Liver free papers 001–011

001 PLASMA INTERLEUKIN-18 (IL-18) LEVELS IN CHRONIC ALCOHOLIC LIVER DISEASE (ALD) AND ALCOHOLIC HEPATITIS (AH) ARE RELATED TO DISEASE SEVERITY

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Aim and Background: IL-18 is a novel pro-inflammatory cytokine of the IL-1 family and is critical in the development of Th-1 responses. Th-1 responses have been implicated in the pathogenesis of ALD. We investigated IL-18 expression in patients with ALD and AH.

Patients and Methods: We studied inpatients with ALD (n = 48, I/P ALD), outpatients with compensated ALD (n = 13, O/P ALD), and healthy volunteers (n = 15, HVs). The mean age of the I/P ALD (46 years) and O/P ALD (47.7 years) matched that of the O/P ALD group 55.2 years. Other forms of chronic liver disease were excluded by standard serological tests. IL-18 levels were measured by ELISA (Diaclone). Whole blood cell culture (WBC) +/- lipopolysaccharide (LPS) was performed to assess IL-18 production. A Childs-Pugh score and a Maddrey’s Discriminant Function were calculated for all patients. The results were analysed by Mann-Whitney U test.

Results: Inpatients consisted of five with Childs grade A, 17 B, and 26 C. Eighteen had a MDF > 24, 9 a MDF of 24–32, and 21 a MDF > 32. Plasma IL-18 levels were significantly elevated in the I/P ALD group when compared with O/P ALD and HVs (all units pg/ml), (174 +/- 1.70, 45 +/- 5.2, and 32 +/- 83; p < 0.01 and p < 0.001).

IL-18 levels in Child’s C inpatients [226 +/- 214] were significantly reduced compared to Child’s A inpatients [27 +/- 38; p < 0.01].

Conclusion: Plasma IL-18 levels were significantly reduced in the I/P ALD group when compared with O/P ALD and HVs [174 +/- 1.70, 45 +/- 5.2, and 32 +/- 83; p < 0.01].

002 TREATMENT WITH ANTI-TUMOUR NECROSIS FACTOR (TNF) ANTIBODY IMPROVES CLINICAL PARAMETERS AND REDUCES PORTAL PRESSURE IN ALCOHOLIC HEPATITIS


Background: Patients with alcoholic hepatitis (AH) and cirrhosis exhibit an increase in inflammatory cytokines and portal hypertension. TNF is a key mediator in AH, promoting a cascade of inflammatory activity. In this study we addressed the effects of the chimeric anti-TNFx antibody, infliximab, on clinical parameters and portal haodynamics, and tested the hypothesis that the development of portal hypertension in AH is associated with inflammation.

Methods: Sixteen patients with biopsy proven AH (mean age 57 +/- 4 and discriminant function 52.4 +/- 6.8) were treated with the chimeric monoclonal anti-TNFx antibody, infliximab, (5 mg/kg body weight). Ten of these patients had assessment of their wedge hepatic venous pressure (WHVP) before, 24 hours, and 28 days after infliximab treatment. Patients’ clinical and biochemical profiles were monitored during the study period.

Results: Significant improvements were noted by 28 days in bilirubin (293 +/- 33 to 130 +/- 21; p < 0.001), CRP (73 +/- 10 to 36.1 +/- 12.7; p < 0.01), white cell count (15.9 +/- 2.1 to 10.5 +/- 1.5; p < 0.05) and SIRS score (2.6 +/- 0.4 to 0.23 +/- 0.12; p < 0.01). Three patients died during the study period, with two developing sepsis, both from Staphylococcus aureus. No patient developed renal failure or hepatorenal syndrome, or required intensive care support. WHVP reduced significantly from 38.63 +/- 2.39 to 29.14 +/- 1.42 mm Hg at 24 hours, and the reduction was sustained at 28 days (27.4 +/- 2.82 mm Hg; p < 0.01) with no significant differences in free HVP or CVP. Mean arterial pressure (MAP) increased significantly (71.6 +/- 1.72 to 81.1 +/- 3.15 mm Hg; p < 0.05 at 28 days).

Conclusion: Anti-TNFx treatment results in a significant reduction in bilirubin, white blood cell count, CRP, and SIRS score, coupled with an apparent improved clinical outcome. This improvement in clinical and inflammatory parameters is accompanied by a highly significant, early, and sustained reduction in HVPG, as well as a significant increase in MAP. We conclude that portal hypertension in AH has a significant inflammatory component that can be partially corrected with anti-TNFx therapy. This provides some insight in to the possible mechanisms of portal hypertension in AH.

003 PREDICTORS OF SHORT AND MEDIUM TERM MORTALITY IN ACUTE ALCOHOLIC HEPATITIS

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Introduction: The modified Maddrey’s Discriminant Function (DF) is used to identify poor prognosis acute alcoholic hepatitis (AAH). This calculation requires conversion of serum bilirubin from mg/dl to μmol/l and a corrected calculation of prothrombin time (PT) prolongation. The DF is therefore awkward to use in a clinical setting. We aimed to identify variables related to mortality in patients with AAH.

Methods: Clinical and laboratory data was collected from 256 patients with clinical AAH. Stepwise logistic regression identified variables associated with mortality.

Results: Day 1 and 7 variables associated with short term (28 days) and medium term (84 day) mortality are displayed in Table 1. The correct predictions for each model and the DF are shown in Table 2.

Conclusions: The DF failed to identify the majority of patients who died. The variables we identified significantly improved the identification of patients with poor short and medium term prognosis.

Abstract 3 Table 1

<table>
<thead>
<tr>
<th>Day 1 Variables</th>
<th>Day 28 Mortality</th>
<th>Day 7 Variables</th>
<th>Day 84 Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Urea</td>
<td>p = 0.019</td>
<td>Serum Bilirubin</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Serum Bilirubin</td>
<td>p &lt; 0.001</td>
<td>PT</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>p = 0.025</td>
<td>Age</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>p &lt; 0.001</td>
<td>Leucocyte Count</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>p = 0.028</td>
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<td></td>
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</tbody>
</table>

Abstract 3 Table 2

<table>
<thead>
<tr>
<th>Prediction Model</th>
<th>Outcome (number)</th>
<th>Predicted Dead as Dead</th>
<th>Predicted Dead as Alive</th>
<th>Predicted Alive as Dead</th>
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</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 28</td>
<td>30</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Variables</td>
<td>(n=245)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 DF</td>
<td>Day 28</td>
<td>10</td>
<td>54</td>
<td>3</td>
</tr>
<tr>
<td>(n=256)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>Day 84</td>
<td>34</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Variables</td>
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<td>Day 7 DF</td>
<td>Day 84</td>
<td>21</td>
<td>45</td>
<td>11</td>
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<tr>
<td>(n=199)</td>
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WORSENING OF CEREBRAL HYPERAEMIA IN ACUTE LIVER FAILURE (ALF) WITH TERLIPRESSIN

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Background: The role of terlipressin in ALF patients is not clear. Terlipressin acts through the V1 and V2 receptors. V1 receptors, distributed in the systemic circulation, mediate vasoconstriction. V2 receptors, distributed in the cerebral vasculature, in contrast mediate cerebral vasodilatation through a nitric oxide dependent mechanism. It is therefore possible that terlipressin may accentuate cerebral hyperaemia and worsen intracranial pressure (ICP) in ALF. This study evaluated the haemodynamic effect of a small dose of terlipressin in six patients (median age 27 (22–46), four female) with ALF (paracetamol four, acute fatty liver of pregnancy one, non A/non B viral one) and grade IV encephalopathy.

