DOMICILIARY ENEMAS FOR OUTPATIENT SIGMOIDOSCOPY
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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 85% 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.

FORMALIN TREATMENT FOR HAEMORRAGIC RADIATION PROCTITIS
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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 transfused 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.

COELIAC DISEASE AND T-CELL RECEPTOR V-BETA GENE USAGE
SA Rose, CJ Smart, F Lancaster, IJ Trediosiewicz, PD Howdle, AW Boylston

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Coeliac disease may represent a human example of a phenomenon where the repertoire of T-cell antigen receptor (TCR) variable region used by lymphocytes is frequently restricted to one or a few gene families. This occurs when the immune system responds to a particular protein restricted by a single MHC molecule. Coeliac disease occurs in individuals expressing one particular combination of HLA-DQ a and b chains, and is triggered by the cereal protein gluten.

Results: Using the Polymerase Chain Reaction (PCR), we have analyzed the TCR variable region beta gene (Vβ) family repertoire used by intra-epithelial lymphocytes (IEL), and lamina propria lymphocytes (LPL) obtained from the small bowel biopsies from 10 untreated and 4 treated coeliac disease patients and 5 non-coeliac disease controls. Using over 20 gene family specific primers, increased expression has been found in the IEL from untreated individuals of one Vβ family. Two other Vβ families also showed increased expression in some, but not all, untreated patients.

These results suggest that there is restricted Vβ gene usage in coeliac disease and have important pathogenetic and therapeutic implications.

CD3 AND V8 LYMOCYTE RESPONSES TO SHORT-TERM RECTAL CHALLENGE IN GLUTEN-SENSITIVE (GS) SUBJECTS.
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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 V8+ 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 a-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+, V8+, CD15+, IL-2R+ and HLA-DR+ cells, which were quantified in absolute terms with respect to a test area of 10μm² muscularis mucosae. Sera were analysed for anti-a-gliadin antibody (IgA and IgG) and soluble IL-2R material by ELISA at 0, 2, 4 and 48h post-challenge. Results: There was a significant rise in CD3+ IEL (but not CD3+ lymphocytes) 4h post-challenge (p<0.005); V8+ IEL in untreated GS subjects also rose, although the increase was only just significant (p<0.05). No significant changes in neutrophils (CD15+); IL-2R 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-a-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 mucosa of GS subjects responds to gliadin challenge with a rise in CD3+, and to a much lesser extent, in V8+ 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-sensitivty: changes in V8+ lymphocytes appear to be far less discriminating, however, in this respect.
Brain-gut axis

F215–F222


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 cycled 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 Concetto 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 were clearly distinguishable from sham stimulation as a triphasic wave with its first negative peak (N1) having a mean latency of 50ms (SD 6.8ms). This was followed by a delayed more general response with a mean latency of 310ms ±7.5ms. 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 sphincter were identical in character and location but the onset of the early wave showed a mean conduction delay of 12.5ms (58ms ±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 velocity indicates transmission via myelinated fibers.
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 myoelectrical disturbances. We sought to investigate: (i) the effect of vection on gastric emptying; (ii) the relationship between somatomatognosy and gastric emptying.

Methods: Healthy male volunteers were studied, each on two occasions. After a 6 hour fast subjects ingested 300ml 150mM saline labelled with 2MBq 99mTc Tc Sulphur colloid. Gastric emptying was measured continuously for 120 minutes using gamma camera techniques. Vection was induced by rotating a drum with black and white stripes around the seated stationary subject. During the test subjects were instructed to count the number of stripes passing between two vertical lines fixed at eye level. Symptom scores were noted throughout.

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>45</td>
<td>18</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Vection</td>
<td>73</td>
<td>66</td>
<td>52</td>
<td>28</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>P value</td>
<td>0.04</td>
<td>0.01</td>
<td>0.02</td>
<td>0.04</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

7/8 subjects experienced symptoms which ranged from mild symptoms of motion sickness (headache, sweating) with or without episodic symptoms, 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.

Conclusion: 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.

MAGNETIC STIMULATION OF EFFERENT NEURAL PATHWAYS TO THE HUMAN OESOPHAGUS: Q Al-Azz, J C Rothwell, J Barbrow, A Hobson, D Whittle, S Alam, D G Thompson, D G Thompson, Dept. of Medicine, Surgery and Neurophysiology, University of Manchester and institute of Neurology, London.

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 response to magnetic stimulation of the human motor cortex and the extracranial vagus nerve.

Methods: Cortical stimulation (CS) was induced by a single series of single pulses delivered 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 18cm 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 valsala 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 (CMCT) of 7.7ms. Response amplitudes increased during valsala manoeuvre and were further enhanced immediately post valsala manoeuvre, indicating true vagal "facilitation". Mean amplitudes for CS at rest, during valsala and post valsala manoeuvre were 69.06mV SEM ± 13.5, 166.32mV SEM ± 32.5 and 213.8 SEM ± 49.1mV respectively. The site of maximal cortical responsiveness was not lateral to either side of the vertex. The effect was not affected by lateralization. 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 SEM ± 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 HEALTHY AND DIARRHOEA-PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)

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Psychotropic drugs are often prescribed in functional bowel disorders. Subsequent symptomatic improvement may be attributed to effects on mood, yet these drugs may alter gut transit. We aimed to compare whole gut transit time (WGGT) and oroacral 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 WGGT, 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 24 y, range 18-34, 11 F) WGGT was mean ± SEM, 39 ± 3.8 h. In 10 IBS patients (median age 35 y, range 24-48, 7 F) WGGT 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 WGGT 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 90 ± 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 WGGT.

