct stimulation of the human motor cortex by externally applied electromagnetic coils has recently been developed for studying somatic motor pathways but so far has not been applied to study visceral motor pathways. We aimed to record oesophageal EMG in response to the stimulation of the human motor cortex and the extracranial vagus nerve.

Methods: Cortical stimulation (CS) was induced by a series of single pulses discharged through either a circular coil to produce diffuse, or a figure of 8 coil for focal stimulation. Vagal stimulation (VS) was performed by placing the focal coil over the neck adjacent to the jugular foramen. Oesophageal responses were detected by a catheter containing three bipolar ring electrodes placed 2cm, 5cm and 10cm below the upper oesophageal sphincter (UOS). Protocol: Ten healthy volunteers were studied. First the circular coil was used to obtain a cortically evoked oesophageal EMG response. The ability of the response to be "facilitated" by valsalva manoeuvre was then studied. The site of maximal cortical responsiveness was also mapped with the figure of 8 coil. Results: CS and VS evoked oesophageal EMG responses were obtained in all subjects. Mean latencies were 10.3ms ±0.3 vs 2.6ms ±0.2 (P<0.01), indicating a mean central motor conduction time (CMCD) of 7.7ms. Response amplitudes increased during valsalva manoeuvre and were further enhanced immediately post valsalva manoeuvre, indicating true vagal "facilitation". Mean amplitudes for CS at rest, during valsalva and post valsalva manoeuvre were 69.6mV ±13.5, 166.32mV ±32.5 and 213.8 ±49.1mV respectively. The site of maximal cortical responsiveness was lateral to the vertex, without evidence of laterality. The latency of oesophageal EMG response increased with recording distance along the oesophagus compatible with a conduction velocity of 10m/sec. A delayed response with a mean latency of 49.8ms ±1.92 was also found after VS indicating additional reflex afferent stimulation. Conclusion: Magnetic stimulation of the cortex and vagus provides a convenient non-invasive method to explore efferent neural pathways to the oesophagus in vivo with major scope for application in disease.

INFLUENCE OF ANTIDEPRESSANTS ON INTESTINAL TRANSIT IN HEALTH AND DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)
DA Gorard, TM Taylor, GW Libby, MJG Farthing
Dept. of Gastroenterology, St. Bartholomew's Hospital, London.

Psychotropic drugs are often prescribed in functional bowel disorders. Subsequent symptomatic improvement can be attributed to effects on mood, yet these drugs may alter gut transit. We aimed to compare whole gut transit time (WGTT) and orocecal transit time (OCTT) in diarrhoea-predominant IBS patients and healthy controls, and to assess the effect of a standard tricyclic antidepressant imipramine and a selective serotonin re-uptake inhibitor paroxetine.

To measure WGTT, 20 radio-opaque markers were ingested on 3 consecutive mornings and an abdominal radiograph taken on the 4th morning. OCTT was measured by lactulose hydrogen breath test. In 25 controls (median age 24y, range 18-34, 11 F) WGTT was mean ±SEM, 39 ±3.8 h. In 10 IBS patients (median age 35 y, range 24-48, 7 F) WGTT was shorter at 21.3 ±5.7 h (p<0.05). OCTT was 83 ±6 min in controls, 58 ±8 in IBS (p<0.05).

12 control subjects and 6 IBS patients had repeat transit studies after taking imipramine for 5 days, increasing the daily dose to 100 mg. Imipramine prolonged WGTT in controls from 38.7 ±5.2 h to 48±6.1 (p<0.05), and in IBS from 14.6 ±6.6 h to 41.3 ±10.2 (p<0.05). Imipramine prolonged OCTT in controls from 79 ±9 min to 98 ±8 (p<0.05), and in IBS from 63 ±10 to 89 ±8 (p<0.05). 8 control subjects underwent repeat studies after taking 30 mg paroxetine for 5 days. Paroxetine shortened OCTT from 69 ±8 min to 41 ±9 (p<0.05), but had no effect on WGTT.

In summary, WGTT and OCTT are reduced in diarrhoea-predominant IBS. Imipramine, which has anticholinergic properties and blocks neuronal re-uptake of amine, delays transit in the small bowel and colon in both health and IBS. Paroxetine, an indirect serotonin agonist accelerates OCTT, but WGTT is unaffected. Antidepressants alter intestinal transit in addition to any central effects on mood.

SLEEP DEPRIVATION AND RECTAL SENSITIVITY.
A. J. BERGIN AND N. W. READ (Centre for Human Nutrition, University of Sheffield, Northern General Hospital, Sheffield S5 7AU)

Gastrointestinal symptoms have been described in groups (eg shift workers) who experience periods of sleep deprivation. Our aim was to investigate whether sleep deprivation induced changes in rectal sensitivity and anorectal motility. The study was conducted in 16 healthy male volunteers. 8 subjects were admitted at 9am on day 1 and kept awake for the next 24 hours. The other 8 subjects were allowed to sleep overnight, otherwise the patterns of eating and activity were the same in the 2 groups.

Anorectal manometry and rectal sensations were recorded in studies carried out at 9am on 2 successive days. The studies were conducted using a water perfused multilumen catheter. Rectal sensitivity was assessed by inflation of an attached balloon, first by a series of rapid intertestaneous inflations (50ml/sec) with air at increasing volumes, and then by a slower ramp inflation (50ml/min) of the balloon with water. Subjects reported the perceived sensations during the balloon distensions. Results of rectal sensitivity:

<table>
<thead>
<tr>
<th></th>
<th>sleep deprived</th>
<th>controls</th>
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<tbody>
<tr>
<td>DD:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgle</td>
<td>150(13)</td>
<td>72(20)</td>
</tr>
<tr>
<td>Disc</td>
<td>219(16)</td>
<td>219(16)</td>
</tr>
</tbody>
</table>

* P<0.05 Results [mean(sem)]

The rectal balloon volumes to induce sensations of desire to defacate(DD), urgency(Urgle) and discomfort(Disc) during rapid intertestaneous inflations were significantly lower on the second day after a period of sleep deprivation whereas values in the control group were not significantly different. There were no corresponding differences in sensitivity during the ramp distensions or in the manometric indices.

[Note: The text is partially cut off and not complete, ending with "...sensitivity during the ramp distensions or in the manometric indices." ]
Changes in Rectal Sensitivity and Gastrointestinal Transit in Persistent Bowel Disturbance Following Salmonella Gastroenteritis. A. Bergin, T. C. Donnelly, M. W. McComb and N. W. Read (Centre for Human Nutrition, University of Sheffield, Northern General Hospital, Sheffield S5 7AU and Lodge Moor Hospital, Sheffield.)

Following food poisoning some people suffer from bowel disturbance that lingers long after the infection has resolved. In this study we examined anorectal manometry and GI transit in 8 patients (7F, 1M; age 28-71) who had persistent diarrhoea predominant IBS for at least 2 years following a bout of salmonella gastroenteritis. None had symptoms of IBS prior to the infection. All had negative stool cultures at the time of these tests. Anorectal manometry and rectal sensitivity were recorded using a water perfused multilumen catheter with an attached balloon which was rapidly inflated with air at increasing volumes. Gastric emptying of a radiolabelled solid meal was measured by gamma camera and small bowel transit by a H2 breath test. Whole gut transit was measured using multiple shaped radiopaque markers and an x-ray of a single stool.

Subjects Controls
Sensitivity(mls)
Wind: 21(3)* 42(7)
Desire
to defaecate: 37(4)* 87(6)
Urgency: 62(6)* 161(10)
Discomfort: 117(12)* 175(12)
Compliance: 3.8(3.9)* 8.1(9)
(mlsr/hr2)
GEI(12 mins): 23(5)* 98(6)
SBT(mins): 282(42) 258(18)
WGT( hrs): 37(5)* 55(5)
results: mean( sem) * significantly different from control

The subjects showed increased rectal sensitivity and decreased rectal compliance compared with a group of normal controls. They also had rapid gastric emptying(GE) and whole gut transit(WGT), but normal small bowel transit(SBT). These results point to a persistent disturbance in the gut motility and sensitivity of these patients a substantial time after their bout of food poisoning.

Familial adenomatous polyposis coli (FAP) occurs in Cowden’s syndrome (1), Bannayan-Riley-Ruvalcaba syndrome (2) and in polyposis coli kindreds, where the disease manifests as a variable occurrence of colorectal adenomas and carcinomas (3).

Some familial clusters of colorectal cancer may be due to chance, but others may be the result of shared environment or inheritance. In sporadic colorectal cancer, kindred studies suggest that most adenomatous polyps and colorectal cancers may be genetically determined. Furthermore, a dominant mode of inheritance best fits the observed incidence of colorectal neoplasia.

This study aimed to determine whether affected siblings of patients with sporadic colorectal neoplasia, as recorded by endoscopic screening, showed evidence of an inherited predisposition to colorectal neoplasia linked to the APC gene. Linked and flanking polymorphic DNA markers to the APC locus were used. Germline genotypes were determined using (CA)n repeats and the polymerase chain reaction at the loci YW5.64, CBB6.6, D3P1 and JWS. The presence of somatic changes in cancers was determined by 'Southern' blotting of RFLPs defined by probes cpl1, RCB7 and YWS.64. Analysis of shared alleles in ten affected sib-pairs of patients with colorectal neoplasia, as recorded by endoscopic screening, showed evidence of an inherited predisposition to colorectal neoplasia linked to the APC gene. Linked and flanking polymorphic DNA markers to the APC locus were used. Germline genotypes were determined using (CA)n repeats and the polymerase chain reaction at the loci YW5.64, CBB6.6, D3P1 and JWS. The presence of somatic changes in cancers was determined by 'Southern' blotting of RFLPs defined by probes cpl1, RCB7 and YWS.64. Analysis of shared alleles in ten affected sib-pairs of patients with colorectal neoplasia, as recorded by endoscopic screening, showed evidence of an inherited predisposition to colorectal neoplasia linked to the APC gene. Linked and flanking polymorphic DNA markers to the APC locus were used. Germline genotypes were determined using (CA)n repeats and the polymerase chain reaction at the loci YW5.64, CBB6.6, D3P1 and JWS. The presence of somatic changes in cancers was determined by 'Southern' blotting of RFLPs defined by probes cpl1, RCB7 and YWS.64. Analysis of shared alleles in ten affected sib-pairs of patients with colorectal neoplasia, as recorded by endoscopic screening, showed evidence of an inherited predisposition to colorectal neoplasia linked to the APC gene.

RFLP - Restriction Fragment Length Polymorphism
APC - Adenomatous Polyposis Coli
ASPIRIN AND NON-Steroidal ANTI-INFLAMMATORY DRUG (NSAID) USE AND RISK OF COLORECTAL ADENOMAS: A CASE-CONTROL STUDY OF SUBJECTS PARTICIPATING IN THE NOTTINGHAM FAECAL OCCULT BLOOD SCREENING TRIAL.  
RFA Logan, J Little, P Hawtin and JD Hardcastle  
University Dept. of Public Health Medicine and Epidemiology, and Surgery, University Hospital, Nottingham.

There is experimental evidence that aspirin and other NSAIDs can inhibit the growth of colonic tumours in rodents and two recent epidemiologic studies have found a reduced risk of colorectal cancer in regular aspirin and NSAID users. We have examined these associations in subjects participating in a large trial of faecal occult blood (FOB) screening for colorectal neoplasia. FOB +ve adenoma cases (n = 147), FOB -ve age and sex matched controls (n = 153) and FOB +ve patients without adenomas (n = 176) were interviewed at home 2 years after investigation. Unconditional logistic regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) adjusted for age, sex and social class.

The RR of a colorectal adenoma in those reporting any aspirin use (113 subjects) was 0.57 (0.3-1.0) in comparison with FOB -ve controls and 0.72 (0.4-1.3) with FOB +ve controls. In those reporting aspirin or NSAID use only (125 subjects) the RR was 0.55 (0.3-1.1) with FOB -ve controls and 0.71 (0.4-1.4) with FOB +ve controls. These negative associations increased with duration of use. The RR for the prescribed aspirin or NSAID use were 0.2 (0.06-0.8) and 0.3 (0.08-1.1) with FOB -ve and +ve controls respectively. In contrast no association with non-aspirin and non-NSAID use was evident. Thus the RRs being 1.5 (0.9-2.4) and 1.1 (0.7-1.8) with FOB -ve and +ve respectively.