Method: ICP was continuously monitored in five/six patients using a subdural fibreoptic system. Cardiovascular haemodynamics were monitored with pulmonary artery, right atrial, and arterial catheters. Jugular venous oxygen saturation (JVOS) was monitored using a reverse jugular catheter and cerebral blood flow (CBF) was measured using a modified Kety-Schmidt technique, prior to and 1 hour after administration of 0.01 mg/kg of terlipressin intravenously as a single bolus.

Results: There was no significant rise in mean arterial pressure (MAP). ICP increased in all patients [median 15 (range 13–20) to 20 (range 16–23) mmHg; p < 0.02] after 1 hour and returned to baseline values after 3 hour. CBF increased significantly at 1 hour [median 69 (range 48–79) to 81 (range 62–97) ml/100 g/min; p < 0.02]. JVOS increased at 1 hour [median 75% (range 67–89) to 87% (range 75–94)].

Conclusions: Administration of even a sub-therapeutic dose of terlipressin increases CBF and consequently ICP, without causing significant change to systemic haemodynamics. Terlipressin may therefore have deleterious consequences through worsening of cerebral hyperaemia and ICP. These data suggest extreme caution and close monitoring if this drug is used in patients with ALF.

ISOLATION AND CHARACTERISATION OF HUMAN HEPATIC STEM CELLS IN FETAL LIVER

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Introduction: Hepatic stem cells have been described in rat which express the surface antigens CD90 (Thy-1) and CD34. We hypothesised that a similar population may exist in human fetal liver, giving rise to hepatocyte precursors after cytokine treatment in vitro.

Methods: Human fetal liver was subject to collagenase digestion. The cells were labelled with anti-CD90 monoclonal antibody, anti-mouse phycocerythrin conjugate and FITC-conjugated monoclonal anti-CD34 antibody. Fluorescence-activated cell sorting provided CD90+ve, CD34+ve or CD90+ve/CD34+ve cells, which were cultured for 7 days in the presence and absence of cytokines giving rise to hepatocyte precursors after cytokine treatment in vitro.

Results: Two per cent of the liver cell suspension was CD90+ve, CK19+ve cells and other slightly larger cells −ve/CD34+ve or CD90+ve/CD34+ve, which expression of the MMP inhibitor TIMP-1 and an increase in hepatic collagenolytic activity accompanied by HSC apoptosis; in advanced cirrhosis, TIMP-1 expression is maintained, and HSC persist. We have previously demonstrated that TIMP-1 can inhibit apoptosis of HSC by mechanisms involving MMP inhibition. We have studied the role of N-cadherin in vitro. Active MMP-2 also promotes apoptosis of HSC. During apoptosis of HSC there is cleavage of N-cadherin into 135kDa and 70kDa fragments. By Western blot both rat and human HSC express 135kDa N-cadherin. Blockade of N-cadherin promoted apoptosis of HSC. During apoptosis of HSC there is cleavage of N-cadherin into fragments of 20–100kDa in size, which is protected by TIMP-1 and a selective inhibitor of MMP-2, but not inhibitors of MMP-1 or MMP-3 or a non functional mutant T2G TIMP-1. Active MMP-2 directly cleaves N-cadherin in vitro. Active MMP-2 also promotes apoptosis of HSC.

Conclusions: These data suggest that the balance of MMP-2 and TIMP-1 determines HSC survival in hepatic fibrosis via stabilising N-cadherin.

TOLL-LIKE RECEPTOR EXPRESSION IN CIRRHOSIS

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Background: Pro-inflammatory cytokines such as tumour necrosis factor α (TNFα) contribute to liver damage in cirrhosis. Relevant to this is the expression of toll-like receptor (TLR) and TLR2, critically involved in TNFα production in response to endotoxin and Gram-positive stimuli, respectively, the first studies on which in cirrhosis are reported here.

Methods: We measured in 36 cirrhotic patients and 32 controls (a) circulating endotoxin and TNFα levels, (b) peripheral blood mononuclear cell (PBMC) expression of TLR4 and TLR2, and (c) in vitro production of TNFα by PBMCs in response to stimulation by endotoxin or Staphylococcus aureus enterotoxin B (SEB), a Gram-positive microbial antigen. To determine the role of Gram-positive gut flora, TLR2 expression and TNFα production were re-assessed after supplementation for 7 days with a symbiotic regimen (Synbiotic 2000; MediPharm, Sheringa) known to increase intestinal levels of Gram-positive bacteria.

Results: Circulating endotoxin and TNFα levels were significantly increased in cirrhotic patients but not correlated. Expression of TLR2, but not TLR4, was significantly upregulated and correlated significantly with serum TNFα levels. In vitro production of TNFα in response to stimulation with SEB was significantly blunted, in keeping with previous work showing chronic stimulation by Gram-positive antigens in vivo. Oral supplementation with the symbiotic regimen resulted in further, significant up-regulation of systemic TLR2 expression. Further impairment of TNFα production in response to SEB occurred in most patients.

Conclusions: Upregulation of TLR2 but not TLR4 in cirrhosis implies, contrary to previous assumptions, an important stimulatory role for Gram-positive microbial antigens but not endotoxin. Such Gram-positive antigens may be derived from the gut. Signalling via TLR2 contributes to increased circulating TNF-α levels in cirrhosis.

BALANCE OF TIMP-1 AND MMP-2 DETERMINES N-CADHERIN CLEAVAGE IN HEPATIC STELLATE CELL APOPTOSIS

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Introduction: The hepatic stellate (HSC) is known to synthesise the majority of excess matrix that characterises liver fibrosis and cirrhosis. Activated HSC also express matrix degrading metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). Whereas during spontaneous recovery from experimental liver fibrosis, there is a fall in the expression of the MMP inhibitor TIMP-1 and an increase in hepatic collagenolytic activity accompanied by HSC apoptosis; in advanced cirrhosis, TIMP-1 expression is maintained, and HSC persist. We have previously demonstrated that TIMP-1 can inhibit apoptosis of HSC by mechanisms involving MMP inhibition. We have studied the role of N-cadherin because it is known to be up regulated during HSC activation and may have a role in determining HSC survival and apoptosis.