In summary, WGGT 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 WGGT 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 incremental inflations (50ml/sec) with air at increasing volumes, and then by a slower ramp inflation (30ml/min) of the balloon with water. Subjects reported the perceived sensations during the balloon dilatations. Results of rectal sensitivity:

<table>
<thead>
<tr>
<th>Sleep deprived controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>day 1</td>
</tr>
<tr>
<td>DD: 7AU</td>
</tr>
<tr>
<td>Urgo 150(13)</td>
</tr>
<tr>
<td>Disc 219(16)</td>
</tr>
</tbody>
</table>

*p < 0.05 Results mean ±SEM

The rectal balloon volumes to induce sensations of desire to defecate (DD), urgency (Urgo) and discomfort (Disc) during rapid inflation and slower ramp inflation 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 dilatations or in the manometric indices.

Gut: First published as 10.1136/gut.33.2.S53 on 1 January 1992. Downloaded from http://gut.bmj.com/ on September 15, 2023 by guest. Protected by copyright.
CHANGES IN RECTAL SENSITIVITY AND GASTROINTESTINAL TRANSIT IN PERSISTENT BOWEL DISTURBANCE FOLLOWING SALMONELLA GASTROENTERITIS. A J Bergin, T C Donnelly, M W McConnell 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(mS) 21(3)* 42(7)
Desire to defaecate: 37(4)* 87(9)
Urgency: 62(6)* 161(10)
Discomfort: 117(12)* 175(12)
Compliance: 3.8(3.9)* 8.1(9.9)
(results: mean(sem) * significantly different from controls)

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.

ILEOECAEL TRANSIT IN CONSTITUTION AND IRITRIBLE BOWEL SYNDROME.
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To determine if delayed transfer of intestinal contents through the ileocecal valve is a feature of constitution, ileocecal transit (ICT) was measured in 16 patients with chronic idiopathic constipation (CIC), 6 patients with constipation-predominant irritable bowel syndrome (IBS), and 5 healthy controls.

The scintigraphic technique involves delivery of a bolus of 111-In radionuclide to the terminal ileum in an entericoated capsule which dissolves at terminal ileal pH. Gamma camera images were acquired half-hourly. ICT was calculated as the time from peak scintigraphic activity in the terminal ileum to peak activity in the caecum.

In control subjects, the ICT of 2.6±1.7 (mean±SD) hours did not differ significantly from that of patients with right sided transit delay (3.2±0.2, n=4), delay in the transverse colon and splenic flexure region (4.8±0.6, n=6) left sided delay (3.2±2.2, n=6), or IBS (1.1±0.3, n=6). However, IBS patients had significantly faster ICT than those with right sided colonic delay (p<0.02) and those with delay in the transverse colon and splenic flexure region (p<0.01).

This study has shown differences in ICT between patients with IBS and those with CIC. Measurement of ileocecal transit may help to differentiate between chronic idiopathic constipation and constipation-predominant irritable bowel syndrome.

HEREDITARY MIXED POLYPOSIS SYNDROME - A NEW DISORDER?
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*Imperial Cancer Research Fund, Lincoln's Inn Fields, London
St Mark's Hospital, City Road, London

Classically, hereditary colorectal cancer has been divided into the polyposis and non-polyposis syndromes. Polyposis syndromes predisposing to malignancy include Familial Adenomatous Polyposis, Peutz-Jeghers Syndrome and Juvenile Polyposis.

While in the majority of cases a clear pathological distinction can be made between the different syndromes, there are cases where polypos of different histology occur in the same individual, or in different individuals in the same family (Mixed Polyposis Syndrome).

We have studied a large kindred (106 members) with a strong family history of colorectal cancer and Mixed Polyposis Syndrome and documented the natural history of the disease. 31 members were known to have been affected; 10 died from colorectal cancer and 21 were found on colonoscopy to have juvenile, hamartomatous and/or inflammatory polyps or true adenoma of varying number and size.

We set out to test whether the susceptibility to colorectal cancer in this family was due to a germline mutation in any of the recognised tumour suppressor genes involved in colorectal carcinogenesis, i.e the APC gene on chromosome 5q, p53 on chromosome 17p, and the DCC gene on chromosome 18q. We also investigated chromosomal regions with a high degree of allele loss in sporadic colorectal carcinomas, as these regions are thought to harbour as yet unidentified tumour suppressor genes.

To test this hypothesis, we performed linkage analysis with more than 60 polymorphic DNA markers using blood taken from 36 members of the family. No linkage has so far been identified, and genetic markers have proven beyond doubt that this condition is not a variant of Familial Adenomatous Polyposis.

We conclude that, with present genetic information, the Hereditary Mixed Polyposis Syndrome appears to be a separate disease entity not related to the different syndromes of hereditary colorectal cancer syndromes. Finding the genetic mutation responsible could identify another gene involved in sporadic colorectal cancer.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) AND THE BAJONAS POLYPOSIS. COLI (APC) GENE ON CHROMOSOME 5q21
Department of Surgery and Centre for Digestive Diseases, Leeds General Infirmary, and ICRP Genetic Epidemiology Laboratory at the University of Leeds.

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, inherited evidence 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 YpH.64, CBBH.6, DP.1 and JWS. The presence of somatic changes in cancers was determined by 'Southern' blotting of RFLPs defined by probes cipli, RCBH7 and YHS.46.

Analysis of shared alleles in ten affected sibling-pairs (0, 1 or 2; expected 25%, 50% and 25% vs. observed 30%, 70% and 0) does not exclude the APC gene as a susceptibility locus. However, individual analysis confirmed that this locus is not solely responsible for familial aggregation.