Our data are consistent with the epidemiologic studies of colorectal cancer and suggest that aspirin and other NSAID's effect is to reduce the frequency of colorectal adenoma formation. Doses required may be quite small as the associations found were as strong for monthly use as for more frequent use.

ASSOCIATED DNA CONTENT OF RECTAL MUCOSA AFFECTS MUCOSAL PROLIFERATION AND RECURRENCE ADENOMA FORMATION  
P.S. Rooney, P.A. Clarke, and N.C. Armitage  
Department of Surgery, University Hospital, Nottingham. M07 2HU

Genetic changes are important in the conversion of normal flat mucosa to neoplastic tissue. Changes in mucosal proliferation are also implicated. We studied both DNA content and mucosal proliferation in rectal biopsies of 85 individuals with increased risk of colorectal cancer (CRC) (adenoma, adenoma surveillance or family history) and a group at low risk with no family history and normal colonscopy. DNA content was measured on rectal biopsies using flow cytometric analysis. Rectal mucosal proliferation was measured using the in vitro metabolism arrest technique Crypt Cell Production Rate (CCPR).

Six individuals (25%) with adenomas n24 had aneuploidy compared to 1 in the family history group n22.1 in the low risk group n12. Proliferation in individuals with aneuploidy n9 (median CCPR 3.2x106 c/hr) had a significantly greater CCPR than individuals in the low risk group who were diploid n10 (median ccpr 0.9x106 c/hr) Mann Whitney P=0.02. Three of eight individuals with recurrent adenomas (37.5%) had aneuploid DNA significantly different from none of 27 adenoma surveillance individuals in whom all was found (Fisher exact test p=0.017).

Aneuploidy was associated with a significantly raised risk of colorectal adenoma formation. The DNA content of normal mucosa may identify individuals at increased risk of recurrent adenoma formation.

THE ROLES OF BILIRUBIN DEOXYCHOLIC ACID (DCB) AND VESICULAR TRANSPORTER (CH) IN THE PATHOGENESIS OF GALLBLADDER STONES (GBS).  
SH Hussaini, M Maghsoodlo, GM Murphy, C Kennedy, JN Wass*, RH Dowling. Gastroenterology Unit & Dept. of Diagnostic Radiology, Guy’s Hosp., a Campsfield Hospital & Dept of Endocrinol, St. Bartholomew’s Hospital, London.

Supersaturation of GB bile with CH (saturation indices: CSI >1.0) and rapid nucleation of CH microcrystals (nucleation time:NT <4 days) are essential steps in GB GBS formation. However, we now know that CH is transported with phospholipids (PL) as vesicles (VCH), as well as in micelles, and that as the vesicles become unstable with high molar CH-PL ratios (VCH:PL), microcrystals of CH may precipitate. Although excess biliary DCA is thought to increase CSI, it’s effects on NT are unknown. We therefore analysed GB bile from a heterogeneous group of 30 patients (16 with CH GBS, 4 taking oral bile acids for CH GBS, 9 with no, and one with pigment, stones), chosen in anticipation of a range of CH and bile acids (BA) conjugates (as a % of total BA) by HPLC. RESULTS: By univariate analyses, CSI correlated positively with: (i) VCH:PL (r=0.78, p<0.001), (ii) VCH (r=0.65, p<0.001), (iii) cholic acid (CA) (r=0.52, p<0.01) and (iv) deoxycholic acid (DCA) (r=0.47, p<0.001) but not with chenodeoxycholic acid (CDCA). CSI correlated inversely with: (i) CSI (r=0.60, p<0.001), (ii) VCH (r=0.59, p<0.001), (iii) VCH:PL (r=0.54, p<0.001) and (iv) DCA (r=0.41, p<0.05) but not with CA or CA. Multiple regression analyses confirmed that VCH:PL was the most important parameter in determining CSI and NT, all biles with a VCH:PL <0.5 had NT <4d.

SUMMARY: (i) As the CSI increases, more CH is transported in vesicles, the VCH:PL ratio rises and the NT becomes more rapid. (ii) An increase in biliary DCA is not only associated with a rise in CSI but also with a short NT.

CONCLUSION: These results lend further support to the concept that DCA plays a central role in the pathogenesis of GB GBS.

OCTREOTIDE (OT) INCREASES THE PROPORTION OF DEOXYCHOLIC ACID (DCB) IN GALLBLADDER (GB) BILE - THE PRIME MOVER IN THE PATHOGENESIS OF OT-INDUCED GALLBLAEDER STONES (GBS)  
SH Hussaini, M Maghsoodlo, GM Murphy, C Kennedy, JN Wass*, RH Dowling. Gastroenterology Unit & Dept of Radiology, Guy’s Campus, UMDcu & Dept. Endocrinol, St. Bartholomew’s Hospital, London.

OT, a somatostatin analogue, effectively treats acromegaly but induces GBS in up to 70% of patients. Inhibition of meal-stimulated CCK release and reduced GB contraction have been implicated but we found cholesterol supersaturation, excess vesicular CH and rapid nucleation of CH microcrystals in GB bile - changes associated in non-acromegalic, non-OT-treated CH GBS disease with increased tages of biliary DCA. Since there are no data on biliary bile acid (BA) composition in OT-treated acromegals, we measured individual BA conjugates by HPLC in GB bile obtained by ultrasound-guided percutaneous needle aspiration (n17) or at cholecystectomy (n5): (i) non-acromegalic patients with CH GBS (n10), (ii) acromegals with OT associated GBS (n5), (iii) stone-free controls studied before (n5) and (iv) after 3 mo OT treatment (n2). RESULTS: The proportion of DCA (% of total biliary BA) was 12.6±5.9 (median 7.3) in stone-free controls compared with 24.2±5.9 in those with OT associated GBS and 24.7±2.2 in CH-GBS disease controls (p<0.05) while in the 2 paired studies, the % DCA increased from 13.7 ± 6.0 to 32.4 ± 21.5 respectively. The greater % DCA in both GBS groups is likely to be due to increased bacterial 7a dehydroxylation of cholic acid (CA) since those who were 50.5% compared to 38.7±3.8 and 36.54±1.4 respectively (p<0.05).

However the proportions of chenodeoxycholic acid remained unchanged at 35.5±1.1, 35.7±2.0 and 38.1±2.8 whilst lithocholate and ursodeoxycholic acid accounted for <2% in all patient groups. INTERPRETATION: (i) The increase in the % DCA in OT-associated GBS is comparable to that seen in non-acromegalic CH GBS disease. (ii) OT induces changes in biliary BA composition which predispose to lithogenic bile and GBS. (iii) The increase in % biliary DCA may result from changes in intestinal microflora or prolongation of intestinal transit, perhaps due to OT inhibition of prokinetic peptides such as CCK.
IS THERE A DOMINANT AXIS OF CONTRACTION IN THE HUMAN GALLBLADDER? 
H Wegstapel*, R Chess-Williams*, TJ Stephenson†, AM Maleed*, NC Bird*, AG Johnson* (Departments of Surgery*, Pathology and Biomedical Science*, University of Sheffield).

The dominant axis of gallbladder (GB) contraction is not known, although it is suggested that the human GB acts as a "bellows" rather than a "pump". In this study, the difference between longitudinal and circular strips in response to CCK-8 was examined.

Eight gallbladders from functioning GB were obtained from cholecystectomy. Three muscle strips parallel to the longitudinal axis and three strips parallel to the circular axis, each measuring 10 mm x 3 mm were taken from the body of the GB. They were mounted in organ baths containing Krebs solution at 37°C, pH 7.4, aerated with 95% O2 and 5% CO2, and connected to an isometric force displacement transducer-recorder, held under 1.6 g tension. A cumulative concentration-response curve to CCK-8 was obtained.

20 longitudinal and 21 circular strips were examined. Maximal contractile responses were 3.52 ± 0.20 g (mean ± standard error of mean) for longitudinal and 3.37 ± 0.32 g for circular strips. EC50 (concentration that produced 50% of maximum contraction) was respectively 6.7 (range 4.5-10.1) nM and 5.6 (4.2-6.9) nM. Differences were not significant (Student's t-test).

Histology showed a varying orientation and bundles. Due to the low number of patients and the small size of the strips, histology was not performed.

In this study the residual volume measured after gallbladder emptying in-vivo reflected contractility more accurately than the calculated ejection fraction.

EFFECTS OF PROSTAGLANDINS ON GALLBLADDER MUSCLE CONTRACTILITY IN VITRO. LJD O’Donnell, CHV Hoyle, MIG Farthing. Dept Anatomy & Developmental Biology, University College London & Dept. Gastroenterology, St Bartholomew’s Hospital, London

Prostaglandins (PGs) play a role in gallbladder smooth muscle and in the contraction of the gallbladder. They may affect the function of the gallbladder in vivo. However, the effects of the naturally occurring PGs on gallbladder contractility are poorly defined. We therefore examined the effects of the five main prostanoiadin agonists on guinea pig gallbladder contractility in vitro in order to define their rank order of potency.

Male guinea pig smooth muscle strips were set vertically in 10 ml organ baths, containing oxygenated Krebs’ solution at 37°C in the presence of 3 x 10-5 M indomethacin to prevent endogenous PG synthase. An initial tension of 1 g was applied and changes in isometric tension were measured using a force-displacement transducer. All the PG agonists produced slow sustained contractions (onset 3-5 min, plateau 5-9 min) apart from PGE2 with produced contractions which steadily declined. The thromboxane A2 mimetic, U46619 and PGE2 were the most potent agonists with EC50s of 1.5 x 10-6 M and 4 x 10-6 M respectively. PGD2 and PGE2 were the least potent with EC50s of greater than 3 x 10-5 M and 4 x 10-6 M respectively. The potency of PGF2α was also low; at a concentration of approximately 4 x 10-6 M it was equipotent with EC50 concentrations of U46619 and PGE2. A true EC50 for PGF2α was unobtainable as maximum contraction had not been achieved at 3 x 10-5 M.

Thus, the rank order of potency of the main PG agonists is U46619 > PGE2 > PGF2α > PGD2 > PGF2β. PG’s are potent stimulants of gallbladder contraction and PGF2α and thromboxane A2 are the most likely agonists under physiological conditions.
INTRAVENOUS AMINO ACIDS PROMOTE GALLBLADDER MOTILITY AND CHOLECYSTOKININ RELEASE. Zoli G, Healy J, Bullinger A, O'Donnell LJD, Clark ML, Farthing MJG. Dept. Gastroenterology & Radiology, St Bartholomew’s Hospital, London

Administration of intravenous amino acids (IVAA) is known to promote gastric acid and pancreatic secretion. The effect of IVAA on gallbladder function is uncertain, although dietary amino acids promote gallbladder emptying. We therefore determined whether administration of IVAA affect gallbladder function and cholecystokinin (CCK) release in humans.

Eight healthy fasted subjects (aged 24-36, 4F) received an intravenous infusion of 250 ml of an amino acid mixture (Synthamin 14, 85 g/l) over 30 min. Gallbladder volumes were determined by ultrasonography before and at 3 min intervals for 5 min after commencing the infusion. Blood was obtained via an indwelling i.v. cannula in the fasting state and at 10, 20, 30, 45 and 60 min after the start of the infusion. Plasma CCK was measured by a bioassay, which relies on the ability of CCK to stimulate amylase release from isolated rat pancreatic acini.

IVAA caused significant contraction of the gallbladder from a mean (+ SEM) fasting volume of 23.3±3 ml to 11.3±3 ml at 40 min after the start of the infusion (p<0.01). Mean Ejection fraction (EF) was 61±12%. Mean minimum volume after the start of infusion was 5±2 ml (p<0.01, compared to fasting). IVAA’s induced a rise in serum CCK from a minimal concentration of 1.6±0.3 pmol/l to a mean peak of 5.9±1.2 (p<0.03). Integrated 60 min CCK release was 840±130 pmol/l min. Taking a lag period of 15 min, plasma CCK and EF were significantly correlated (r=0.62, p<0.03).