Aims: To determine the effect of blockade of N-cadherin binding on HSC; observe the fate of N-cadherin during HSC apoptosis; determine which MMP is involved and its direct effect on HSC.

Methods: By Western blot both rat and human HSC express 135kDa N-cadherin. Blockade of N-cadherin promoted apoptosis of HSC. During apoptosis of HSC there is cleavage of N-cadherin into fragments of 20–100kDa in size, which is protected by TIMP-1 and a selective inhibitor of MMP-2, but not inhibitors of MMP-1 or MMP-3 or a non functional mutant T2G TIMP-1. Active MMP-2 directly cleaves N-cadherin in vitro. Active MMP-2 also promotes apoptosis of HSC.

Conclusions: These data suggest that the balance of MMP-2 and TIMP-1 determine HSC survival in hepatic fibrosis via stabilising N-cadherin.

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IMPROVEMENT IN INDOCYANINE GREEN CLEARANCE FOLLOWING SYNBIOtic TREATMENT IN CIRRHOSIS

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Background: Intervention aimed at reducing intestinal levels of endotoxin containing Gram-negative bacteria is reported to improve systemic haemodynamic disturbance in cirrhosis. Any beneficial effect on hepatic blood flow is unknown. This study addressed this issue.

Methods: We studied 15 cirrhotic patients (hepatitis C virus, n = 7; alcohol, n = 6; primary biliary cirrhosis, n = 1; idiopathic, n = 1; Child-Pugh grade A, n = 6; B, n = 5; C, n = 4) and 11 patients with chronic hepatitis (hepatitis C, n = 9; hepatitis B, n = 1; non-alcoholic steatohepatitis, n = 1). Indocyanine green retention at 15 min (ICGR15) following an intravenous bolus of 0.5 mg/kg body weight was assessed as an index of hepatic blood flow, using a non-invasive transcutaneous system (LiMon, Pulson, Germany). ICGR15 was measured at baseline and following oral supplementation for 7 days with a synbiotic (probiotic and fermentable fibre) preparation including Lactobacillus plantarum 23622, L paracasei subsp paracasei 19, Pedicoccus pentosaceus 5–33–3, and L raffinolactis 32–77–1, designed to increase the intestinal content of Gram-positive bacteria (Synbiotic 2000, MediPharm, Sweden).

Results: ICGR15 was significantly higher in cirrhotic patients (median 38.3, range 5.0–60%) than those with chronic hepatitis (median 5.3, range 1.8–9.7%) (p < 0.0005). Supplementation with the synbiotic regimen was associated with a significant reduction in ICGR15 in the cirrhotic group (p < 0.0002). ICGR15 was reduced by a median 17.5% (range 1.4–65%) of baseline values in 14/15 (93%) such patients and increased by 4.1% in the other patient. Treatment led to no significant change in ICGR15 in patients with chronic hepatitis (p = 0.65).

Conclusions: Use of a Gram-positive synbiotic preparation significantly improves ICGR clearance in cirrhotic patients, presumably by reversing a disturbance in gut flora occurring in cirrhosis but not chronic hepatitis that adversely affects hepatic blood flow.

CHARACTERISATION OF DIFFUSE LIVER DISEASE IN PATIENTS WITH HEPATITIS C USING 13P MAGNETIC RESONANCE SPECTROSCOPY (MRS)

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Purpose: Liver biopsy remains the gold standard for characterising and staging diffuse liver disease. This invasive test is associated with significant morbidity and, rarely, mortality. Our aim was to investigate whether a non-invasive technique, in vivo 13P(MRS) could grade the severity of diffuse liver disease in patients whose liver disease was attributable to hepatitis C (HCV) infection only.

Materials and Methods: Twelve controls and 47 patients with biopsy-proven HCV infection were studied prospectively. Based on their histological fibrosis (F) and necroinflammatory (NI) scores, subjects were divided into mild hepatitis, n = 17 (F 2/6, NI 3/18); moderate/severe hepatitis, n = 19 (F 3/6, NI 4/18); and cirrhosis, n = 11 (F 6/6). Hepatic 13P MR spectra were obtained using a 1.5 Tesla spectroscopy system (TR: 10 000; TE: 2).

Results: There was a monotonic increase in the mean ± 1 s.e. phosphomonoester (PME) to phosphodiester (PDE) ratios for the phosphomonoester (PME) to phosphodiester (PDE) ratios of the control, mild hepatitis, moderate hepatitis and cirrhosis groups: 0.16 ± 0.01 (n = 19) vs. 0.37 ± 0.07 (n = 25) vs. 0.58 ± 0.04, respectively (ANOVA p < 0.001). No other significant spectral changes were observed.

Conclusion: 13P MRS cannot diagnose HCV infection, but in patients with proven infection, this test can characterise the severity of liver disease. We have shown that the ratio of PME to PDE resonance in 13P MRS is able to separate mild from moderate hepatitis and these two groups from cirrhosis. The ability to differentiate these populations has therapeutic implications and 13P MRS, in some situations, would not only complement a liver biopsy but could replace it.

DETECTION OF HEPATIC BLOOD FLOW USING MICROBUBBLE ENHANCED ULTRASOUND IN THE DIAGNOSIS OF CIRRHOSIS

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Background: It has been previously shown that alterations in hepatic haemodynamics can be assessed in cirrhotic patients by measuring the hepatic vein transit time of an ultrasound contrast agent.

Aim: To evaluate the clinical usefulness of a new contrast agent (SonoVue, in differentiating between patients with cirrhosis, hepatitis C and normal subjects.

Methods: We studied 13 healthy controls, 14 subjects with biopsy proven hepatitis C and 18 subjects with proven cirrhosis, using a Philips-ATL 5000 scanner with a 3.5 MHz curvilinear scanner. An intercostal scan including the hepatic vein (HV), the hepatic artery (HA), and the portal vein (PV) was selected. Colour-Doppler gain was reduced until no signal was displayed and MI was set at 0.8. A bolus injection of 1 ml SonoVue was given. The transit time, defined as the time interval in seconds between the start of the injection and first appearance ofcolour-Doppler signal in the vessel, was recorded for the HA, HV, and PV. The “Intrahepatic time index” (ITI) was defined as the difference between the HV arrival time and the HA arrival time. Each scan was recorded on SVHS tape for offline review.