RFLPs - Restriction Fragment Length Polymorphisms
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 NSAIs 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 (+) adenoma cases (n = 147), FOB (-) age and sex matched controls (n = 153) and FOB (+) 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 (-) controls and 0.72 (0.4-1.3) with FOB (+) controls. In those reporting aspirin or NSAID use only (125 subjects) the RR was 0.55 (0.3-1.1) with FOB (-) controls and 0.71 (0.4-1.4) with FOB (+) controls. These negative associations increased with duration of use: the RR in prescribed aspirin or NSAID use were 0.2 (0.06-0.8) and 0.3 (0.08-1.1) with FOB (-) and +ve controls respectively. In contrast no association with pancreatectectomy (acetonemoh) use was evident the RR being 1.5 (0.9-2.4) and 1.1 (0.7-1.8) with FOB (-) and +ve controls 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.

THE ROLES OF BILIRINARY DEOXYCHOLIC ACID (DCA) AND VESICULAR CHOLESTEROL (CH) IN THE PATHOGENESIS OF CH GALLBLADDER STONES (GBS): SH Hussaini, M Maghsoodloo, GM Murphy, C Kennedy, JAN Wasse, RH Dowling. Gastroenterology Unit & Dept. of Diagnostic Radiology, Guy’s & St Thomas’ Hospitals & Dept of Endocrinol, St Bartholomew’s Hospital, London.

Supersaturation of GB bile with CH (saturation indices: C:SI >1.0) and rapid nucleation of CH microcrystals (nucleation time: MT <4 days) are essential steps in CH GBS formation. However, we now know that CH can be transported with phospholipids (PL) as vesicles (VCH), as well as in micelles, and that as the vesicles become unstable with high mol fraction PL ratios (VCH:PL), microcrystals of CH may precipitate. Although excess biliary DCA is thought to increase C, it’s effects on MT 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 anticipat- ion of a wide range of C10 SI & Ws, and measured total biliary lipids (to derive C10s), F’OB, VCH and VCH:PL (density gradient ultracentrifugation) and bile acids (BA) conjugates (as a % of total BA) by HPLC. RESULTS: By univariate analyses, C10 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<0.01, but not with chenodeoxycholic acid (CDCA). MT correlated inversely with: (i) C10 (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 C10 and MT, all biles with a VCH:PL C of <0.6.

SUMMARY: (i) as the C10 increases, more CH is transported in vesicles, the VCH:PL ratio rises and the MT becomes more rapid. (ii) An increase in biliary DCA is not only associ- ated with a rise in C10 but also with a short MT.

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

ABNORMAL DNA CONTENT OF RECTAL MUCOSA AFFECTS MUCOSAL PROLIFERATION AND RECURRENT ADENOMA FORMATION

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Department of Surgery, University Hospital, Nottingham. 07 2SU.

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 colonoscopy. DNA content was measured on rectal biopsies using flow cytometric analysis. Rectal mucosal proliferation was measured using the in vitro metaphase arrest technique Crypt Cell Production Rate (CCPR).

Six individuals (25%) with adenomas n=24 had aneuploidy compared to, 1 in the family history group n=23,2 in the low risk group n=12. Proliferation in individuals with aneuploidy n=9 (median CCPR: 2.2/hr) had a significantly greater CCPR than individuals in the low risk group who were diploid n=10 (median ccpr 0.1/hr: Mann-Whitney P<0.02). Three of eight individuals with recurrent adenomas (37.5%) had aneuploidy DNA significantly different from none of 27 adenoma surveillance individuals in whom all was found (Fisher exact test p=0.017).

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

OTCOTYROID (OT) INCREASES THE PROPORTION OF DEOXYCHOLIC ACID (DCA) IN GALLBLADER (GB) BILE - THE PRIME MOVEx IN THE PATHOGENESIS OF OT-INDUCED GALLBLADER STONES (GBS): SH Hussaini, M Maghsoodloo, GM Murphy, C Kennedy, JAN Wasse, RH Dowling. Gastroenterology Unit & Dept of Radiology, Guy’s Campus, UMDS & Dept of Endocrinology, 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 (CH) 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 acromegalics, we measured individual BA conjugates by HPLC in GB bile obtained by ultrasound-guided percutaneous needle aspiration (n=17) or at cholecystectomy (n=5): (i) non-acromegalic patients with CH GBS (n=10), (ii) acromegalic with OT associated GBS (n=9), (iii) stone-free somatostatin studies before (n=5) and (iv) after 3 mo OT treatment (n=2).

RESULTS: The proportion of DCA (% of total biliary BA) was 17±SEM 3.8 in stone-free individuals compared with 24.2±5.9 in those with OT associated GBS and 24.7±2.1 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. The greater % DCA in both GBS groups is likely to be due to increased bacterial 7a dehydroxylation of cholic acid (CA) since the CA content was 50.3% compared to 38.7±5.6 and 36.5±4.1 respectively (p<0.05). However the proportions of chenodeoxycholic acid remained unchanged at 35.4±1.1, 35.7±2.0 and 36.1±2.6 whilst lithochol- ate and ursodeoxycholic acid for CA 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 prokin- etic peptides such as CCK.
IS THERE A DOMINANT AXIS OF CONTRACTION IN THE HUMAN GALLBLADDER? 
H Wegostapel*, R Chess-Williams*, TJ Stephenson*, 
M Maleed*, M 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" (1). In this study, the difference between longitudinal and circular strips in response to CCK-8 was examined.