Rapid infusion of IVAA is a potent stimulant of CCK release and gallbladder contraction. This observation may have therapeutic potential in situations where there is prolonged fasting with associated gallbladder inertia.

Stomach/duodenum F235-F246

PITUITARY ADENYLYL CYCLASE ACTIVATING PEPTIDE IN THE HUMAN DUODENUM. J M Sayer, J A Smith AND R G Long. Medical Research Centre, City Hospital, Nottingham NG5 1PB.

Pituitary adenylate cyclase activating peptide (PACAP) is a 38 amino acid peptide with 68% homology with vasoactive intestinal peptide (VIP). VIP is a potent stimulator of cyclic adenosine monophosphate (cAMP) in isolated human duodenal epithelial cells. We therefore assessed the effects of PACAP on CAMP synthesis in these cells. We also studied the ability of competitive VIP analogs, (1-38), (1-27), (1-27)NH2 and (3-36), to inhibit the actions of PACAP.

Epithelial cells were isolated from endoscopically obtained duodenal biopsies. They were incubated with PACAP or VIP for 5 min at 37°C. Where appropriate, the cells were preincubated with antagonists for 60 min on ice. A competitive binding assay was used to measure CAMP production.

PACAP caused a 10-fold increase in CAMP production by 1100% above a mean (SEM) basal level of 0.5±0.7 pmol/l. VIP at 10-7 M stimulated CAMP production by 160%. PACAP produced a significant (p<0.05) progressive increase in CAMP production from 10-9 M to 10-7 M.

D-n-Cl-Phe4,Leu6-VIP (1µM) inhibited PACAP- stimulated CAMP production by 50% and 10% respectively. Lys2', Pro2', Arg2', tyrosine-stimulated CAMP production by 25% but VIP-stimulated CAMP production was increased by a further 50%. Lys2', Pro2', Arg2', Tyr2'-VIP alone had no effect.

Thus PACAP is a potent stimulator of CAMP production in human duodenal epithelial cells. The differential actions of these antagonists suggest that PACAP and VIP may be acting through distinct receptors.

ABSORPTION OF FLUCONAZOLE AND INTRA CONAZOLE UNDER CONDITIONS OF LOW GASTRIC ACIDITY. S G Lim, A M Sawyer, M Hudson, J Sercombe, R E Pounder. University Department of Medicine, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3, UK

Orally absorbed anti-fungal agents are being used increasingly for local and systemic fungal infections, and adequate absorption of such drugs is important for their efficacy. The aim of the current study was to investigate the absorption of two new triazole anti-fungal agents, fluconazole and itraconazole, under conditions of low gastric acidity. Such a study is particularly relevant, as some patients with AIDS have achlorhydria.

METHODS: 12 healthy male volunteers participated in a study with a latin crossover design. Subjects were randomised to 4 different dosing regimens: itraconazole 200 mg alone, itraconazole 200 mg and famotidine, fluconazole 100 mg alone, fluconazole 100 mg and famotidine. Two doses of famotidine 40 mg, taken the evening before the study day and with the anti-fungal medication, were used to induce hypochlorhydria. There were 4 studies, 2 weeks apart to allow washout of drug. Bloods for drug levels were taken pre and at 30 min, 1h, 2h, 3h, 5h, 8h, 24h and 48h. Fluconazole and itraconazole levels were measured by HPLC.

RESULTS: 1 subject was excluded due to a rash (itraconazole).

Mean 48-h integrated serum drug concentration (mg/l ± SD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean concentration (mg/l) ± SD</th>
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<tr>
<td>Fluconazole</td>
<td>3.8 ± 2.0</td>
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<tr>
<td>Itraconazole</td>
<td>3.6 ± 2.0</td>
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There was a significant decrease in the 48-h integrated serum itraconazole concentration and the peak itraconazole concentration during hypochlorhydria (p<0.05). Hypochlorhydria did not affect the 48-h integrated or peak fluconazole concentration.

CONCLUSION: Unlike fluconazole, itraconazole absorption is decreased significantly during gastric hypochlorhydria. Consequently, the therapeutic efficacy of itraconazole may be affected by such conditions.
CONSENSUS AND CHAOS IN THE MANAGEMENT OF HELICOBACTER PYLORI

N.P. Thompson, I.L. Woolf, A.B.S. Mitchell
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To audit practice in the management of H. pylori infection questionnaires were sent to all gastroenterologists in the United Kingdom and the East Thames Region. Of 49 questionnaires sent 40 were returned, 37 completed. Histology and urease-based tests were most popular diagnostic methods, being used frequently by 51% and 49% of respondents respectively. Only 25% ever cultured H. pylori (only 1 respondent cultured routinely). Serological and breath tests were never used.

54% of respondents screen for H. pylori when a duodenal ulcer, not previously treated with an H2 antagonist, was diagnosed at endoscopy but only 39% would attempt its eradication. Where an H2 antagonist had previously been used 78% would screen for and 94% treat H. pylori. Surprisingly 73% of respondents would screen for and 65% attempt to eradicate H. pylori in non-ulcer dyspepsia.

In the attempted eradication of H. pylori, 86% of respondents used Denol but the duration of therapy varied - 2.4 and 6 weeks being equally popular. Anti-microbials were used by 92% - 90% using either amoxycillin or tetracycline and a similar number metronidazole - the period of use again variable, from 3-28 days. Advice as to when to take medication with food was given by less than half.

This survey demonstrated varying degrees of consensus in the management of H. pylori related disease and in some aspects the absence of consensus verged on chaos.

S60

INTRODUCTION: Ascorbic acid, the reduced form of vitamin C, may protect against gastric cancer and is secreted by the normal stomach. Secretion is impaired in Helicobacter pylori-associated chronic gastritis. In this study we have determined whether eradication of H. pylori restores ascorbic acid secretion.

METHOD: Fasting gastric juice and plasma samples were collected at endoscopy from patients participating in trials of H. pylori eradication for duodenal ulcer disease (113 samples) and intestinal metaplasia (18 samples) before and 1 to 12 months after treatment. The treatments used were "triple therapy", bismuth monotherapy or placebo. H. pylori status was determined by histology of at least 2 antral biopsies. Ascorbic acid and total vitamin C concentrations were determined by HPLC.

RESULTS: Gastric juice ascorbic acid was higher in patients in whom H. pylori had been eradicated (75.8 ± 12.9 μmol/l, mean ± S.E.M., n = 26) than in patients before treatment (23.5 ± 3.8, n = 45, p < 0.0001 Wilcoxon) or after failed eradication (41.2 ± 5.4, n = 60, p < 0.05). Gastric juice total vitamin C was ≥ 100 μmol/l in 10/26 eradicated cases (p < 0.01, χ²) and 4/60 cases after failed eradication (p < 0.01). The ratio of gastric juice to plasma vitamin C was greater in eradicated patients (2.38, median) than in pre-treatment cases (1.08, p < 0.01 Wilcoxon) but not cases where eradication failed (1.88, n.s.). Plasma vitamin C was higher in eradicated patients compared to the other two groups (p = 0.05 and p < 0.05 respectively).

CONCLUSION: Eradication of H. pylori is associated with increase in gastric juice ascorbic acid concentrations. Whether this is due to elevated intake, secretion or both, it may lead to increased protection against gastric cancer.

CYTOPROTECTIVE EFFECT OF ALLOPURINOL ON GASTRIC MUCOSA IN RATS

A.O. Yigit et al.
Gastroenterology Clinical of Ege University Izmir, TURKEY (Introduced by Philip Johnson)

Recent studies have shown that oxygen-derived free radicals (OFR) play an important part in damage to the cells. The enzyme xanthine oxidase (XO) is one of the potential sources of OFR in the organism. The present study was conducted in an effort to investigate the effect of allopurinol, an inhibitor of the XO enzyme, on the gastric mucosal lesions produced with ethanol in rats.

The rats (n=10) divided into three groups were given:
1. 5% allopurinol or (orogastric)
2. 10% allopurinol or
3. 1 ml of saline or

One hour later all animals were given 1 ml of 96% ethanol or and were sacrificed 1 hour later, followed by the removal of their stomachs and evaluation of the developing lesions in respect of number, length, and area.

The results showed that the gastric mucosal lesions produced with ethanol in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Area (mm²)</th>
<th>Length (mm)</th>
<th>Number</th>
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<tbody>
<tr>
<td>Salline</td>
<td>79.85</td>
<td>104.32</td>
<td>13.825.52</td>
</tr>
<tr>
<td>Allopurinol(5%)</td>
<td>20.45</td>
<td>27.72</td>
<td>5.63</td>
</tr>
<tr>
<td>Allopurinol(10%)</td>
<td>18.64</td>
<td>19.77</td>
<td>6.21</td>
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In conclusion, 5% and 10% solutions of allopurinol appear to reduce significantly (p < 0.01) the gastric mucosal lesions produced with ethanol in rats.

CHOLECYSTOKININ (CCK) EXERTS A TONIC INHIBITORY INFLUENCE ON GASTRIC ACID SECRETION AND GASTRIN RELEASE VIA TYPE A CCK RECEPTORS

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CCK was shown to inhibit gastrin-induced gastric acid secretion but its influence in the physiological control of the gastric secretion has not been established in men. In this study, loxiglumide, a potent type A CCK receptor antagonist was used to elucidate the biological effects of CCK. Blocking CCK in two groups (A and B) of 16 healthy young subjects.

In group A, exogenous CCK (1-250 μg/kg/b) and natural analog of CCK and endogenous CCK (25-500 μg/kg/b) were infused i.v. in graded doses and gastric acid secretion was measured by aspiration technique while plasma gastrin was determined by RIA.

CCK infused alone produced a dose dependent increase in acid output, but the peak response only reached about 26% and 34% of pentagastrin maximum. When combined with loxiglumide, which failed to affect gastric secretion induced by pentagastrin alone.

In group B subjects, 12-hour pH-metry revealed that the intragastric pH was between 1.5 for most of the interdigestive period. After 500 ml semi-liquid meal (Fresenius, Fresenius, Bad Honningen, Germany), the pH rose up to 6-7 and this was elevated by CCK 1250 μg/kg/b kg after being accompanied by an increase in plasma gastrin from basic 2.1 μg/l to 12.5 μg/l. After pretreatment with loxiglumide (12.0 mg/kg/b), both basal and meal pentagastrin pH values in the postprandial periods were significantly lower and lasted only a short period. Gastrin secretion was increased by twice as high as in the placebo treated controls.

We conclude that the antagonism of type A CCK receptors convert carazol from partial into full gastric-like agonist of gastric acid secretion and that endogenous CCK released by CCK cells exerts a tonic inhibitory influence on gastric acid secretion and gastrin release in humans.
SOMATOSTATIN REGULATES ANTRAL GASTRIN SYNTHESIS IN PERNICIOUS ANAEMIA

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In the rat gastric neutralisation causes hypergastrinaemia through increasing somatostatin mRNA. To test whether achlorhydria in man produces similar changes we have studied gastrin and somatostatin gene expression in normal individuals and in patients with pernicious anaemia (PA) by Northern blotting.

Endoscopic antral biopsies were taken from 5 hypergastrinaemic PA patients and 5 normal controls. The tissue was snap frozen and homogenised in acid guanidinium isothiocyanate and the total RNA extracted. 10 µg total RNA per patient was run on 1% agarose formaldehyde gel and transferred to a nylon filter. Hybridisation was with appropriate 32P labelled human cDNA probes, with correction for loading differences with an 18S rRNA probe. The results are expressed as specific mRNA/ribosomal RNA ratios.

The median (range) plasma gastrin concentration in PA patients was 500 (420–3500) pmol/l compared with 5 (3–6) in the control group. P < 0.001. Gastrin mRNA was also significantly higher in the PA patients; 1.3 (0.7–3.8) arbitrary units in the PA group and 0.2 (0.1–0.5) in normals, P < 0.001 and correlated strongly with plasma gastrin (r = 0.97, p < 0.0001). Somatostatin mRNA levels were 0.8 (0.6–2.3) in the PA group and 2.1 (1.7–6.5) in normals, P < 0.05.