Results: Overall differences between groups were significant for all variables (p < 0.001). Pairwise differences between the cirrhotic group and each of the other two groups were all statistically significant (p < 0.05), and those between the hepatitis C group and controls were significant for all variables except HA (p < 0.05). An ITI 9 sec showed a sensitivity of 0.90 in detecting cirrhosis, and specificities of 0.93 and 1.00 in distinguishing cirrhosis from hepatitis and controls respectively. An ITI between 9 and 13 sec showed a sensitivity of 0.64 and specificity of 0.90 in distinguishing hepatitis from the control groups.

Conclusion: ITI is accurate in detecting cirrhosis and may be useful in identifying hepatitis C patients with underlying cirrhosis.

NATIONAL NEEDS ASSESSMENT FOR HEPATITIS C

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Background: Hepatitis C virus (HCV) infection is a major health care problem. The publication of the National Strategy for Hepatitis C emphasised the need to scope the current service configuration, workloads, and capacity in the UK in order to implement the improvements in care detailed by the strategy, and to inform future planning of services. BASL and the Liver section of the BSG commissioned this national needs assessment of hepatitis C to gain this knowledge.

Aim: To conduct a national survey to determine the workload and configuration of current services available to manage patients with hepatitis C, and to identify models of good practice.

Methods: A questionnaire survey was conducted on a purposive sample of consultant members of BASL (n = 49), consultants in infectious diseases (n = 42), and 1.5 sample of GUM and GI physicians (n = 47, n = 186) stratified by Health Region. In-depth field interviews and semi-structured telephone interviews were conducted where novel or innovative models of care were identified.

Results: Preliminary data are reported, with full results available for the BSG meeting. Questionnaire response rate was 75%. Forty percent of respondents provided a complete service from various clinical
settings: hepatology (34%), GI (50%), and infectious diseases (16%). Total number of patients managed by the respondents was > 23 000 with upward trend over the past 3 years. Seventy-five per cent of referrals to these specialist service providers came with an established diagnosis of HCV. There is variation in practice for treatment decisions. Eligibility for treatment was in range 25–49% with 50–74% receiving treatment. Twenty-four per cent of specialist service providers have outreach clinics. Identified barriers to management include staffing capacity, patient non-attendance, and funding of treatment.

**Conclusions:** Detailed quantitative and qualitative data from this survey will inform the future planning of hepatitis C services. Preliminary data suggest significant variation in service delivery.

### Endoscopy free papers 012–021

**012 COLONOSCOPIC APPEARANCES HELP PREDICT DYSPLASIA RISK IN ULCERATIVE COLITIS**

M.D. Rutter, G. Schofield, K.H. Wilkinson, A. Forbes, B.P. Saunders. St Mark’s Hospital, Harrow, UK

**Background and aim:** Colonoscopic surveillance attempts to reduce the excess cancer risk in ulcerative colitis (UC). We aimed to assess whether colonoscopic appearances help predict cancer risk.

**Methods:** A case control study of patients on UC surveillance; 68 patients with dysplasia/carcinoma (CRC) and 136 patients without dysplasia/CRC were matched for age at onset of UC, duration, and extent of UC and sex. Medical and colonoscopic reports were reviewed, and data on colonoscopic appearances documented.

**Results:** 204 patients underwent 1217 colonoscopies. Patients who had one or more macroscopically normal surveillance colonoscopies were at reduced risk of dysplasia/CRC (p = 0.004, OR 0.4 [0.2–0.7]). Patients with one or more segments of severe inflammation at any of their surveillance colonoscopies were at increased risk of dysplasia/CRC (p < 0.001, OR 4.9 [2.0–12.2]). Other results are shown in the table.

**Conclusion:** Colonoscopic features can help predict cancer risk in UC. Severe inflammation, strictures, a shortened colon, and postinflammatory polyps appear to confer significant increased dysplasia risk, whereas a macroscopically normal colonoscopy confers a reduced (although not zero) risk of subsequent dysplasia development. Contrary to a recent report, we did not find that patients with backwash ileitis were at greater risk of developing colorectal cancer.

### DYSPLASIA IN ULCERATIVE COLITIS IS USUALLY VISIBLE AT COLONOSCOPY

M.D. Rutter, K.H. Wilkinson, B.P. Saunders. Wolfson Unit for Endoscopy, St Mark’s Hospital, Harrow, UK

**Background and aim:** During colonoscopic surveillance for dysplasia in longstanding extensive ulcerative colitis (UC), multiple non-targeted “random” biopsies of colonic mucosa are advised, based on historical data suggesting dysplasia may only be detectable microscopically. We aimed to assess what proportion of dysplastic lesions were macroscopically evident at colonoscopy.

**Methods:** All cases of colonoscopically detected dysplasia in a major UC surveillance programme from 1/1/88 to 1/1/02 were reviewed. Details were obtained from our colonoscopy database, case notes (including colonoscopic photographs), and histology reports. All dysplasia was assumed to be macroscopically invisible unless stated otherwise at the time.

**Results:** During the study period, 300 patients underwent 2189 colonoscopies. Fifty-six patients had one or more biopsies showing colorectal dysplasia. In total, 92 colonoscopies yielded 106 positive biopsies. Eighty-one (76%) dysplastic biopsies were from macroscopically visible lesions, and 25 sites of dysplasia (24%) were macroscopically invisible. Thirty-three lesions were considered endoscopically and histologically to be tubular adenomas. Excluding these, there were 73 dysplastic biopsies (38 patients, 65 colonoscopies). 48 (66%) of these were from macroscopically visible lesions. Overall, 50 patients (82%) had macroscopically detectable dysplasia during the study period, and six patients with dysplasia (18%) had only macroscopically invisible lesions.

**Conclusion:** Over 80% of patients with dysplastic lesions in ulcerative colitis will develop a colonoscopically visible lesion. Even after excluding tubular adenomatous lesions, the majority of dysplasia is colonoscopically visible. Colonoscopists should concentrate on careful mucosal scrutiny for dysplastic lesions, rather than relying solely on detection by random biopsies.

### EUS GUIDED FINE NEEDLE ASPIRATION FOR UNDIAGNOSED HILAR STRICTURES SUSPICIOUS OF CHOLANGIOCARCINOMA

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**Background:** Despite improvements of diagnostic modalities differentiation between benign and malignant strictures at the liver hilum remains a challenge. Extensive hepatic resections with intention to cure or modern palliative concepts require preoperative diagnosis, to avoid risk of misdiagnosis and inappropriate surgical treatment for the patients. Preoperative tissue diagnosis, most commonly achieved during ERCP, can be difficult. We used endosonography guided fine needle aspiration (EUS-FNA) for preoperative diagnosis of hilar cholangiocarcinoma.