Eight functioning GBs were obtained from patients (n=8). Three muscle strips were parallel to the longitudinal axis and three strips were parallel to the circular axis. Each strip was 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 gram (mean ± standard error of mean) for longitudinal and 3.37 ± 0.32 gram for circular strips. EC50 (concentration that produced 50% maximum contraction) was respectively 6.7 (range 4.5-10.1) nM and 4.6 (2.6-8.9) nM. Differences were not significant (Student's t-test).

Histology showed a varying orientation but no dominant direction of muscle fibres. Gallbladder muscle strips taken along the longitudinal or circular axis of the gallbladder show a similar response to CCK-8.


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

Prostaglandins (PGs) have been isolated from gallbladder smooth muscle and indomethacin is known to affect gallbladder motility in vivo. Prevent gallstones and is effective in relieving biliary pain and preventing its progression to cholecystitis. However, the effects of the naturally occurring PGs on gallbladder contractility is poorly defined. We therefore examined the effects of the five main prostaglandins 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 10ml organ baths, containing oxygenated Krebs' solution at 37°C in the presence of 3x10-5 M indomethacin to prevent endogenous PG synthesis. An initial tension of 1g 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 PGD2, which produced contractions which steadily declined. The thromboxane A2 mimetic, U46619 and PGE2 were the most potent agonists with EC50's of 1.5 x 10-9 M and 4x10-9 M respectively. PGD2 and PGF2 were the least potent with EC50's greater than 3x10-9 M and 4x10-6 M respectively. The potency of PGF2α was also low; at a concentration of approximately 4x10-6 M it was equipotent with EC50 concentrations of U46619 and PGE2. A true EC50 for PGD2 was unobtainable as maximum contraction had not been achieved at 3x10-7 M.

Thus the rank order of potency of the main PG agonists is U46619 > PGE2 > PGF2α > PGD2 > PGJ2. PG's are potent stimulants of gallbladder contraction and PGD2 and thromboxane A2 are the most likely agonists under physiological conditions.

IN-VIVO EMPTYING VS IN-VITRO CONTRACTILITY OF THE GALLBLADDER (GB) IN PATIENTS WITH GALLSTONES. H Wegastapel*, R Chess-Williams*, B Ross*, TJ Stephenson*, AM Maleed*, MC Bird*, AG Johnson*, (Departments of Surgery*, Radiology*, Pathology* and Biomedical Science*, University of Sheffield).

Gallbladder contractility in response to a standard fatty meal stimulus was measured by ultrasonography in 11 patients with GB stones. Fasting volume, residual volume and ejection fraction were calculated. After removal, six strips measuring 10 mm x 3 mm each, taken from the body of the GB, 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. EF n MCR ± SEM RV n MCR ± SEM

A. 25±0.3% D. 3.1±0.3% D. 15±15 ± 178.8 2.0±0.10 B. 50.7±3.3% 3.79±0.31 E. 1.1±1.6% 2.89±0.30 C. 75±100% 3.47±0.52 F. <10mls 5.4±10±.36

EF= Ejection fraction in %, n= number of patients MCR = SEM= Maximal contractile response in gram ± standard error of mean. RV = Residual volume. Subsequent histology of these strips was correlated with these findings and poor emptying in-vivo and reduced contractility in-vitro were associated with increased fibrosis.

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

Galbladder Function and Plasma Cholecystokinin (CCK) in Patients with Gallstones.

I S Bailey, J Stumpf, C D Johnson
University Surgical Unit, Southampton General Hospital.

Abnormal gallbladder emptying is well recognized in patients with gallstones and has been reported to be associated with abnormal post prandial plasma CCK.

Gallbladder emptying (dynamic isotope scanning) and plasma cholecystokinin (radio-immunoassay) was measured in normal controls and patients with gallstones after a standard meal of corn oil.

Gallstone patients (GS) had functioning (n=17) or non-functioning (n=10) gallbladders. The patients with functioning gallbladders demonstrated two abnormal patterns of emptying; 'non-contractors' and/or 'late emptiers'.

Integrated plasma CCK pmol/l was controls (n=15) 116.5 (16), GS non-functioning (n=10) 190.3 (30.4) (p<0.01), GS controls (n=9) 178.8 (47.2), GS non-contractors (n=8) 154.3 (54), GS early emptiers (n=8) 97.2 (16.1), GS late emptiers (n=7) 280.6 (60) (p<0.01) (Mean (SEM) p = Mann-Whitney versus controls.)

Abnormal emptying in the presence of gallstones is associated with abnormally high plasma CCK after a corn oil meal. This is likely to be an effect rather than a cause of the abnormal emptying.
INTRAVENOUS AMINO ACIDS PROMOTE GALLBLADDER MOTILITY AND CHOLECYSTOKININ RELEASE. Zoli G, Healy J, Bullinger A, O'Donnell LJ, Clark ML, Fashing MJG. Dept. Gastroenterology & Radiology, St Bartholomew's Hospital, London

Administration of intravenous amino acids (IVAAs) is known to promote gastric acid and pancreatic secretion. The effect of IVAAs on gallbladder function is uncertain, although dietary amino acids promote gallbladder emptying. We therefore determined whether administration of IVAAs affects 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 amino acids) over 30 min. Gallbladder volumes were determined by ultrasonography before and after 5 min intervals for 60 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.