CONCLUSION: Hypergastrinaemic PA patients have decreased somatostatin mRNA and an increase in antral gastrin gene expression. This strongly suggests that luminal acid modulates gastrin synthesis via somatostatin in man.

A COMPARISON OF SIZE AND PATHOLOGY OF VESSEL AND ULCER IN PATIENTS DYING FROM BLEEDING GASTRIC AND DUODENAL ULCERS. KC Lai, D Pollock, A Kalouchak, A Grandison, CP Swain. Departments of Gastroenterology and Anatomy, the Royal London Hospital, Whitechapel, London E1 1BB.

It has been suggested that patients with duodenal ulcer (DU) bleeding tend to have larger vessels compared with patients with gastric ulcer (GU) bleeding and bleeds from these bigger arteries may be more difficult to treat at endoscopy or with drugs. We therefore compared size and pathology of vessel and ulcer in patients with fatal gastric ulcer and duodenal ulcer bleeding. From a consecutive series of 16,364 postmortem examinations (1981–1990), we examined, macroscopic postmortem reports (60 in DU patients and 70 in GU patients) and histological slides, and in 25 DU patients and 18 GU patients adequate assessment and measurements could be made.

Macrosopic study recorded a vessel visible in 14/18 of GU patients vs 23/60 of DU patients (78% vs 45%, p < 0.05) and vessel size in 1 large eroded gastric ulcer vs 10 duodenal arteries. Evidence of recent major bleeding (blood in gut) was detected in 17 GU patients and in 36 DU patients (94% vs 60%, p < 0.05). Both GU and DU size were large (range 1–11.5cm vs range 0.5–7.0cm), but the GU size was significantly larger than DU (p < 0.05).

Microscopic measurements of 18 arteries in GU showed a mean diameter of 1.2, range 0.3–3.54mm, 5(27.6%) measured 1.5–3.54mm while measurements of 29 arteries in DU showed a mean diameter of 0.9, range 0.1–3.45mm, 8(27.6%) measured 1.5–3.45mm. There was no significant difference in the overall size of eroded artery (p > 0.2) between GU and DU patients nor was there any difference in size of large vessels (>1.5mm) (p > 0.2) or proportion of patients with large vessels (GU, 27.6% vs DU, 27.6%, p > 0.2). Fibrosis i.e. chronic ulceration was equally common in GU and DU patients (66% vs 64%, p > 0.2). Significantly fewer GU penetrated to the pancreas compared with DU (27.8% vs 64%, p < 0.05). This complication occurred only in chronic ulceration. Focal pathological changes were common in eroded GU and DU arteries: intramural thrombosis in 9/16 (56%) GU patients vs 17/29 (59%) DU patients and arteries in 4/18 (22%) GU vs 17/29 (59%) DU patients.

These results do not suggest that there are important differences in the nature of the pathology between patients with fatal gastric or duodenal bleeding ulcer and in particular indicate that the size of the eroded artery is similar.

REDUCED LIFE EXPECTANCY IN PATIENTS SURVIVING UPPER GASTROINTESTINAL BLEEDING

N Hudson, G Faulkner*, SJ Smith*, MJ Langman, RFA Logan, CJ Hawkey, Dept of Therapeutics, "Dept of Public Health and Epidemiology, University Hospital, Nottingham," Dept of Medicine, Queen Elizabeth Hospital, Birmingham.

Upper gastrointestinal bleeding (UGIB) is associated with an appreciable hospital mortality although subsequent long term survival is unknown. To determine this we performed a follow up study of 500 patients aged 60 years and over, admitted to the Nottingham hospitals with UGIB between 1986 and 1991. Four hundred and eighty seven patients who were alive 30 days after admission were compared with age and sex matched community controls. Information derived from general practitioner records and death certificates was available for 487 patients and 480 controls covering a mean follow up period of 34.2 months (SD 15.5 months).

There were 140 (29%) deaths in the UGIB patients compared with 58 (12%) in the control group (relative risk 2.39 [95% confidence limits, 1.84–3.14], p < 0.0001). However, only 6 of these deaths were ulcer related, most being due to other causes, principally cardiovascular and respiratory disease and non-gastric malignancy. In the UGIB group 297 (59.4%) patients had taken aspirin or non-steroidal, anti-inflammatory drugs (NSAIDs) within 3 months prior to admission compared to 203 non-users (mean age ± SD: 74 ± 8.6vs. 73 ± 8.9 years respectively). Survival from 30 days after presentation was 201 (70.0%) in patients taking aspirin or NSAIDs at presentation and 143 (72.6%) in the non-user patients, with no clear differences in causes of death.

Conclusion: Life expectancy is significantly reduced in patients who survive UGIB compared to controls. However, few of these subsequent deaths are ulcer related, and UGIB may be a marker for disease in other systems. Aspirin or NSAID use at presentation is not associated with an increased subsequent death rate.

HEALTHY MALES RECEIVING H2-RECEPTOR ANTAGONIST INFUSION AND PARENTERAL OR ENTERAL FEEDING SHOW NO DIFFERENCES IN PLASMA GASTRIN LEVELS. D. G. Morgan, N. J. P. Bell, J. Pedal, K. H. Hunt. Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada.

Patients often receive H2-receptor antagonist infusion in an attempt to prevent upper GI bleeding and may also receive enteral or parenteral feeding. The effects of such supplemental feeding on gastrin levels are not well understood. H2-receptor antagonists can maintain a consistently elevated intragastric pH when parenteral or enteral nutrition is administered simultaneously, but the effects on serum gastrin levels is unclear. Low gastric acidity is usually a stimulus to gastrin secretion. Changes in serum gastrin levels could alter gastric acid and pepsinogen secretion and affect gastric blood flow, cell turnover rates and contraction of the muscularis mucosa. These may have important therapeutic implications. This study was a randomized, third party blinded, 2-way cross over design with two arms each containing eight healthy male volunteers. Volunteers underwent two 24-hour studies. One arm consisted of enteral feeding (delivered into the duodenum) and iv saline infusion or enteral feeding (delivered into the duodenum) and iv ranitidine infusion. The second arm consisted of parenteral feeding and iv saline infusion or parenteral feeding and iv ranitidine infusion. Iv ranitidine infusion was controlled by Gastrojet (MIC AG Solothurn) to maintain a constant gastric pH 5.0. Blood samples were taken hourly for the first six hours and then 2 hourly. Plasma gastrin concentrations were measured by RIA. Integrated 24-hour plasma gastrin values were calculated from the area under the plasma gastrin, time curve. In subjects receiving enteral feeding, the mean(SD) integrated 24-hour gastrin was 10.9(7.1)pg/ml with ranitidine and 6.7(4.5)pg/ml with placebo (NS, p = 0.14). In subjects receiving parenteral feeding, the mean(SD) integrated 24-hour gastrin was 21.2(17.0)pg/ml with ranitidine and 6.8(3.5)pg/ml with placebo. In this case, the difference between groups was statistically significant (p < 0.052). No significant differences were seen therefore in plasma gastrin levels between ranitidine or plasma infusion groups receiving either enteral or parenteral infusion. Low gastric acidity did not therefore increase plasma gastrin in these subjects.
GASTRIC ACID SUPPRESSION AND HEALING OF GASTRO-ESOPHAGEAL REFUX DISEASE: CAN PHYSIOLOGICAL STUDIES PREDICT RESPONSE? N J V Bell, D W Burget, C W Howden, D G Morgan, R H Hunt
Division of Gastroenterology, McMaster University, Hamilton, Ontario.

Healing of gastric and duodenal ulcer is dependent upon the degree and duration of suppression of gastric acidity.

To determine the relationship between pharmacological gastric acid suppression and healing of gastro-oesophageal reflux disease (GERD), we have performed regression analysis. A fully recursive computer assisted literature search identified 53 randomized controlled trials assessing endoscopic healing of erosive reflux oesophagitis. Since there are few gastric acid suppression data available from GERD patients, raw pharmacoodynamic data from 11 treatment arms were reviewed. A meta-analysis of the literature on the effect of pharmacological acid suppression on oesophageal acid exposure was also performed. Intra-oesophageal pH data were included. Healing data from trials in 2024 GERD patients were matched for the analysis.

Least squares regression showed a correlation between GERD healing at 8 weeks and duration in hours intragastric pH >4 (r=0.87, p<0.05). A strong correlation was seen between healing and intragastric acid exposure expressed as % time pH <4 (r=0.82, p<0.05).

Preliminary stepwise regression analysis indicates that intra-gastric and intra-oesophageal acid exposure are correlated and that the degree of intra-gastric acidity suppression is correlated with decreased intra-oesophageal acidity. The best correlates for healing of esophagitis are expression of intragastric pH >4 and when treatment is maintained for 8 weeks. Both the degree and duration of gastric acid suppression and the length of treatment are therefore important in the healing of GERD.

Surgery F247–F255

EARLY PAIN RELIEF IN THE MANAGEMENT OF THE ACUTE ABDOMEN IS SAFE.
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Introduction - The administration of opiate analgesia by general practitioners and junior doctors to patients with acute abdominal pain seems kind but is not conventional teaching since it may mask physical signs and delay diagnosis and treatment. We conducted a randomised double blind placebo controlled trial to determine whether this is true.

Aim - 1. To determine the efficacy of papaveretum in treating pain when administered early in the acute abdomen; 2. To assess its effect on subsequent diagnosis and management.

Method - 100 consecutive patients with acute abdominal pain, of severity sufficient to warrant opiates, were entered into the study. The admitting house officer assessed their pain and abdominal tenderness using a linear analogue scale and made a diagnosis. Patients were randomised to receive a blinded intramuscular injection of either saline (n=50) or papaveretum (n=50). Patients were reviewed by the surgical registrar 1 hour post-injection who used an identical scale to assess pain and tenderness, made a diagnosis and decided management. An assessment of patient comfort and accuracy of diagnosis and management was also made.

Results - Median pain and tenderness scores were lower after papaveretum (pain score: 3.1 in treatment group, 8.1 in controls, p<0.0001; tenderness score: 5.1 in treatment group, 8.1 in controls, p<0.0001). 96% of patients were deemed comfortable after papaveretum compared to 18% after saline. Incorrect diagnoses and management decisions were made in 2 patients after papaveretum compared to 9 patients after saline. Wilcoxon paired sum test.

Conclusion - Early administration of opiate analgesia in patients with acute abdominal pain can greatly reduce pain. This does not interfere with diagnosis which may even be facilitated despite a reduction in the severity of physical signs. These patients should not be denied early effective pain relief.

ANATOMY OF THE CARDIA AND GASTRO-ESOPHAGEAL REFUX.
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It is unfashionable to consider the anatomy of the hiatal region as important in controlling gastro-oesophageal reflux. We have studied the anatomy of the cardia, with particular emphasis on its valvular structure at endoscopy, in 51 patients with and without gastro-oesophageal reflux. A further 22 patients were studied following Nissen fundoplication. The yield pressure of the cardia was also measured and the lower oesophageal sphincter assessed by conventional manometry and 24-hour pH studies. There was a significant correlation between yield pressure and the DeMeester composite score of reflux (p<0.05), but no direct correlation between yield pressure and the pressure and length of the lower oesophageal sphincter. There was a close correlation between yield pressure and the anatomy of the cardia using two different grading systems (p<0.005). Yield pressure allowed complete separation of successful and unsuccessful fundoplication and the distinction could also be made by endoscopic inspection.

The cardia is a complex structure. Its competence in controlling reflux depends as much on its anatomical form as on its function. Following surgical correction of reflux anatomical factors become even more important.

PELVIC SEPSIS AFTER RESTORATIVE PROCTOCOLLECTOMY: ALWAYS A HARBINGER OF DOOM?
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The complication of pelvic sepsis represents the Achilles' heel of restorative proctocolectomy (RP) and is without doubt a major reason for subsequent clinical failure. The aim of this study was to determine the clinical and functional outcome in patients who suffered this complication in a series of 115 consecutive RP.