**Methods:** Prospective evaluation of 44 patients (31 male, age 37–74, mean age 59) with strictures at the liver hilum diagnosed by computed tomography and/or ERCP. All were highly suspicious of hilar cholangiocarcinoma but had inconclusive brush cytology or biopsy, and subsequently underwent EUS-FNA with a linear echoendoscope and 22 gauge needles.

**Results:** Adequate material was achieved in 43 out of 44 patients. Cytology revealed cholangiocarcinoma in 26 patients, hepatocellular carcinoma, Hodgkin’s disease, metastasis of colon and ovarian cancer, and neuroendocrine tumour in one each. Twelve patients had benign diseases with chronic fibrosing inflammation in four, inflammation in two, sarcoid like changes in one and primary sclerosing cholangitis (PSC) in five. Four of the benign results were false negatives. Thirty-five patients underwent surgery. Patients with benign results and PSC were followed up, patients with Hodgkin’s disease and metastases of other primaries had chemotherapy. In one patient adenocarcinoma was discovered at repeat surgery. No complication occurred. Accuracy, sensitivity, and specificity were 91%, 90%, and 100%, respectively. EUS and EUS-FNA changed preplanned surgical approach in 22/43 patients.

**Conclusion:** These results suggest that EUS-FNA may be a valuable, less invasive approach for tissue diagnosis of unknown hilar strictures. It proved to be technically feasible without significant risks, when other diagnostic tests were inconclusive and was able to change preplanned management in about half of the patients.

<table>
<thead>
<tr>
<th>Colonoscopic feature</th>
<th>Case n=68 (%)</th>
<th>Control n=136 (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-inflammatory polyps</td>
<td>42 (62)</td>
<td>53 (39)</td>
<td>2.5 (1.4–4.6)</td>
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<tr>
<td>Colonic strictures</td>
<td>10 (15)</td>
<td>4 (3)</td>
<td>5.7 (1.7–18.9)</td>
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<td>Backwash ileitis</td>
<td>7 (10)</td>
<td>12 (9)</td>
<td>1.2 (0.4–3.2)</td>
<td>0.8</td>
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<tr>
<td>Scarring</td>
<td>19 (28)</td>
<td>26 (19)</td>
<td>1.6 (0.8–3.2)</td>
<td>0.157</td>
</tr>
<tr>
<td>Shortened colon</td>
<td>6 (9)</td>
<td>0 (0)</td>
<td>28.4 (1.6–512.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tubular colon</td>
<td>24 (35)</td>
<td>31 (23)</td>
<td>1.8 (0.98–3.5)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

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**015 RADIOATION EXPOSURE TO PERSONNEL PERFORMING ERCP**

S. Singhal, L. Naidu, D.E. Preece, A. Vohra, D.E. Lofth. Department of Gastroenterology, University Hospitals Coventry and Warwickshire NHS Trust; Department of Clinical Physics and Bioengineering, University Hospitals Coventry and Warwickshire NHS Trust; Department of Radiology, University Hospitals Coventry and Warwickshire NHS Trust

**Background:** ERCP relies on the use of ionising radiation but the risks to operator and patient associated with radiation exposure (in terms of subsequent biological damage) are unclear. The aim of this prospective study was to estimate the radiation dose received by personnel performing fluoroscopic endoscopic procedures, mainly ERCP.

**Methods:** Consecutive procedures over a 2 month period were included. The use of thermoluminescent dosimeters to measure radiation exposure to the abdomen, thyroid gland, and hands of the operator permitted an estimation of the annual whole body effective radiation dose (ED) equivalent to be made.

**Results:** During the study period 66 fluoroscopic endoscopic procedures (61 ERCP) were performed and the estimated annual whole body ED equivalent received by consultant operators ranged between 3.35 and 5.87 mSv. These values are similar to those received by patients undergoing barium studies and equate to an estimated additional lifetime fatal cancer risk between 1 in 7000 and 1 in 3500. Although within the legal safety limits for radiation exposure to personnel, these radiation doses are considerably higher than the levels deemed acceptable for the general public.

**Conclusions:** We suggest that personnel as well as patients may be exposed to significant levels of radiation during ERCP. We emphasise the need to carefully assess the indication for, and to employ measures that, minimising radiation exposure during any fluoroscopic procedure.

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**016 COULD CANCER STAGING AND TUMOUR MEASUREMENTS BE IMPROVED BY USING 3D ENDOSCOPIC ULTRASONOGRAPHY?**

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**Introduction:** Endoscopic ultrasound (EUS) is routinely used to stage upper G1 cancers. This technique estimates depth of invasion, but may not provide reliable information on tumour length. 3D EUS could improve staging and treatment monitoring by providing complete datasets, detailing the progression of the tumour along the oesophagus and accurate dimensional measurements.

**Aims:** To compare (a) the measurement capabilities of 2D and 3D EUS in an oesophageal cancer phantom; and (b) the staging of patients with oesophageal cancer from 2D and 3D EUS.

**Methods:** Two experienced endoscopists used the Olympus GF-UM200 scope/EU-M30 processor to scan the phantom and patients at 7.5 and 12 MHz. Images were captured at 25 frames/sec. (a) In vitro 3D data were acquired from an EUS anthropomorphic oesophageal cancer phantom with known dimensions. (b) In vivo 3D data were obtained during conventional 2D EUS as the scope was withdrawn. 3D volumes were reconstructed from a series of parallel B-mode images. Dimensional measurements and cancer staging was performed during the routine test. A retrospective comparison was made between the cancer staging and dimensions obtained from 2D EUS and from our 3D EUS system.

**Results:** Routine 2D length measurements performed on the phantom had a mean error of 9% (max 23%). Identical measurements performed using 3D EUS had a mean error of 1.7% (max 3.7%). 3D EUS could visualise nodes < 5 mm and detected nodes not observed during routine EUS. The 3D system improved the reproducibility of the X, Y, and Z measurements of tumour and nodes with mean intra and inter observer coefficient of variation < 5%. **Conclusions:** This study has shown that the 3D technique can accurately measure tumour and node dimensions with good reproducibility. Since the main in vitro error was estimating the length of embedded objects, it is likely that 2D EUS cannot estimate tumour and node length as accurately as previously thought. This preliminary work suggests that 3D EUS may increase diagnostic accuracy of node staging and introduce a fifth criterion (length) to diagnose malignant nodes.