IVAAs caused significant contraction of the gallbladder from a mean (±SEM) fasting volume of 23.3±3 ml to 11.4±3 ml at 40 min after the start of the infusion (p<0.01). Mean Ejection fraction (EF) was 61±12%. Mean minimal volume after the start of infusion was 8±2 ml (p<0.01, compared to fasting). IVAAs induced a rise in serum CCK from a minimal fasting concentration of 1.6±0.3 pmol/l to a mean peak of 5.9±1.2 pmol/l (p<0.03). Integrated 60 min CCK release was 840±130 pmol/min. Taking a lag period of 15 min, plasma CCK and EF were significantly correlated (r=0.62, p<0.03).

Rapid infusion of IVAAs 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.

PITUITARY ADENYLYL CYCLASE ACTIVATING PEPTIDE IN THE HUMAN DUODENUM
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Medical Research Centre, City Hospital, Nottingham NG5 1PB

Pituitary adenyl 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. In this study, we assessed the effects of PACAP on cAMP synthesis in these cells. We also studied the ability of competitive VIP antagonists, [Arg8, Pro28, Tyr3]-VIP and [Lys4, Pro28, Arg3]VIP, 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.

Results: PACAP at 10-6M stimulated cAMP production by 1190% above a mean (SEM) basal level of 0.53±0.07 pmol/l. VIP at 10-6M stimulated cAMP production by 1600%. PACAP produced a significant (p<0.05) progressive increase in cAMP production from 10-6M to 10-3M. D-Phe8, Leu11-VIP (1μM) inhibited PACAP-(10-6M) and VIP-(10-5M) stimulated cAMP production by 50% and 10% respectively. Lys2-, Pro28, Arg3 VIP antagonised PACAP-stimulated cAMP production by 25% but VIP-stimulated cAMP production was increased by a further 50%. Lys2-, Pro28, Arg3, Tyr3-VIP alone had no effect.

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

ABSORPTION OF FLUCONAZOLE AND INTRAOCANAZOLE UNDER CONDITIONS OF LOW GASTRIC ACIDITY
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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 present study was to investigate the absorption of two new triazole anti-fungal agents, flucloxacine 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 cross over design. Subjects were randomised to 4 different dosing regimens: itraconazole 200 mg alone, itraconazole 200 mg and famotidine, flucloxacine 100 mg alone, flucloxacine 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 post dose, 30 min, 1h, 2h, 3h, 5h, 8h, 24h and 48h. Flucloxacine and itraconazole levels were measured by HPLC.

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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>No famotidine</th>
<th>Famotidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacine</td>
<td>38.4 ± 20.4</td>
<td>40.1 ± 14.3</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>3.8 ± 2.3</td>
<td>2.1 ± 1.4</td>
</tr>
</tbody>
</table>

There was a significant decrease in the 48-h integrated serum itraconazole concentration and the peak serum itraconazole concentration during hypochlorhydria (p<0.05). Hypochlorhydria did not affect the 48-h integrated or peak flucloxacine concentration.

CONCLUSION: Unlike flucloxacine, 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

North Middlesex Hospital Trust, London

To audit practice in the management of H. pylori infection questionnaires were sent to all gastroenterologists in the 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 22% 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 H2 antagonists, 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 varied on chaos.

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CYTOPROTECTIVE EFFECT OF ALLOPURINOL ON GASTRIC MUCOSA IN RATS

Gastronoterology Clinics of Ege Universitesi 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 ORF 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 3 groups were given:
1. 5% allopurinol (orogastric)
2. 10% allopurinol
3. 1 ml of saline

One hour later all animals were given 1 ml of 96% ethanol 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.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Area (mm²)</th>
<th>Length (mm)</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saine</td>
<td>79.85±14.34</td>
<td>104.3±25.67</td>
<td>13.8±5.52</td>
</tr>
<tr>
<td>Allopurinol(%)</td>
<td>20.45±4.45</td>
<td>27.7±5.71</td>
<td>6.6±3.50</td>
</tr>
<tr>
<td>Allopurinol(10%)</td>
<td>18.06±3.28</td>
<td>19.77±5.16</td>
<td>6.1±2.07</td>
</tr>
</tbody>
</table>

In conclusion, 5% and 10% solutions of allopurinol appear to reduce significantly (p < 0.01) the gastric mucosal lesions produced with ethanol in rats.

F240

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

Department of Medicine, University of Muenster, Muenster, Germany and Institute of Physiology, University of Krakow, Krakow, Poland.

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

In group A, lipoglutamide (12-400 mg/kg-b, natural analog of CCK) and exogenous GRP (25-400 mg/kg) were infused i.v. in graded doses and gastric acid secretion was measured by aspiration technique while plasma gastrin was determined by RIA. Cessatin or GRF infused alone produced a dose dependent increase in acid output, but the peak responses reached only about 28% and 36% of pentagastrin maximum and this was accompanied by significant (2-3 fold) increase in plasma gastrin response. Cessatin (100IU/kg-b) added to pentagastrin (0.65 mEq/kg-b) infusion reduced acid secretion and this effect was completely reversed by the pretreatment with lipoglutamide, 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 1.5-2.5 at the beginning of the interdigestive period. After 500 ml semi-liquid meal "Freuseli, Freuseli, Bad Nauheim, Germany," the pH rose to 7 after 3 hours, and the elevated pH was maintained by its gradual rise in the stomach which was accompanied by an increase in plasma gastrin from basal 2±1 to 3±1.5 pmol/L. After pretreatment with lipoglutamide (15mg/kg, p.o., both intragastric and plasma pH values in the postprandial periods were significantly lower and lasted only about half of the gastrin increase was about twice as high as in the placebo treated controls.

We conclude that the antagonism of type A CCK receptors converts casuelia from partial into full gastric-like agonist of gastric acid secretion and that endogenous CCK released by GRP. Moreover, CCK exerts a tonic inhibitory influence on gastric acid secretion and gastrin release in humans.