Minor pelvic sepsis was defined as the development of fever and the discharge of pus per anum. If anastomotic dehiscence and/or abscess formation developed in addition to the above, it was classified as major pelvic sepsis. Eight out of 28 patients with major sepsis (P<0.001), 0 of 8 with minor sepsis, and 3 out of 79 without pelvic sepsis, eventually required a permanent ileostomy. Sixty-two of the 115 patients underwent ano-rectal function studies.

Groups: No sepsis Minor sep. Major sep.
Number/patients: 40 7 15
Rectal freq/24hr: 5 4 6
Faecal leakage: 13 2 6
(Patient)
Max.RAP(cm H2O): 65 84 65
MSP (cm H2O): 178 135 135
Max.tol.vol(ml): 277 240 250
Follow up(month): 48 32 31

Figures are median , P = N.S.
(Max.RAP:Max. resting anal pressure, MSP:Max. squeeze pressure, Max. tol. vol: Maximum tolerated volume).

As expected, the risk of clinical failure was significantly increased after major pelvic sepsis. Nevertheless, 20 of the 28 patients with major sepsis (72%) had a satisfactory outcome. Thus the development of pelvic sepsis should not automatically be considered a harbinger of doom.
POST-OPERATIVE PAIN AND ANALGESIA REQUIREMENT AFTER LAPAROSCOPIC AND MINI-CHolecystECTOMY: A PROSPECTIVE RANDOMISED TRIAL
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Laparoscopic cholecystectomy is claimed to result in less post-operative pain than open cholecystectomy, but this claim has never been tested objectively. The aim of this randomised study was to assess post-operative pain and analgesia requirement after laparoscopic cholecystectomy (LC, group n=59) and mini-cholecystectomy (MC, group 5-10 cm subcostal incision, n=60). Linear analogue pain scores (LAPS) were completed after a single interview on the 1st, 2nd, 10th and 30th post-operative day. Morphine was given by a patient controlled analgesia device for 24-48 hours as required. LAPS (0-100mm) are expressed as means (95% confidence intervals) and morphine consumption (mg/hr) as medians (interquartile range), with statistical analyses on the unpaired t-test and Mann Whitney U test respectively.

LAPS 24h LAPS 48h Morphine 24h Morph. 48h
MC 61 (54-72) 39 (30-52) 10 (3-32)
LC 43 (37-50) 28 (22-35) 24 (14-40) 0 (0-16)
P value 0.0001 0.0003 0.04 0.011

On the 10th and 30th post-operative day wound discomfort was assessed on a 4 point descriptive scale for 5 different physical movements to give a total discomfort score of 0-15. Discomfort scores were significantly less at 10 days after LC (MC 5 vs LC 2 P=0.012) but not at 30 days (P=0.76). Analgesia requirement and LAPS at 10 and 30 days were not significantly different. These data confirm that laparoscopic cholecystectomy is significantly less painful than minimal trauma open cholecystectomy.

EFFECT OF INHIBITION OF ENDOGENOUS GASTRIN ON GROWTH OF GASTROINTESTINAL TUMOURS
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Hypergastrinaemia consequent on prolonged achlorhydria underlies development of carcinoid tumours in the stomach. A number of reports have indicated that exogenous gastrin is able to stimulate growth of various transformed cell lines grown in culture or as transplanted tumours. These responses can be inhibited by high doses of proglumide, a weak non-specific antagonist of CCK/gastrin receptors. The present study was designed to establish whether growth of common GI tumours depends on endogenous gastrin. Four lines, MDCK5 (human gastric), AB22 (rat pancreatic), MG26 (mouse colonic) and CS23 (human colonic), were grown as xenografts in nude mice. Detection of high affinity G-17 binding sites and/or stimulation of proliferation in vitro by 0.1-1 nM gastrin was used to indicate the presence of functional gastrin receptors. Two different strategies of inhibiting the action of gastrin were used; synthetic receptor antagonists (M24624 and M26770) in the form of slow release depots and immunoneutralisation with either a monoclonal antibody (CURE Gas-93) or polyclonal antisera (ICI-925 and Dako-Patts) given i.v. Groups of 7-10 mice were treated from the day of tumour implantation and growth measured for a period of 18-36 days. All treatment regimes were demonstrated to inhibit the action of gastrin as evidenced by abolition of its ability to stimulate acid secretion. However, none of the treatments influenced growth of any tumours with the exception of ICI-925, an antiseraum which selectively bound to the N-terminal region of gastrin, which markedly inhibited both AB22 and CS23. Although these findings are largely negative, gastrin is but one of numerous growth factors capable of stimulating GI tumours. It therefore seems unlikely that inhibiting gastrin will have a major impact in therapy of GI cancer.

WHICH PATIENTS SHOULD HAVE LAPAROSCOPIC APPENDICECTOMY?
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Laparoscopic appendicectomy (LA) is advocated because of reduced hospital stay and peri-operative morbidity. However, not all cases are suitable for a laparoscopic approach. We have analysed our results to determine factors which affect outcome.

Data was obtained prospectively in 106 consecutive patients with suspected acute appendicitis. Laparoscopy was performed in all and removal of the appendix attempted when the diagnosis was confirmed.

Appendicectomy was indicated in 100 patients and was successful in 85%. The remaining 15% underwent conversion to open operation. Failure of laparoscopic treatment was most frequently associated with symptoms of more than 48 hours duration; 10/15 patients (67%) in the conversion group versus only 5/85 (6%) in whom laparoscopic appendicectomy (LA) was successful (P<0.05). Four (40%) of the conversions had a palpable mass preoperatively; there were none in the LA group. Other reasons for conversion were inability to visualize a retro-ileal appendix in 2 cases, intraoperative complications in 2 cases and inflammation involving the caecum in one patient.

We conclude that laparoscopic appendicectomy is most suitable for patients with symptoms of less than 48 hours duration.

REMOVAL OF BULKY OR STONE-LADEN GALLBLADDER AT LAPAROSCOPIC CHOLECYSTECTOMY: THE SIGMOIDOSCOPIC TECHNIQUE
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Removal of a stone-laden or grossly diseased gallbladder through the abdominal wall at laparoscopic cholecystectomy is a problem. Vigorous traction can tear the gallbladder causing wound contamination, spillage of calculi or tissue to drop back inside. This study compares two techniques for managing the problem.

Of 60 consecutive patients undergoing laparoscopic cholecystectomy, the gallbladder was difficult to extract in 22 (36%). Either one incision was extended (n=12) or the epigastric cannula was replaced with an adapted sigmoidoscope inserted through the same track (n=10).

Of those having wound extension, bile or stones were spilt in 9 (75%) cases and in one a large stone fell back inside the abdomen; bleeding from the wound occurred in six (50%) - all stopped spontaneously. Of those having per-sigmoidoscopic removal, no stone or bile spillage occurred and in 9 (90%) cases the cannula was kept in situ. There was no statistically significant difference in hospital stay or analgesic requirement in the two groups.

The advantages of this method are simplicity, reduced wound contamination and easy restoration of pneumoperitoneum after gallbladder removal. The technique is of value in selected cases where difficulty in removing a bulky or severely diseased gallbladder through a standard portal is anticipated.
THE COST IMPLICATIONS OF LAPAROSCOPIC VS OPEN CHOLECYSTECTOMY
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Laparoscopic cholecystectomy has become the treatment of choice for symptomatic gallstones despite few comparative studies with the open operation. This study has analysed the cost to the health service of laparoscopic vs open cholecystectomy.

60 consecutive patients with symptomatic gallstones were randomly allocated to either laparoscopic or open cholecystectomy, based on the availability of laparoscopic equipment. The cost of their treatment was then calculated including the operating time, instrument use, staff costs and in-patient stay. Finally the financial implication of using disposable rather than re-usable instruments was assessed. Results were compared between groups using a Mann Whitney U Test and median values are shown.

30 patients had a laparoscopic procedure of which 6 were converted to open. Of the 30 patients having open surgery 26 had a standard cholecystectomy. The laparoscopic cholecystectomies took longer to perform than the open operation (119 vs 68 min, p<0.01) and therefore the staff and theatre costs were higher (£1236 vs £651). The laparoscopic cholecystectomy group (n=24) had a shorter and therefore less expensive hospital stay than those undergoing an open procedure (n=26) (3 vs 6.5 days, p<0.01) (£702 vs £1821).

Overall the mean treatment cost for laparoscopic cholecystectomy with re-usable instruments (£1638) was lower than an open cholecystectomy (£2172). However with disposable instruments (clip applicator, ports x 3 and scissors) the mean cost saving per patient of £234 is converted to an increased expenditure of £226.

Laparoscopic cholecystectomy may only be cost effective to the health service if re-usable instruments are employed.

ILEOSTOMY PATIENTS - THEIR QUALITY OF LIFE AND PSYCHOLOGICAL MORBIDITY
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Recent advances in pouch surgery to improve the quality of life of patients undergoing total colectomy for ulcerative colitis have opened the debate regarding the effect of the ileostomy on the patients quality of life.

We examined the patient's quality of life and also assessed psychological morbidity using a postal questionnaire for ileostomates. The questionnaire (n=113) was designed to find out the effect of the ileostomy on the patients eating habits, social and daily activities and the use of medication in controlling ileostomy effluent. A copy of the General Health Questionnaire (GHQ 30) was included to detect any psychologically morbidity.

82 patients returned the completed questionnaire giving a response rate of 72.5%. Only 39 patients answered specifically the 'indication for surgery question': 36 patients had surgery for ulcerative colitis and 13 patients for Crohn's disease. The presence of the ileostomy had no effect on the patients daily and social activity as compared to their status before surgery. The GHQ score with a threshold of 4/5 as verified by Goldberg was used for analysis of the results. Only 3 patients (4.3%) had psychological morbidity.

We conclude that panproctocolectomy and terminal ileostomy, in patients with inflammatory bowel disease, had little psychological morbidity and also did not significantly affect the patients' quality of life.

Since it is now very unlikely that prospective randomised trials could be mounted to compare procedures, surgeons will have to rely on audit techniques such as those outlined in this paper to evaluate their results with regard to the outcome of restorative pouch procedures.

THE EFFECT OF GONADECTOMY (ORCH OR OOPH) Vs SIALADENECTOMY (SIAL) ON EGF LEVELS IN THE STOMACH, SMALL INTESTINE AND COLON.
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It is recognised that testosterone and oestrogen affect the expression of mRNA for EGF and production of the peptide in the submandibular gland but little information is known of their effects on EGF in the gut.

We studied the effects of gonadectomy ± sialadenectomy on EGF concentration in the gut measured by specific RIA (μg EGF/g wet weight) 4 weeks after surgery in 7 wk old mice (n=12 for each group) compared with sham operated controls. In the stomach orchiectomy (or) significantly decreased [EGF] by 2 fold (p<0.05) and orch + sial > 50 fold (p<0.001); ooph + increased [EGF] by 5 to 9 fold (p<0.001), and ooph + sial reduced [EGF] by 1.4 to 2.6 fold (p<0.05). In the small intestine (S.I) orch reduced [EGF] by 1.6-2.3 fold but orch + sial produced a 6-9 fold decrease (p<0.001); ooph had no effect at 7 weeks but increased [EGF] by 1.3-1.5 fold at 11 wks (p<0.05) in S.I.; ooph + sial at 11 weeks decreased [EGF] by 3.4-5 fold in S.I. (p<0.001). In the colon orch alone decreased [EGF] by 9.6 fold at 7 wks and by 7.4 fold at 11 wks (p<0.001); orch and sial produced greater reduction by 13.6 fold at 7 wks and by 10.5 fold in [EGF] at 11 wks. Ooph alone increased [EGF] by 2 fold in the colon (P<0.05) whereas ooph + sial produced a 5-7 fold decrease in colonic [EGF] (p<0.001). We conclude that [EGF] in the gut is greatly influenced by testicular - ovarian secretion removing the former decreasing the growth factor concentration, the latter increasing it significantly. In addition removal of the submandibular glands together with oroph or orch always resulted in significantly lower immunoreactive [EGF] in all regions of the gut suggesting a secretory and regulatory role in this species.

Non-steroidal --- Anti-inflammatory --- Drugs --- inhibit Gastric Cell turnover
Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used and therapeutically effective. Gastric anti-inflammatory effects are a complication of chronic ingestion. The mechanism of gastric damage by NSAIDS is complex. It is thought that there is inhibition of prostaglandin and epithelial cell regeneration by chronic NSAID use.