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**017 CHROMOENDOSCOPY WITH METHYLENE BLUE IN BARRETT’S OESOPHAGUS: ADDING INSULT TO INJURY?**

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Chromoendoscopy with methylene blue (MB) is increasingly being applied during endoscopic examination of Barrett’s oesophagus (BO). MB selectively stains specialised intestinal metaplasia as it is specifically absorbed by the goblet cells characterising this tissue. Experimental studies show that photosensitisation of MB with visible light stimulates the formation of singlet oxygen species leading to the generation of single strand breaks and oxidative alterations to guanine residues of which the promutagenic DNA adduct, 8-hydroxydeoxyguanosine (8-OHdG) predominates. We hypothesised that the application of MB to the oesophagus followed by exposure to endoscopic light may stimulate high levels of DNA damage in BO. Biopsies were collected before and after MB exposure from immediately adjacent sites within BO mucosa from 15 patients. Biopsies were subject to DNA damage analysis using the comet assay to detect strand breaks and alkali-labile sites. In addition the enzyme Fapy-DNA glycosylase (FpG) was incorporated into the assay to allow the detection of FpG sensitive sites, including 8-OHdG. For each patient studied, DNA damage levels increased (range 6.0–71.9%) following MB chromoendoscopy. Statistical comparison of matched biopsies revealed a significant difference (p < 0.005) in the DNA damage level before (28.8% [24.6–32.4%], median percentage tail DNA (1st–3rd quartile)) compared to after chromoendoscopy (36.5% [32.1–42.7%]). Following MB chromoendoscopy the percentage of cells with highly damage DNA attributable to FpG sensitive sites, approximately doubled. Barrett’s mucosa is a recognised neoplastic tissue, which exhibits many genetic and epigenetic alterations. Exposing this and any associated further promutagenic DNA damage, via MB chromoendoscopy warrants caution as it could potentially accelerate the carcinogenic process.
Conclusion: This study emphasises the importance of detecting cancer at an early stage with a low threshold for multiple biopsies of an abnormal finding.

**019** PAN-COLONIC INDIGO CARMINE DYE SPRAYING FOR THE DETECTION OF DYSPLASIA IN ULCERATIVE COLITIS

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Background and Aim: Patients with longstanding extensive ulcerative colitis (UC) are at increased risk of colorectal cancer. Colonoscopic surveillance is often performed, and relies heavily on multiple non-targeted mucosal biopsies detecting occult dysplasia. Chromoendoscopy can aid detection of subtle mucosal abnormalities. We hypothesised that the routine use of pan-colonic indigo carmine dye spray would improve the macroscopic detection of dysplasia while reducing the dependence on non-targeted biopsies.

Methods: One hundred patients with longstanding extensive UC attending for colonoscopic surveillance underwent "back-to-back" same day colonoscopies. During the first examination, all visible abnormalities were biopsied and quadrantic, non-targeted biopsies were taken every 10 cm throughout the colon and rectum (20–40 biopsies per patient). Indigo carmine dye (0.1%) was used to coat the entire mucosal surface during the second colonoscopic withdrawal, and additional abnormalities detected with dye spray were biopsied.

Results: Exubation times for first and second colonoscopies were 11 and 10 min, respectively. Forty-three mucosal abnormalities (from 20 patients) were detected by pre-dye spray targeted biopsies, and following indigo carmine dye-spraying 114 additional abnormalities (in 55 patients) were detected. Pre-dye spray targeted biopsies detected lesions considered to be dysplasia associated lesions/masses (DALMs) in two patients. Dye spraying detected seven additional dysplastic lesions (2–6 mm) in five patients. All seven were considered histologically and colonoscopically to be sporadic adenomas. No dysplasia was detected in 2904 non-targeted biopsies.

Conclusions: Pan-colonic indigo carmine dye spraying increased the number of dysplastic mucosal areas, but the vast majority of these were non-dysplastic. Chromoendoscopy may be more time-effective than taking high numbers of non-targeted biopsies, however most significant abnormalities can be detected by careful mucosal examination and targeted biopsies.

**020** IMPROVING COLONOSCOPY COMPLETION RATES: THE IMPACT OF AUDIT

A. Bassi, P. O’Toole. University Hospital Aintree, Liverpool, UK

Introduction: The BSG National Colonoscopy Audit reported that colorectal intubation rates in the UK fell short of the recommended 90%. Addressing this requires both national and local initiatives. The audit process is one tool for producing local service improvement. We report our experience of colonoscopy audit in a large teaching hospital.

Methods: All colonoscopy reports produced between 1 February and 31 July 2000 were reviewed retrospectively. Completion rates and main reasons for failure were recorded for each operator. Procedures were regarded as complete if the ileum was entered or the ileo-caecal valve identified, or if scope advancement was prevented by strictures, tumour, or severe colitis. Based on these findings, several changes were implemented. The audit was then repeated using an identical method, for the same six month period in 2001.

Results: During the first six month period 676 colonoscopies were performed. Overall completion rate was 75%. This was influenced by the poor performance of a small number of endoscopists. The commonest reason for failure was poor bowel preparation (35%). Following this, new bowel preparation guidelines were introduced, three endoscopists were retrained and the principal trainer attended the Training the Trainers course. During the second audit period there were 729 colonoscopies. Overall completion rate had improved to 89%, with improvement across all subgroups (Table). No perforations occurred in either audit period.

Discussion: We acknowledge the obvious limitations of using self-reported caecal intubation rates, but believe this study confirms the value of audit as a tool for improving colonoscopy performance.

**021** IS THE UK GASTROINTESTINAL ENDOSCOPY TRAINING ADEQUATE? THE TRAINEE’S AND TRAINER’S PERSPECTIVES

T. Mahmood, A. Darzi, D. Baucier-Hayes, S. Bann. Academic Surgical Unit, St Mary’s Hospital NHS Trust, London

Objectives: To measure the training standards in gastrointestinal endoscopy from the perspective of the specialist registrars (SpRs) and the trainers.

Design: Content validated, computer coded, mailed questionnaire.

Setting: Academic Surgical Unit, Imperial College of Medicine, London.

Participants: Randomly selected 100 SpRs and 100 consultants throughout the United Kingdom from attendants of BSG meeting 2000 or members of the society.

Main Outcomes: Level of training already achieved in endoscopy, according to the year of training, compared with the standard expected by the SpRs and the consultant trainers.

Results: There was an unequivocal lack of training in gastroscopy, flexible sigmoidoscopy, and colonoscopy acknowledged by both the trainees and the trainers. The SpRs in the final year of training had not achieved level five training (therapeutic endoscopy) in 4% gastroscopy, 15.4% flexible sigmoidoscopy, and 37.5% colonoscopy (<0.001 for all).

Conclusions: Almost one third of the SpRs in the final year of training (appointable as a consultant), and their trainers did not feel that appropriate level of training had been achieved in colonoscopy to run independent endoscopy lists. Courses and ongoing objective assessment in endoscopy should be an integral part of training in gastroenterology. Guidelines regarding standards required should be validated. Should we have a system of training and assessment in GI endoscopy with basic, therapeutic, and advanced levels?