F241

INCREASE IN GASTRIC JUICE ASCORBIC ACID CONCENTRATIONS AFTER ERADICATION OF HELICOBACTER PYLORI: PRELIMINARY REPORT.


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 paper we have determined whether eradication of H. pylori restores ascorbic acid secretion.

Method: 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 mmol/l, mean ± SEM, n=26) than in patients before treatment (25.9 ± 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 mmol/l in 10/26 eradicated cases (p < 0.01), 2/46 cases pre-treatment (p < 0.01) and 1 case after failure 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.
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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 formamide/7M urea 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/nisomolar 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 < 0.01 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 (1.7–5.1) 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.

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REDUCED LIFE EXPECTANCY IN PATIENTS SURVIVING UPPER GASTROINTESTINAL BLEEDING

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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 60yrs 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 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 ± 8yrs, 73 ± 8yrs 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 upper GI bleeding as 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.

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A COMPARISON OF SIZE AND PATHOLOGY OF VESSEL AND ULCER IN PATIENTS DYING FROM BLEEDING GASTRIC AND DUODENAL ULCERS. KC Lai, D Pollock, A Kalotkas, A Grandison, CP Swain, Therapeutics 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 radiology. 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 (1984–1989), 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.

Macroscopic recording a vessel visible in 1/18 of GU patients vs 23/60 of DU patients (p<0.05) and vessel size in 1 large eroded gastric artery vs 10 duodenal arteries. Evidence of recent major bleeding (blood in gut) was detected in 17 DU patients and in 36 DU patients (94% vs 60%, p<0.05). Both GU and DU size were large (range 11.5–cm vs range 0.5–7cm), but the GU size was significantly larger than DU (p<0.05).

Macroscopic measurements of 18 arteries in GU showed a mean diameter of 1.2, range 0.3–3.45mm (27.8%) measured 1.3–3.45mm while measurements of 29 arteries in DU showed a mean diameter of 0.9, range 0.1–3.45mm, 8(27.6%) measured 1.3–3.45mm. 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 (GU27.8% vs DU27.6%, p=0.2). Fibrosis i.e. chronic ulceration was equally common in GU and DU patients (66% vs 64% p=0.4). 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 arteritis 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.

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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. Foddy, R. N. 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 have 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 gastrin activity 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 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 Gastrotec (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)pmol/l with ranitidine and 6.7(4.5)pmol/l with placebo (NS, p=0.14). In subjects receiving parenteral feeding, the mean(SD) integrated 24-hour gastrin was 21.2(17.0)pmol/l with ranitidine and 6.8(3.5)pmol/l with placebo. In this case, the differences did not reach statistical significance (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 gastrin activity did not therefore increase plasma gastrin in these subjects.

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 pharmacodynamic data from 11 treatment comparisons were extracted from a pre-existing database of DU patients. Meta-analysis of the literature on the effect of pharmacological acid suppression on oesophageal acid exposure was also performed. Intra-esophageal 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 intra-oesophageal acid exposure expressed as % time pH <4 (r=0.82, p<0.05).

Preliminary stepwise regression analysis indicates that intra-gastric and intra-esophageal acidity are correlated and that the degree of intra-gastric acidity suppression is correlated with decreased intra-esophageal acidity. The best correlates for healing of esophagitis on treatment from a single study are 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.

EARLY PAIN RELIEF IN THE MANAGEMENT OF THE ACUTE ABDOMEN IS SAFE. A R Attard, M J Corlett, N J Kidner, A P Leslie, I A Fraser Dept. of General Surgery, Watlgrave Hospital, Coventry

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 randomized 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 8% 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 REFLUX. T. Ismail, J. Bangewicz University of Manchester, Department of Surgery, Hope Hospital, Salford M6 8HD

It is fashionable 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 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.


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 15
Bowel 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
Depts of Surgery, Western and Royal Infirmary, Glasgow UK

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 (L.C. group; n=59) and mini-cholecystectomy (MC group; 5-10 cm subcostal incision, n=60). Linear analogue pain scores (LAPS) were completed after examination by a single investigator on the 1st, 2nd, 10th and 30th postoperative 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/24hrs) as medians (interquartile range), with statistical analyses with the unpaired t-test and Mann-Whitney U test respectively.

LAPS 24h LAPS 48h Morphine 24h Morph. 48h
L.C. 43 (37-50) 28 (22-35) 24 (14-40) 0 (0-16)
P value 0.0001 0.0003 0.0004 0.011

On the 10th and 30th postoperative 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 L.C. (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, MDCK65 (human gastric), AR42J (rat pancreatic), MG62 (mouse colonic) and C523 (human colonic), were grown in nude mice. Detection of high affinity G-17 binding sites and/or stimulation of proliferation in vitro by 0.01-1 nM gastrin was used to indicated the presence of functional gastrin receptors. Two different strategies of inhibiting the action of gastrin were used: synthetic receptor antagonists (M242642 and M227670) 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 AR42J and C523. 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?
JLT Tate, J Dawson, SCS Chung, HT Leong, A Chan, WY Lau, AKC Li
Department of Surgery, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong.

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
JLT Tate, JW Dawson, WY Lau, AKC Li
Department of Surgery, Chinese University of Hong Kong, Prince of Wales Hospital, Sha Tin, Hong Kong.

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 calculus 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%) 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 (193 vs 168 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 (£1938) was lower than an open cholecystectomy (£2172). However with disposable instruments (clip applicator, ports 3 x 3 and scissors) the mean cost saving per patient of £234 is converted to an increased expenditure of £236.