The aim of this study was to assess whether gastric cell turnover was affected by chronic NSAID ingestion.

Twenty patients presenting for endoscopy were studied. Eleven patients were on chronic NSAIDS (daily > 3 months) for osteoarthritis and there were 9 age-matched controls not on any medication. Four antral biopsies were taken from each patient and in an in vitro method of Bromodeoxyuridine (BrdU) uptake and immunohistochemistry was applied to the gastric tissue. BrdU is an analogue of thymidine which incorporates into DNA during the S-phase of the cell cycle. Ten entire gastric glands of greater than 100 cells were counted and the labelling index percent (LIX) calculated as a percentage ratio of proliferating cells to the total number of cells in the gland.

Although upper gastrointestinal endoscopy was macroscopically normal in the NSAID group, seven of the 11 patients had histological evidence of gastritis. In the control group, endoscopy and histology specimens were normal.

There was a significant difference in the LIX between the NSAID and control groups (p<0.001). The mean LIX for the NSAID group was 3.90 (SEM 0.19) and that for the control group was 4.74 (SEM 0.72).

These results suggest that chronic NSAID ingestion reduces gastric cell proliferation. This leads to a failure of the normal reparative process and is likely to contribute to the high prevalence of NSAID gastropathy.
IN VITRO NEUTROPHIL SHAPE CHANGE INDUCED BY COLONIC HOMOGENATES IN COLITIS: INHIBITION BY LEUKOTRIENE B4 RECEPTOR ANTAGONIST-SC41930.

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Leukotriene B4 (LTB4) is a neutrophil chemoattractant in inflamed mucosa and this study addresses the extent of the LTB4 contribution to the neutrophil motile response. Neutrophils when exposed to chemotactic stimulus change shape from spherical (stationary) to amoeboid (motile) morphology (J Immuno Methods 1985:81:229). The aim of this study was to investigate whether LTB4 accounts for the majority of the neutrophil shape change (NSC) induced by inflamed colon homogenates. Methods. Inflamed and uninfamed colonic mucosa was obtained at operation (3 ulcerative colitis 1 Crohn's colitis and 2 colonic neoplasia). Tissue was homogenised in Hank's balanced salt solution and the supernatant used to stimulate neutrophils from healthy volunteers. NSC was assessed as the percentage of amoeboid forms

The specific LTB4 receptor antagonist SC41930 (10^-7 M) was used to inhibit induced responses. Results. LTB4, 6.4x10^-10 M, induced mean 49.2% NSC this was inhibited to negative control levels (-1% below control) (C1-7%) to +5.2% by SC41930. Intra and inter observer differences on repeated counting showed SD 3% and 2.7% respectively. Inflamed tissue homogenate at 1.88 mg/ml (mean) induced 50% NSC; uninfamed mucosa homogenate 5.4ng/ml induced 50% shape change (90% C1 for difference 0.04 to 7.09; p=0.1). SC41930 inhibited the 50% NSC induced by inflamed colitic mucosa by 97.5% (95% CI 76% to 119%). This was more than the 56.5% reduction in NSC with SC41930 and uninfamed mucosa (difference 41% p=0.05).

Conclusions. Inflamed colonic mucosal homogenate tends to induce greater NSC activity than uninfamed colonic mucosal homogenate; neutrophil shape change induced by mucosal homogenates of inflamed colon is LTB4 dependent. LTB4 is an important mediator of neutrophil motile responses to inflamed mucosa and inhibitors may be therapeutic in colitis.

LACK OF CORRELATION BETWEEN BROMODEOXYURIDINE AND PCNA LABELLING IN GASTRIC BIOPSIES

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PCNA is increasingly used as a marker for cell proliferation. However, as it has a half life of 20 hours, PCNA labelling will overestimate the number of actively proliferating cells. Bromodeoxyuridine (BrDU) labelling is a more specific marker of cell proliferation. Using pulse labelling and immunohistochemical staining of gastric biopsy material we have compared BrDU and PCNA labelling in 12 endoscopic biopsies (7 antrum, 5 body).

For the purposes of this study, the gastric glands were divided into 3 zones; zone 1 representing the gastric pit, zone 2 the isthmus, and zone 3 the base of the gland. The proportion of PCNA positive cells was much greater in all biopsies (range 60-90%). BrDU positive cells were virtually all confined to zone 2 (0-16% of cells in this zone were positive) whereas PCNA positive cells were present in all 3 zones (1 = 22.9%-82.7%, S = 51.4%-90.1%, 3 = 0%-66.9%). A comparison of PCNA versus BrDU percentage positivity was made for each zone in each biopsy. There was no correlation at any level. For the purposes of this study we took BrDU staining to be the gold standard for cell proliferation. We conclude that PCNA does not accurately reflect cell proliferation in gastric biopsies.

EFFECT OF NIFEDIPINE ON ORGANELLAR MARKER ENZYMES IN CARBON TETRACHLORIDE (CCl4)-INDUCED CIRRHOSIS IN RATS

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Nifedipine has a protective effect upon hepatocytes subjected to ischaemia-, toxic- and heat-induced damage, possibly by preventing a damaging influx of Ca2+. The effect of nifedipine upon the cirrhotic liver was examined by the assay of marker enzymes in serum and liver homogenates. Cirrhosis was induced by treatment with phenobarbitone in drinking water and weekly intra gastric doses of CCl4 (2 groups of 15 rats for 9 weeks). One group was then fed with a pellet diet containing nifedipine (1000 ppm) and the other with a control diet. After 6 weeks the rats were killed and enzyme activities measured.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Serum activity</th>
<th>Liver homogenate activity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nifedipine treated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td>N-acetylgalactosaminidase</td>
<td>1.201 ± 0.015</td>
<td>1.506 ± 0.04</td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>15.521 ± 0.083</td>
<td>18.544 ± 1.854</td>
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<tr>
<td>α-galactosidase</td>
<td>2.129 ± 0.020</td>
<td>2.046 ± 0.032</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>91.966 ± 7.649</td>
<td>84.176 ± 11.5</td>
</tr>
<tr>
<td>α-glucosidase</td>
<td>2.204 ± 0.129</td>
<td>1.736 ± 0.026</td>
</tr>
<tr>
<td>Neutral α-glucosidase</td>
<td>0.683 ± 0.006</td>
<td>0.654 ± 0.02</td>
</tr>
<tr>
<td>Malate dehydrogenase</td>
<td>35.876 ± 39.599</td>
<td>33.972 ± 7.889</td>
</tr>
</tbody>
</table>

Nifedipine causes a rise in lysosomal enzymes in liver, implying enzyme induction. Alkaline phosphatase and microsomal enzymes also rise in liver (contrary effects to those observed with the induction of cirrhosis), suggesting a protective effect on the plasma membrane and microsomes. Serum MDH falls, which could represent a membrane stabilising effect. Nifedipine treatment may provide beneficial effects in the cirrhotic liver.
CONCENTRATION AND TIME RESPONSE RELATIONSHIPS BETWEEN EXPOSURE TO HYDROGEN PEROXIDE AND INJURY TO A COLONIC EPITHELIAL CELL LINE (HT-29)

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Epithelial cell injury in colonic inflammation is, at least partly, caused by reactive oxygen metabolites (ROMs), however the mechanisms underlying injury are not understood. In this study a model system of intestinal epithelial injury due to ROMs has been developed and the time course of events following oxidative injury studied. HT-29 subclone 18 C1 cells (a cell line derived from a human colonic carcinoma) were exposed to graded concentrations of H2O2. Cellular integrity was assessed by intracellular ATP content, the MTT test (an assay of mitochondrial function and cell number), crystal violet staining (an assay of cell number only), trypan blue and ethidium bromide staining (both assays of plasma membrane integrity). Loss of intracellular ATP was the earliest change detected. Exposure of cells to 10 mM H2O2 for 150 sec caused a 46% loss of ATP content while no loss of cellular integrity could be detected by the MTT test, trypan blue staining or ethidium blue staining. However exposure to 0.1 mM H2O2 for 1 hr caused a 56.5 ± 10 loss of integrity as assessed by the MTT test while there was only a 14.1 ± 6.9 reduction in cell number (crystal violet). There was complete inhibition of cellular division following exposure to 1 mM H2O2 for 1 hr demonstrating that injury from this concentration of H2O2 is irreversible. Exposure to 90 mM H2O2 for 2 hours caused lysis of only 27% of cells as assessed by both trypan blue and ethidium bromide staining demonstrating that HT-29 cells are more resistant to cellular lysis by H2O2. Aminotriazole (0.5 mg/ml), an inhibitor of cellular catalase, increased injury to 1 mM H2O2 (69.3 ± 8.3 versus control 41.6 ± 7.1, p<0.0001). This was confirmed by direct assay of catalase activity in HT-29 cells of 116.9 ± 18.4 U/mg protein (n=5). We conclude 1) that changes in cellular energy metabolism are an early event in cellular injury while 2) cellular lysis is a late event, 3) cells are protected against H2O2-induced injury by cellular catalase and 4) that exposure of HT-29 cells to H2O2 is a good model of oxidant injury in intestinal epithelial cells.

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EXPRESSION OF PLASMINOGEN ACTIVATOR INHIBITOR TYPE-2 AND ELASTASE IN HUMAN PAPILLITIS

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The peritoneum can be shown to possess fibroblastic activity which is thought to play a role in the prevention of intra-abdominal adhesion formation. Recently extracts of normal peritoneum tissue have been shown to contain reduced plasminogen activator activity necessary to increased levels of plasminogen activator inhibitors 1 and 2 (PAI-1, PAI-2), but the site of production of these molecules remains unclear. The aim of this study was to localise the production of PAI-1 in appendix tissue using in-situ mRNA hybridisation.

Sections of normal (n=2) and inflamed (n=6) appendix were hybridised with a cDNA oligonucleotide labelled probe and detected using a specific anti-digoxigenin antibody labelled with alkaline phosphatase. PAI-1 production was localised to both the mesothelial and sub-mesothelial blood vessel endothelium in all inflamed appendix samples. Cell identities were confirmed using immunohistochemistry directed against mesothelial and endothelial markers. Staining was not seen on sections of normal appendix incubated with PAI-1 probe or on control hybridisations with plasmid DNA and PAI-1 probe following ribonuclease digestion.

The identification of the cells responsible for the production of PAI-1 in inflamed peritoneum increases our understanding of the pathophysiological changes in fibrinolytic activity which lead to adhesion formation.

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Endothelial metaplasia in chronic active gastritis—any correlation to Helicobacter pylori infection?

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INTRODUCTION: The criteria most widely applied to categorize different endometriomas are whether endomestrioma continuity is maintained or how endometrioma discontinuity is achieved. We have previously shown that in the case of HB endometriomas do not undergo metaplasia while in contrast this change has been demonstrated to occur in liver cirrhosis and in the formation of tumor vessels. The aim of the present study was to assess the influence of chronic active gastritis on endometrioma differentiation. In this context, for the first time the monoclonal antibody HB-1 and the presence of Helicobacter pylori; cryosections 5 µm were treated with trypsin and stained by immunoperoxidase technique.

RESULTS: In chronic active gastritis and in controls endometrioma cell express HB-1, a marker specific for continuously growing endometrioma cells. For HB-1 an mAb specific for discontinuously growing cells, we observed no immunohistological staining in controls. In contrast, in eight of eleven cases of severe chronic active gastritis (HI-II), we found a low to moderate expression for the monoclonal antibody HB-1, which correlated with microscopical grading of inflammation. All of these patients suffered from Helicobacter pylori infection. In three cases of severe chronic active gastritis neither staining for HB-1 nor H. pylori infection was demonstrable.