Cell/molecular biology free papers 022–030

**022** REPLENISHMENT OF THE ENTERIC NERVOUS SYSTEM IN AGANGLONIOSIS


In humans aberrant development of the enteric nervous system (ENS) manifest as motility disorders. The commonest is Hirschprung’s disease. Mutations in a number of genes implicated in ENS development, isolation, and characterisation of ENS progenitor cells (EPCs), and their use to replenish aganglionic bowel. Myenteric plexus from wild type and mutant postnatal mouse guts were dissected out and cell cultures established. After culturing in defined medium large clusters of cells or neurosphere like bodies (NLBs) were isolated. Dissociated NLBs were infected with a retroviral vector containing a fluorescent protein incorporated into dividing cells. Positive cells were selected using a FACS cell sorter and characterised for the properties of stem cells. The effects of various growth factors, eg ET3 and GDNF, were studied. Labelled cells were injected into wild type and mutant gut in organ culture to assess their ability to migrate, colonise the gut, and differentiate into mature ENS cell types. Cultures of cells isolated from postnatal wild type and mutant gut gave rise to NLBs with 30% of sorted cells exhibiting EPC characteristics. At clonal density single colonies gave rise to both neurons and glia. In sub-clonal studies such colonies when replated at clonal density showed self-renewal and

Table

<table>
<thead>
<tr>
<th>Operator group (n)</th>
<th>2000</th>
<th>2001</th>
<th>p value</th>
</tr>
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<tr>
<td>Consultant Gastroenterologists (2)</td>
<td>85%</td>
<td>98%</td>
<td>0.02</td>
</tr>
<tr>
<td>Consultant Surgeons (2)</td>
<td>47%</td>
<td>90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Staff Grade / GP Practitioner (2)</td>
<td>71%</td>
<td>86%</td>
<td>&lt;0.001</td>
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<tr>
<td>Junior Trainees (supervised) (3)</td>
<td>80%</td>
<td>96%</td>
<td>0.006</td>
</tr>
<tr>
<td>Senior Trainees (unsupervised) (5)</td>
<td>82%</td>
<td>85%</td>
<td>NS</td>
</tr>
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</table>

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DYSREGULATION OF THE MAJOR SQUAMOUS CELL STRESS RESPONSIVE SYSTEM IN BARRETT’S METAPLASIA

H.H. Dalziel, E. Pollier, A.L. Craig, N. Kernohan, D. Harwood, J.F. Dillion, T.R. Hupp. GI Research Laboratories, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK

The epithelial cells of the oesophagus are routinely exposed to unique environmental pressures, including thermal stress, acid and bile reflux, and dietary carcinogens, which appear to play a role in development of metaplasia, increased selection pressure for early mutation of p53, and therefore a heavy burden on stress-responsive and cell-cycle checkpoint control systems. The human oesophageal epithelium is easily accessible by endoscopy and provides a unique opportunity to integrate biochemical and clinical studies of stress protein responses relevant to understanding mechanisms of initiation of the cancer progression sequence to the intermediate Barrett’s metaplasia. To begin to address these issues, we have performed a comprehensive analysis on the nature of the stress responsive systems in normal squamous epithelium and Barrett’s metaplasia. We have unexpectedly found that the major stress-responsive genes (SEPS3, SEPS70, and Trans-glutaminase) of normal epithelium represent a novel stress control system generally confined to normal squamous epithelium. Strikingly, these stress responsive proteins are shown to be differentially expressed in Barrett’s epithelium from different patients, thus identifying a likely epigenetic pathway involved in modulating disease progression. Transfection of the SEPS3 gene into cells enhances proliferation as judged by colony formation assays. This ability of SEPS3 to enhance cellular proliferation is similar to oncogenic mutant p53, indicating that SEPS3 functions as a proto-oncogenic survival factor. Together, these data suggest two functions for SEPS3 depending upon cell type: (a) in normal epithelium, the ubiquitous expression of SEPS3 suggests a role in maintaining normal tissue integrity; and (b) in patients with Barrett’s metaplasia, high levels of expression of SEPS3 are likely to result in enhanced cellular proliferation, whereas patients with no SEPS3 are likely to have higher rates of cell death. These biochemical studies identified a novel pathway whose dysregulation may play a role in modulating the rates of tissue injury and ultimately assist in developing novel therapies.

OESOPHAGEAL CELL LINES SHOW DIFFERENTIAL SUSCEPTIBILITY TO BILE ACID INDUCED APOPTOSIS THAT IS P53 INDEPENDENT

J. Darrogh1, P.E. Ross1, J.F. Dillon1, N.M. Kernohan1, P.W. Detmar2. 1Ninewells Hospital and Medical School, University of Dundee, UK; 2Reckitt Benckiser Healthcare Ltd

Aim: Bile acids are one component of gastric contents that can reflux into the oesophagus in patients with GORD. Bile acids have been shown to induce apoptosis in colonic epithelium and hepatocytes. Similar activity on oesophageal epithelium may contribute to the pathogenesis of GORD. As the effect of bile acids on the oesophagus has not been examined in detail we have investigated the effects of bile acids on apoptosis of established oesophageal cell lines. Methods: Oesophageal cell lines (OE19, OE21, OE33 and KYSE30), a wild type p53 colon cell line (HCT116), and it’s derived isogenic p53 null cell line were grown in medium containing different biochemically pure bile acids. Apoptosis was identified by cell cytometry and detection of activated caspase-3 by Western blot. No. biopsies 10 28 6 6 16 10
No. patients 10 20 3 3 10 7

CONCLUSION: Bile acid and chenoDCA induce p53 independent apoptosis in some oesophageal cell lines, although those that exhibit squamous differentiation are resistant. The proapoptotic activity of particular bile acids. We may contribute to mucosal damage. Our results also suggest that this response may compensate for loss of p53 activity that occurs in oesophageal cancers and that loss of this bile acid induced effect in vivo may favour tumour progression.