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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Academic Department of Surgery, Keele University, Stoke on Trent, UK

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 patients’ 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.’ 26 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 these 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 SLAIDESENDECY (SIAL) ON EGF LEVELS IN THE STOMACH, SMALL INTESTINE AND COLON

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It is recognised that testosterone and oestradiol affect the expression of mRNA for EGF and production of the peptide in the submucosal gland but little information is known of their effects on EGF in the gut. We studied the effects of gonadectomy ± slaidecendectomy on EGF concentration in the gut measured by specific RIA (mg 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 orchidectomy (ororch) 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 (I.) orch reduced [EGF] by 1.6 - 2.3 fold but orch + sial produced a 6-9 fold decrease (p<0.01); 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 submucosal glands together with ooph or orch alone 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. Gastrointestinal side-effects are a complication of chronic ingestion. The mechanism of gastric damage by NSAIDS is complex. It is thought that there is inhibition of gastric 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 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 (LI) 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<.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 normal reparative processes and is likely to contribute to the high prevalence of NSAID gastropathy.
LACK OF CORRELATION BETWEEN BROMODEOXYURIDINE AND PCNA LABELLING IN GASTRIC BIOPSIES

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Centre for Digestive Diseases, The General Infirmary at Leeds, Leeds LS1 3EX

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 0-90%). BrDU positive cells were virtually all confined to zone 2 (0-16% of cells in this zone were positive) whilst PCNA positive cells were present in all 3 zones (1 = 22.9%-82.7%, 2 = 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 ORGANELLE MARKER ENZYMES IN CARBON TETRACHLORIDE (CCl4)-INDUCED CIRRHOSIS IN RATS

CB Summerton and CA Seymour, Addenbrooke's Hospital, Cambridge & Dept of Clinical Biochemistry, St George's Hospital Medical School, London.

Nifedipine has a protective effect upon hepatocytes subjected to ischaemic-, 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 homogenerate activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control diet</td>
<td>Nifedipine treated</td>
</tr>
<tr>
<td>N-acetyl-p-glucosaminidase1</td>
<td>1.20±0.01</td>
<td>1.10±0.04</td>
</tr>
<tr>
<td>Acid phosphatase1</td>
<td>15.52±0.983</td>
<td>18.544±1.854</td>
</tr>
<tr>
<td>Leucylaminopeptidase</td>
<td>2.123±0.039</td>
<td>2.046±0.036</td>
</tr>
<tr>
<td>Alkaline phosphatase2</td>
<td>98.366±7.692</td>
<td>84.176±11.511</td>
</tr>
<tr>
<td>L-glutaminase3</td>
<td>2.204±0.164</td>
<td>1.736±0.156</td>
</tr>
<tr>
<td>Neutral α-glucosidase4</td>
<td>0.683±0.036</td>
<td>0.654±0.026</td>
</tr>
<tr>
<td>Malate dehydrogenase4</td>
<td>48.376±1.047</td>
<td>39.559±0.034</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) Watson A.M., Askew J.N., Department of Medicine, Hope Hospital, University of Manchester, Eccles Old Road, SALFORD M6 8HD

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 B1 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 56.3% ± 10% loss of integrity as assessed by the MTT test while there was only a 14% ± 6% 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 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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Explanation of Figures

Figure 1

Sections of normal and inflamed appendix were hybridised with a CDX DNA probe and detected using a digoxigenin antibody labelled with alkaline phosphatase. PAI-1 production was detected by 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 appendix increases our understanding of the pathophysiological changes in fibrinolytic activity which lead to adhesion formation.
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 ulcer 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

M J Weldon, S H Saverymuttu, A R A Joseph, J D Maxwell (St. George's Hospital Medical School, London.)

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 PROCTIS'? A. Enari, D.E. Loft, M.N. Marsh, K.J. Moriaty, S.Morgan. Department of Medicine, University of Manchester, Hope Hospital, Salford M6 8HD, U.K.

That rectal mucosa of untreated coeliac disease (CD) patients may either be subject to lymphocytic infiltration following exposure to wheat in the faecal stream, or manifest a non-specific proctitis (akin to idiopathic ulcerative colitis), 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 removed 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 and stained with outline. Immunocytochemistry was carried out by computerized image-analysis. Other specimens were snap-frozen in liquid N2-cooled isopentane; cryotome sections (5-6um) were used in a paired immunoperoxidase technique for visualization of CD3+; γδT, IL-2R, CD15+ and HLA-DR+ cell populations; these were standardized and enumerated with respect to a constant test square (10um) of muscularis mucosa, and analyzed by non-parametric statistical methods. 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-CD3 revealed significantly increased populations of IEL, and in lamina propria lymphocytes compared with disease controls (p<0.01, p<0.01, resp.). γδT 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 during treatment. Epithelium, while IL2R and CD15 expression was confined to lamina propria. Conclusions: 1. There are elevated populations of CD3+ and γδT 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 high endothelial venules in lymph nodes and Peyer's patches. We therefore set out 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 a-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 6.5um and examined with the immunoperoxidase technique for ELAM-1; ICAM-1 and VCAM-1 expression, which was arbitrarily graded (1-3). The mucosa was scored for differences in neutrophils, CD8+ and CD15+ cells on September 15, 2023 by guest. Protected by copyright. Gut: first published as 10.1136/gut.33.2_Suppl.S53 on 1 January 1992. Downloaded from http://gut.bmj.com/ on 15 January 2023 by guest. Protected by copyright.
COELIAC DISEASE: CHARACTERISING THE ANTIGENICITY OF WHEAT a-GLIADIN WITH MONOCOLONAL ANTIBODIES
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Introduction. Coeliac disease is exacerbated by ingestion of prolamin-containing foods, e.g. wheat, rye, barley and oats. Toxicity lies in the ethanol soluble prolamin fractions. Rice, maize, millet and sorghum contain prolamins that are non-toxic to coeliac patients. In vitro studies have implicated the N-terminal domain of wheat a-gliadin in the pathogenesis of the condition.