CONCLUSION: Our data show for the first time that in patients with chronic active gastritis endometrioma cells are definitively differentiated and can undergo metaplasia. Preliminary results suggest a possible relationship between endometrioma metaplasia and H. pylori infection in chronic gastritis grades H-I-HII. More studies will be necessary to further elucidate the way in which endometrioma cells may alter their phenotype in response to H. pylori.
A ROLE FOR METALLOPROTEINASE ENZYMES IN A RABBIT MODEL OF CHRONIC INFLAMMATORY COLITIS.
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Crohn's disease is associated with significant connective tissue turnover. Breakdown of the extracellular matrix (ECM) is probably carried out by the matrix metalloproteinases, which are able to degrade all the components of the ECM. Normally their activity is tightly controlled by tissue inhibitor of metalloproteinases (TIMP), but in pathological conditions excessive activity of these enzymes may lead to tissue destruction.

We have investigated the role of the metalloproteinases and their inhibitor TIMP in the pathogenesis of hapten induced chronic inflammation and ulceration in rabbit colon. Frozen sections were stained with an indirect immunolocalization technique using an FITC-labelled second antibody. Collagenase, gelatinase and a lesser extent stromelysin were all observed on the ECM in regions of mucosal ulceration and smooth muscle cell proliferation 24 hours after initiation of colitis. At 72 hours and one week the expression of collagenase declined and from two weeks until the ulcers resolved stromelysin and gelatinase were found at the junction of normal and ulcerated tissue. TIMP was present after 72 hours and remained until the ulcers resolved. None of the enzymes or TIMP were expressed in normal colon.

The model has allowed us to establish a pattern of expression with time; not feasible with human tissue. Comparison of our study with Crohn's disease has shown close agreement; extensive expression of stromelysin and gelatinase. Collagenase, however, was not seen in human Crohn's possibly because tissue from early disease was not examined. Modulation of these enzymes could provide the basis of an alternative treatment.

TECHNETIUM (Tc) HMPAO WHITE CELL SCANNING CAN DISTINGUISH BETWEEN CROHN'S AND ULCERATIVE COLITIS
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Tc HMPAO white cell scanning can be used to assess both the extent and activity of Crohn's and ulcerative colitis (UC). The distinction between these two conditions has important implications for management and prognosis.

The aim of this study was to distinguish between Crohn's colitis (CC) and UC using TcHMPAO scan criteria alone and to compare this result with the final clinicopathological diagnosis.

30 consecutive positive TcHMPAO scans of colitis patients (15 CC, 15 UC) were analysed blindly. Scans were scored according to the presence or absence of the following diagnostic features: predominantly right sided disease (+1,0), ileal disease (+1,0), rectal sparing (+1,-1), skip lesions (+1,0), perianal disease (+1,0) and predominantly left sided disease (-1,0).

All of the patients with CC produced a positive score (1-4) and all of those with UC a negative score (-1 or -2). (CC vs UC p<0.01).

Interestingly two patients initially with indeterminate colitis scored positively, both of whom subsequently developed histological features of Crohn's disease.

Tc HMPAO white cell scanning which is a safe, noninvasive test, can reliably distinguish between Crohn's colitis and ulcerative colitis.

IS THERE AN ENTITY TERMED 'COELIAC PROCTITIS'?
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That rectal mucosa of untreated coeliac disease (CD) patients may either be subject to lymphocytic infiltration following exposure to wheat digesta in the faecal stream, or manifest a non-specific proctitis (akin to idiopathic ulcerative proctitis), has often been suggested in the past. In order to evaluate these claims, rectal mucose were analyzed from a prospective series of untreated CD patients and compared with treated CD patients, and a series of disease-control (DC) patients. Methods: Rectal mucose were taken from untreated CD patients, and compared with those from 11 treated CD and 10 DC subjects. For cytologic studies, mucose were fixed in glutaraldehyde, processed through Epon, sectioned (thick sections) and stained with toluidine blue. Sections were quantitated by computerised image-analysis. Other specimens were snap-frozen in liquid N2-cooled isopentane: cryotome sections (5-6μm) were used in a paired immunoperoxidase technique for visualization of CD3+, γδ+ IL-2R+, CD15+ and HLA-DR+ cell populations: these were standardized and enumerated with respect to a constant test square (10μm2) of muscularis mucosae, and analyzed by non-parametric statistical results. Results: There was no difference between either group in terms of volumes of surface or crypt epithelium, or lamina propria: although on histologic criteria lymphocytes and plasma cells were elevated, differences were not significant. Mast cell populations were elevated and remained so during treatment. Use of anti-C1D revealed significantly increased populations of IEL, and in lamina propria lymphocytes compared with disease controls (p<0.005, p<0.01, resp.). γδ+ IEL were also elevated in both untreated and treated CD groups relative to disease controls (p<0.005; p<0.01, resp.). There were no significant differences between either group in terms of IL-2R or HLA-DR expressing cells, and neither neutrophil populations (CD15+) significantly altered when present. Lamina propria and crypt epithelium, while IL2R and CD15 expression was confined to lamina propria. Conclusions: 1. There are elevated populations of CD3+, and γδ+, lymphocytes in the rectal epithelium and lamina propria of untreated CD patients. 2. Neutrophilia (CD15+) is not a feature of coeliac rectum, thus discounting an inflammatory proctitis. 3. While IEL and plasma cells tended to fall on treatment, mast cells appeared to remain elevated: the reason for this phenomenon is uncertain.

EXPRESSION OF ADHESION MOLECULES IN GLUTEN-CHALLENGED, COELIAC DISEASE (CD) RECTAL MUCOSA
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Ligand-receptor binding between endothelium and recirculating cells, such as monocytes, neutrophils and lymphocytes, is a key factor in localising the inflammatory response, including sites of immune reactivity within the lamina propria as well as the epithelial lining of the lymph nodes and Peyers patches. We therefore sought to investigate the inflammatory response of rectal mucosa to local gluten challenge, as a dynamic model during which the expression of such adhesion molecules could be observed. Methods: 6g of gliadin was infused into 10 untreated and 8 treated CD patients, and 5 disease-control (DC) subjects. With a short-challenge, mucose were obtained 4h later: With a long-challenge, mucose were obtained at various points over 24h. Tissue samples were snap-frozen in liquid N2-cooled isopentane, cut at 6.5μm and examined with the immunoperoxidase technique for ELAM-1; ICAM-1 and VCAM-1 expression, which was arbitrarily graded (1≤0,2≤1,4≤2,6≤3). To avoid inter-subject variability percentage change in expression was calculated and significance determined between each group of subjects. Changes in lymphocyte and neutrophil populations were monitored by counting CD3+, and CD15+, cells respectively, and standardizing counts to a constant test area (10μm2) of muscularis mucosae. Results: ELAM-1 was mainly found on lamina propria vessels and macrophages, while ICAM-1 was widely distributed on inflammatory cells and endothelial cells. ICAM-1 was markedly elevated in gluten exposed CD patients compared on lymphocytes, neutrophils and monocytes. Expression of ELAM-1 was very weak or absent. None were expressed by epithelial cells, and their characteristic pattern of distribution did not change through challenge. VCAM-1 was markedly elevated in gluten exposed CD patients compared on lymphocytes, neutrophils and monocytes. Expression of ELAM-1 was very weak or absent. None were expressed by epithelial cells, and their characteristic pattern of distribution did not change through challenge. VCAM-1 was markedly elevated in gluten exposed CD patients compared on lymphocytes, neutrophils and monocytes. Expression of ELAM-1 was very weak or absent. None were expressed by epithelial cells, and their characteristic pattern of distribution did not change through challenge. VCAM-1 was markedly elevated in gluten exposed CD patients compared on lymphocytes, neutrophils and monocytes.
COELIAC DISEASE: CHARACTERISING THE ANTIGENICITY OF WHEAT α-GLIADIN WITH MONOCLONAL ANTIBODIES

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Introduction Coeliac disease is exacerbated by ingestion of prolains from wheat, rye, barley and oats. Toxicity lies in the ethanol soluble prolamin fractions. Rice, maize, millet and sorghum contain prolains that are non-toxic to coelieal patients. In vitro studies have implicated the N-terminal domain of wheat α-gliadin in the pathogenesis of the condition.

Methods Monoclonal antibodies were raised against a sequenced 54 amino acid peptide, B3144, which was derived from peptic-tryptic digests of α-gliadin with single amino-acid differences, and two chymotryptic cuts of domain 1, suggested that antibody WC2 binds to α-gliadin in the region of amino-acid 36, a proline residue.

Summary Sequence homologies exist between domain 1 of α-gliadin and non-toxic cereal prolamin antibodies. Antibody WC2 binds only coeliac toxic prolamin, and reacts in the region of a proline residue at position 36 of α-gliadin. This proline forms part of a tetrapeptide motif, QCQG, which is thought to be present in all peptides that exacerbate coeliac disease. Conformational studies have suggested that this residue may form part of an antigenic β-reverse turn.

Conclusion The evidence suggests that the proline residue at position 36 of wheat gliadin may be of crucial importance to cereal toxicity in coeliac patients.

STIMULATION OF COLONIC ION TRANSPORT BY ACTIVATION OF CELLS OF THE IMMUNE SYSTEM

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The aims of this study were to characterise electrogeneric ion transport responses to mast cell activation in human tissue in vitro. Histologically normal colonic mucosa obtained during surgical resection were stripped of underlying smooth muscle, mounted in Ussing chambers and voltage clamped by continuous application of short circuit current (SCC). Drugs were added to the serosal side. Polyclonal antibodies to human IgE which activate mast cells (or other immunocytes) by cross-linkage of bound IgE produced a rapid onset, transient inward SCC. Using paired preparations obtained from the same donor, the antibody-evoked response was significantly attenuated by the loop diuretic bumetanide (100 μM; p<0.05) which is a known inhibitor of electrolyte chloride secretion. Meprumin (100 μM), a histamine H1 receptor antagonist, virtually abolished the SCC response to mast cell activation (p<0.05). Application of histamine mimicked anti-IgE since histamine also stimulated bumetanide and meprynamine sensitive inward SCC without colonic preparation. These results suggest that activation of mast cells within the lamina propria may result in release of histamine in amounts which activate colonic epithelial cells. Consequently chloride ions will enter the mucosal layer, the consequence of this activity in vivo would be gradient driven secretory diarrhoea. Our findings show that human colonic ion transport may be regulated by elements of the immune system which may occur normally in response to enteric-dwelling parasites or pathologically as an inappropriate response to dietary antigens. Further studies will be designed to investigate whether the lamina propria are the primary effectors of this immunoregulation of ion transport.

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INTESTINAL TRANSIT TIME CAN BE PREDICTED FROM CLINICAL OBSERVATIONS

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Our understanding and treatment of constipation is limited by our lack of a simple clinical means of assessing intestinal transit time (ITT).

We investigated the extent to which simple observations of stool form, characteristics of defaecation and inter-defaecation time intervals (IDTI) can predict ITT in 62 women and 59 men selected from the general public. The stool form was recorded prospectively using a validated 1-6 scale sensitive to transit time, type 1 was pellet-type - type 6 was fluffy/mushy. Each subject recorded stool form from three consecutive defaecations and stool type numbers were summed to give a stool form score (SFS). Other characteristics of defaecation were recorded over the same period, including the IDTI. Simultaneously the mean ITT was measured using a four marker two stool X-ray technique described previously (Gut 1986; 27: 550). Multiple regression analysis was used to assess the extent to which ITT could be predicted from the defaecatory data.

Perceived constipation and straining had little predictive value. In women ITT was best predicted (PTT) by the equation ITT = 103-1.23 (DF)+4.69 (SFS)+0.638 (IDTI), where DF is defaecation frequency per week, for which the correlation coefficient = 0.736. 64% of PTT were in the correct quartile and 73% of the slowest people were correctly identified. For men ITT = 79-1.31(DF)-1.88 (SFS)+0.329 (IDTI), for which the correlation coefficient = 0.541. 50% of PTT were in the correct tertile.

Clinical observation can be used in a mathematical model to predict intestinal transit time, particularly in women, with reasonable accuracy. The model could be used epidemiologically.

CELL PROLIFERATION IN HUMAN COLONIC ABERRANT CRYPTS EVALUATED WITH IN VIVO BROMODEOXYURIDINE.