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

Summary. Sequence homologies exist between domain 1 of a-gliadin and non-toxic cereal gliadins. Antibody WC2 binds only coeliac toxic prolams, and reacts in the region of a prolinc residue at position 36 of a-gliadin. This prolinc residue part of a tetraptupeptide motif, QGQP, 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 b-reverse turn.

Conclusion. These data suggest that the prolinc residue at position 36 of wheat gliadin may be of crucial importance to cereal toxicity in coeliac patients.

STIMULATION OF COLONIC CYTOKIN 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 mM; p<0.05) which is a known inhibitor of electrogenic chloride secretion in the colon. Morphine (100 μM), a histamine H3 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 morphynepine sensitive inward SCC. The consequence of these results is that barbiturate resistant mast cells may exist in the mucosal layer of normal colon preparations. The number of cells per hemiCrypt 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 highest in crypt penetrating portions 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.

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 interval (IDT) 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 pellety - 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 observations of defaecation were measured over the same period, including the IDT. 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 = 103.1-2.23 (DF)-4.69 (SFS)+0.638 (IDT), 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 lowest people were correctly identified. For men ITT = 79-1.33 (DF)-1.88 (SFS)-0.329 (IDT), 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.
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, led us to look for damaging effects of H₂S on the colonic mucosal barrier, using single pass perfusion in a vascularized rat colon model. Tris-HCl 50 mM; pH 7.5 was equilibrated with H₂S gas at 37°C, suitably diluted with nitrogen to enable us to regulate the H₂S concentration from 0.2 - 1.0 mM, covering the physiological range. A 5 cm section of vascularized proximal colon isolated in an anaesthetised rat (n=24) was perfused for 4 hours with the H₂S-buffer. Control animals (n=6) 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 relationship of carbohydrate (μg/ml) was found (y = 141.84 + 567.81 x; r²=0.495). DNA outputs in the perfusates 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 changes result from H₂S toxicity to mucosal cells and may additionally involve chemical reduction of mucus glycoproteins in the surface mucus layer. Damage to colonic mucosal barrier 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 anion secretion (measured by the short current circuit, 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±3.3μA/cm², 21.6±2.9 μA/cm² and 27.2±3.5μA/cm², compared to 13.1±2.3μA/cm², 22.9±4.3 μA/cm² and 23.9±2.6μA/cm² in the presence of 10mM ASA (p=0.038, n=8 pairs), 10mM 4ASA (ns, n=8pairs), or 10mM olsalazine (ns, n=5pairs), respectively. Serosal 10mM indomethacin abolished the SCC response to PAF (0.2±0.5μA/cm², controls 27.7±2.7μA/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 14±18%, 61±24% and 84±31% in controls, compared to 53±16%, 13±5% and 6±28% in the presence of 5ASA, 4ASA and olsalazine respectively (p=0.016; 0.090; 0.214, all relative to 5-6 controls, paired t-test).

In conclusion, mucosal 5ASA attenuates PAF-induced anion secretion and increased permeability, which may contribute to control of diarrhoea when 5ASA is used therapeutically. 4ASA and olsalazine have a lesser, but not significant influence. The mechanism for 5ASA 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.

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

We assessed the prevalence of constipation using RC, self perception and, as gold standard, predicted TT > 5SD over the mean of a population with normal bowel habit. In a community based study 724 women and 556 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 26 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.

VICIOUS FIBRE DELAYS OR-O-COLIC 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 (Pygost)1.5g in 100ml water t.d.s. for two periods of 3 days, treatment sequences being randomised. After an overnight fast, on day 4, a test meal comprising 300ml clarified labelled with 3H5PC-5H2MIP and 111mIn-111IndTA 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 Isipaghula significantly increased the time for 50% of the dose to reach the colon which rose from 12±11 to 16±31 min, p<0.02, n=9. Gastric emptying was delayed, the effect being most obvious towards the end of gastric emptying, with significant delay on the time to 75% emptying which rose from a control value of 10±12 to 11±57 min, p<0.04, n=6. While isipaghula produced no consistent change in colonic transit there was a striking correlation between oro-colic and ascending colon transit during isipaghula treatment, (r=0.79, p<0.01, n=9) not seen without isipaghula (r=0.51 p=0.16, n=9). Conclusion: Isipaghula delays gastric emptying and oro-colic transit in lactulose-induced diarrhoea. The effect of isipaghula 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 25 (37%). Patients 3 of these patients also had current (within last 3 months) faecal incontinence and 10 had previous (more than 3 months) faecal incontinence. 15 (16%) patients had current faecal incontinence only and 11 (16%) had previous faecal incontinence only. The overall prevalence of current and previous faecal incontinence was 53%. 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, Fischer 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 DEFAECATION ARE MORE SENSITIVE TO ANORECTAL EVENTS THAN THOSE WITH SLOW TRANSIT CONSTIPATION AND NORMAL SUBJECTS.

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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 4-28] per record p < 0.01) compared with N (5 [0-15]) and STC (5 [0-13]) 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 unproductive 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.

Aim: 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 dietician, 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 difference was found between dietary fibre intake between low and high risk groups (24.7 ± 8.9 vs 21.1 ± 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.