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Aberrant crypt foci (ACF) are slightly elevated and enlarged colonic crypts that can be observed in colorectal mucosa during experimental carcinogenesis. Several lines of evidence suggest that these lesions may be precursors of adenomatous polyps and large bowel cancer. ACF can be identified and quantified on fixed or unfixed methylene-blue stained mucosal surface of the human colon. Using the in vivo labelling of replicative cells with Bromodeoxyuridine (BdUr), an analog of Thymidine, we are purposed to characterize the kinetic activity of ACF as compared to normal colorectal mucosa. BdUr (500 mg) was given intravenously to 3 patients with colorectal cancer 4-6 hours before surgery. After operation, and area of normal colonic mucosa of 13-15 cm2 was excised, fixed in 70 % ethanol and scored for ACF under a light microscope after methylene-blue staining. After identification of ACF (No. 15) these were excised, embedded in paraffin and sectioned perpendicularly to the mucosal surface. The slides were then processed with standard immunohistochemical technique in order to identify cells which had become labelled during the S phase. The number of cells per hemycrypt was significantly higher in ACF than in control mucosa (106.8 ± 12.7 SDM vs. 84 ± 7.7). Total Labelling Index (L.I., fraction of labelled cells) was 15.4 ± 5.2 in ACF versus 12.6 ± 5.8 in normal mucosa (P<0.01). Moreover, L.I. tended to be higher in different proportions of the aberrant crypts but no clear upwards expansion of the proliferative zone was observed. Thus, the pattern of cell kinetics in ACF shows an increased cell replication along the crypt without any further derangement of the replicative profile. ACF might represent a preneoplastic lesion from normal mucosa to colorectal tumours.

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HYDROGEN SULPHIDE INDUCED DAMAGE TO THE COLONIC MUCOSAL BARRIER IN THE RAT

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Anaerobic sulphate reducing bacteria in the bowel lumen, couple sulphate reduction to the formation of hydrogen sulphide (H₂S) by their oxidative phosphorylation. Epidemiological evidence linking dietary sulphate with bowel disease and the high toxicity of H₂S in an anaesthetised rat (n=24) was perfused for 4 hours with the H₂S buffer. Control animals (n=5) were perfused with buffer without H₂S. Affluent and effluent H₂S was assayed in the perfusate by the methylene blue method and damage to the mucosal barrier assessed histologically and by measuring carbohydrate and DNA in the perfusate.

A linear dose dependent release of carbohydrate (µg/h) was found (y = 141.84 + 56.71x; r² = 0.495). DNA outputs in the perfusate were variable but significantly higher than controls (P<0.05). Histology showed apoptosis and loss and shrinkage of surface goblet cells. There were areas of superficial ulceration, and crypts were widely separated. The severity of these changes were dependent on the concentration of H₂S and were absent in the controls.

These results show that H₂S toxicity to mucosal cells and may additionally involve chemical reduction of mucus glycoproteins in the surface mucus layer. Damage to the mucosal barrier induced by H₂S may be an important pathological mechanism by which potential carcinogens and other toxins may diffuse into the mucosa.

MODULATION OF THE COLONIC EPITHELIAL RESPONSE TO PLATELET-ACTIVATING FACTOR

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Since PAF has been implicated in the pathogenesis of ulcerative colitis, the influence of mucosal application of aminosaliclylate (ASA) derivatives on PAF-induced ion secretion (measured by the short circuit current, SCC) and increased epithelial permeability (measured by mannitol flux) has been examined in epithelial sheets of rabbit distal colon mounted in Ussing chambers.

PAF (50nM, serosal) induced a peak rise (mean±SE) in SCC in controls of 20.9±3.9µA/cm², 21.6±2.9 µA/cm² and 27.2±3.0µA/cm² compared to 13.1±2.3µA/cm², 22.9±4.3 µA/cm² and 23.9±2.0µA/cm² in the presence of 10mM ASA (P=0.038, n=8 pairs), 10mM 4ASA (ns, n=5pairs), or 10mM olsalazine (ns, n=5pairs), respectively. Serosal 10mM indomethacin abolished the SCC response to PAF (0.2±0.5µA/cm², controls 27.9±3.7µA/cm², n=5pairs, P=0.001) but mucosal indomethacin had no effect.

Basal 14C-mannitol flux (1.5±0.2pmol/cm²/hr) increased after PAF by 144±18%, 61±24% and 84±31% in controls, compared to 53±16%, 13±15% and 6±28% in the presence of ASA, 4ASA and olsalazine respectively (P=0.016, 0.090; 0.214, all relative to 5-6 controls, paired t-test).

In conclusion, mucosal ASA attenuates PAF-induced ion secretion and increased permeability, which may contribute to control of diarrhoea when ASA is used therapeutically. 4ASA and olsalazine have a lesser, but not significant influence. The mechanism for ASA is uncertain, but could not be matched by mucosal indomethacin.

REALITY GAP - THE DIFFERENCE BETWEEN TRUE AND APPARENT CONSTIPATION

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The prevalence of constipation is not known and there is no scientifically validated, clinically useful definition of constipation now.

True constipation is best defined as prolonged intestinal transit time (TT). Whole gut TT can be predicted from a mathematical model using stool form, interdigestive time interval and defaecatory frequency. An international working team has proposed criteria based on stool frequency, bowie form, straining and incomplete evacuation (Rome criteria RC).

We assessed the prevalence of constipation using RC, self-perception and, as gold standard, predicted TT > 2SD over the mean of a population with normal bowel habit. In a community based study 724 women and 586 men completed a questionnaire about their bowel habit and a prospective diary about their stool form, using a validated 1-6 scale. Constipated people were identified by each of the three criteria.

The overlap between the three definitions was poor.

Of 80 men with slow transit constipation only 6 had self diagnosed constipation, only 9 were classified as constipated by RC and only one met all three criteria. There were 25 false positive diagnoses.

Of 93 women with slow transit constipation only 33 had self diagnosed constipation, only 31 were classified as constipated by RC and only 18 met all three criteria. There were 69 false positive diagnoses.

True constipation (slow transit) relates poorly to self perception and Rome criteria.

VISCOS FIBRE DELAYS OR-OCAL TRANSIT DURING LACTULOSE-INDUCED DIARRHOEA: IMPACT ON TRANSIT THROUGH THE ASCENDING COLON


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Gelling agents, such as ispaghula, which increase the viscosity of proximal gut contents have been reported to have antidiarrhoeal properties, even though they are substantially degraded in the colon. The aim of the present study was to determine if their effect on colonic function is secondary to changes induced in the proximal gut. Methods: 9 healthy subjects took lactulose 20ml t.d.s. with or without ispaghula (Pyoghon) 3.5g in 100ml water t.d.s. for two periods of 3 days, treatment sequences being randomized. After an overnight fast, on day 4, a test meal comprising 300ml clarified labelled with 3HPO4 and In-111DPA indium together with 20ml lactulose ± 7g ispaghula was ingested and gastric emptying, small bowel, and ascending colon transit was assessed by scintigraphy for 15h. Results: (Mean±SEM) ispaghula significantly increased the time for 50% of the dose to reach the colon which rose from 12±5 to 13±3 min, p<0.02, n=9. Gastric emptying was delayed, the effect being most obvious towards the end of gastric emptying, with significant delay of the time for 75% emptying which rose from a control value of 10±3 to 11±6 min, p<0.04, n=9. While ispaghula produced no consistent change in colonic transit there was a striking correlation between oro-occal and ascending colon transit during ispaghula treatment, (r=0.79, p<0.01, n=9) not seen without ispaghula (r=0.51 p=0.16, n=9). Conclusions: Ispaghula delays gastric emptying and oro-occal transit in lactulose-induced diarrhoea. The effect of ispaghula on ascending colonic transit in this model is largely secondary to these more proximal effects.
PREVALENCE OF BOWEL DYSFUNCTION IN MULTIPLE SCLEROSIS PATIENTS WITH BLADDER DYSFUNCTION.

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Bladder dysfunction is common in multiple sclerosis (MS) patients with prevalence as high as 78%. The neural pathways for control of defaecation and micturition probably lie in close proximity and bowel dysfunction might be expected to be similarly affected. The aim of this study was to determine the prevalence of bowel dysfunction in MS patients with bladder dysfunction.

Method: Consecutive patients with MS attending a Urology clinic for management of their bladder dysfunction were interviewed over a 6 months period. A questionnaire on bowel, bladder, sexual, neurological and obstetric history was completed. Constipation was defined as less than 3 bowel movements per week or straining for more than 25% of the time.

Results: 70 questionnaires were completed. 47(67%) patients had bowel dysfunction. Of these, constipation occurred in 26(37%). Patients 5 of these patients also had current (within last 3 months) faecal incontinence and 10 had previous (more than 3 months) faecal incontinence. 19(27%) patients had current faecal incontinence only and 11(16%) had previous faecal incontinence only. The overall prevalence of current and previous faecal incontinence was 55%. There was no significant correlation between the type of bladder symptoms, the degree of severity of MS or patients age with the type defaecatory disturbance (P>0.05, Fisher Exact Test).

Conclusion: In this group of patients, all of whom had troublesome bladder dysfunction, only 67% had disorders of bowel function. There is no significant correlation between bowel and bladder dysfunctions.

PATIENTS WITH OBSTRUCTED DEFACATION ARE MORE SENSITIVE TO ANORECTAL EVENTS THAN THOSE WITH SLOW TRANSIT CONSTIPATION AND NORMAL SUBJECTS.


We developed an ambulatory system in an attempt to make anorectal assessment more physiological. This analogue system recorded anal canal and rectal pressures, external anal sphincter and internal anal sphincter electromyography, for up to 24 hours. 11 normal subjects (N), 15 patients with Slow Transit Constipation (STC) and 10 with Obstructed Defaecation (OD), were recorded.

Three types of motility events were observed: Marked samples when equilibration is recorded as a feeling of wind involving an anal pressure reduction and rectal pressure rise; unmarked samples, are similar but unappreciated by the patient. Although qualitatively the same, quantitatively there are more appreciated events in OD patients (median 13 [range 4-26] per record p<0.01) compared with N (5 [0-16]) and STC (5 [0-12]) and fewer (p<0.01) unmarked samples (OD 4 [0-16]; N 12 [5-23]; STC 12 [3-31]). No differences in pressure drops were recorded.

This suggests patients with OD are significantly more sensitive to anal and rectal pressure equalisations. This may help explain their frequent conscious call to stool, since they respond to minimal changes in anorectal motility by attempted defaecation.

Minimal rises in rectal pressure suggest this is inappropriate, thus elucidating the pathogenesis.

COLONIC pH AND DIETARY FIBRE INTAKE IN SUBJECTS AT LOW AND HIGH RISK OF COLORECTAL CANCER.

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A higher colonic pH has been hypothesised to promote the development of colorectal cancer. Colonic pH is determined by short chain fatty acid concentration, produced from fermentation of dietary fibre.

Aims: To test this hypothesis subjects at high risk (colorectal polyps found on colonoscopy) and low risk (healthy, no past history or family history of bowel disease) for colorectal cancer had colonic pH and dietary fibre intake measured.

Method: 21 subjects (13 M/8 F) were enrolled; 13 subjects in the high risk group, 8 subjects low risk. The intracolonic pH was measured using a radiotelemetry pH capsule, which gave readings every 6 seconds for a 24 hour period and was able to be regionalised in the colon by means of a radio-detector. Dietary fibre intake for 24 hours prior to and during the study was recorded by a dietitian, using a combination of diaries and subject interviews with standard portions and check lists of foods.

Results: Mean colonic pH was lower in right, mid and left colon for subjects from the lower risk group (pH 5.70, 5.62, 6.01) compared to the high risk group (pH 5.89, 5.84, 6.50), but t-test gave p > 0.05 for difference between means. No significant differences were found between dietary fibre intake between low and high risk groups (24.7 ± S.D. 10.6 g/day vs 21.1 ± S.D. 7.0 g/day). A significant negative correlation (r = -0.48, p < 0.05) was found between dietary fibre intake and caecal pH. A positive correlation was found (r = 0.75, p < 0.05) between dietary fibre intake and left colon pH.

Conclusions: Dietary fibre intake was shown to be associated with changes in colonic pH. Subjects at higher risk for large bowel cancer tended to have lower colonic pH and fibre intakes. These findings support the view that dietary fibre may have a protective role in colorectal cancer, but this needs further study.