EFFECT OF CHOLESTEROL ON THE GUT MICROBIOME: A MOUSE MODEL OF INTESTINAL DYSBIOSIS

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INTRODUCTION: The gut microbiome is essential for host health and is likely to be affected by dietary interventions. The gut microbiome is complex and host immune responses to the gut microbiota are highly variable. CHOL was recently shown to modulate the gut microbiome in the germ-free mouse model. The role of CHOL in modulating the gut microbiome in chow-fed mice remains unclear. METHODS: In a 2x2 factorial design, male C57BL/6J mice were fed a low or high CHOL diet (0.4% or 3.7% CHOL) and fed with chow or CHOL-enriched chow diet. The gut microbiome was assessed by 16S rRNA genotyping and gut microbial bile acid, cholesterol, and glucose levels were measured in the cecal contents. RESULTS: CHOL diet increased gut microbial bile acid and cholesterol levels and decreased glucose levels in both groups of mice. Comparison of bacterial community structures in the cecal contents of mice fed a low CHOL diet revealed a significant difference between those fed with chow or CHOL diet. The gut microbiome of mice fed a high CHOL diet was not significantly different between those fed with chow or CHOL diet. Diets with no difference in gut bacterial community structure had similar gut microbial bile acid, cholesterol, and glucose levels. CONCLUSION: CHOL diet increases gut cholesterol levels, microbial bile acid levels, and decreases glucose levels in both groups of mice. To our knowledge, this is the first study to show a paradoxical effect of CHOL diet on gut bacterial community structure and to show that the effect of CHOL diet on gut bacterial community structure is independent of gut microbial bile acid, cholesterol, and glucose levels. Further studies are needed to determine if the gut microbiome is causally linked to CHOL diet effects on lipid metabolism.
The expression of the epithelial apical membrane calcium transporter, ECAC2/ CAT1 (TRPV6 gene) differs tenfold between individuals. Approximately 1.5 kb of the 5' flanking region of this gene was sequenced in DNA from 15 subjects, including 13 with known levels of duodenal ECAC2/CAT1 RNA expression. Only one DNA contained a single nucleotide polymorphism (SNP) and this was from a subject with expression in the midrange. A novel polymorphism in the vitamin D receptor (VDR) gene has recently been associated with differences in bone density in a Japanese population. This SNP (G or A) is in a causal-related homeobox (CDX2) binding element and has been shown to affect transcription of the VDR gene. It was hypothesised that differences in expression of the VDR in the intestine could then affect the expression of vitamin D dependent genes involved in calcium absorption. In 82 British patients the allelic frequencies of this SNP were G:A = 0.76:0.24 different to those found in Japanese where there were relatively few AA homozygotes, and no significant differences could be demonstrated in bone mineral density.

The SNP genotypes were not associated with differences in mean levels of expression of duodenal calcium transport genes (ECAC2/CAT1, calbindin-D9k, or PMCA1), although there was evidence of significantly different responsiveness to 1,25-(OH)2D. In summary, no significant SNP has been found in the promoter of the gene for ECAC2/CAT1, but the effect of the CDX2 binding element SNP in the VDR gene merits further study.

**027 ELEVATED PLASMA CONCENTRATIONS OF AMIDATED GASTRIN CAUSE INCREASED CRYPT SURVIVAL IN MURINE INTESTINAL EPITHELIUM AFTER γ RADIATION**

P.D. Otterwill, A.J.M. Watson1, T.C. Wang, A. Varro1, G.J. Dockray2, D.M. Pritchard. Department of Medicine, University of Liverpool, UK; 2University of Massachusetts Medical Center, Worcester, MA, USA.

**Background and Aims:** Amidated gastrin has well characterised mitogenic and morphogenic properties in the stomach, but its role in the distal intestine remains unclear. We have previously demonstrated no differences in the levels of apoptosis and mitosis in small intestinal and colonic epithelia of mice that overexpress amidated gastrin (INS-GAS) compared to their wild-type counterparts, either in the untreated state or 4.5 hours following 8 Gy γ radiation. In order to complete our analysis of the effects of hypergastrinaemia upon the distal intestine in vivo, we have now investigated the effects of elevated plasma concentrations of amidated gastrin upon intestinal crypt survival following γ radiation.

**Methods:** Mice analysed were adult INS-GAS and their wild-type counterparts (FBV/N). Clonogenic crypt survival was assessed by light microscopy of small intestinal and colonic crypts four days after 10, 12, or 14 Gy γ radiation. We confirmed that the differences observed were specifically induced by hypergastrinaemia by analysing INS-GAS mice treated with the specific gastrin/CCKB receptor antagonist YF476 and FBV/N mice treated with omeprazole.

**Results:** Four days following 12 and 14Gy γ radiation, INS-GAS mice exhibited significantly higher (~3 fold) small intestinal and colonic crypt survival compared with their wild-type counterparts. INS-GAS mice treated with YF476 showed significantly lower (~4 fold) small intestinal and colonic crypt survival after 14Gy γ radiation compared with mice receiving vehicle alone. FBV/N mice dosed with omeprazole to induce hypergastrinaemia showed significantly increased (~4 fold) survival of small intestinal and colonic crypts after 14Gy γ radiation.

**Conclusions:** (a) Increased small intestinal and colonic crypts survival is observed in mice with elevated plasma concentrations of amidated gastrin following γ radiation. (b) This protective effect of hypergastrinaemia occurs as a result of signalling via the gastrin/CCKB receptor.

**028 MONITORING M CELL CONVERSION IN VITRO: THE ROLE OF LYMHOCYTE EPITHELIAL CELL CONTACT**

S.W.J. Cochran1, D.P. O’Donoghue2, A.W. Baird1. University College Dublin; 2St Vincent’s University Hospital Dublin

M cells are of paramount importance in microbial-intestinal cross talk. There is sparse data on human M cells due to their distribution and the lack of specific markers, however, in vitro co-culture models have been described. The nature of lymphocyte epithelial cell interactions required for M cell transformation as well as the degree of phenotypic specificity in vitro never-the-less remain unclear. We compared co-cultures of polarized Caco-2 cells and Raji B lymphocytes with monocultures of Caco-2 cells in two configurations: one in which there is direct contact between the two cell types (mode 1) and one in which the epithelial cells are exposed to B cell secreted factors only (mode 2). M cell like transformation was assessed by (a) scanning and transmission electron microscopy (EM), (b) apical membrane enzyme activity; (c) translocation of FITC labelled microparticles; and (d) assessing the interaction of the co-cultures with Salmonella typhimurium and Clostridium difficile. EM demonstrated transformed cells with M like morphology in both co-culture models. Down regulation of alkaline phosphatase expression could only be proven in mode 1 (p < 0.005). Monoculture transport was increased in both co-culture configurations compared to caco-2 cell monoculture but was much greater in mode 1 (mode 1 1629+/−453 v 104+/−11 events, n = 36, p < 0.0001; mode 2 265+/−99 v 121+/−29 events, n = 34, p = NS). Adherence of S typhimurium to mode 1 was increased by FACS analysis. No significant apoptosis was observed. In conclusion, these results indicate that H pylori can alter the expression of key regulatory transcription factors controlling gene expression in the cell cycle.

**029 HELICOBACTER PYLORI REGULATES ID-1 AND ID-3 EXPRESSION, BUT NOT ID-2**

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H pylori can induce both apoptosis and proliferation of gastric epithelial cells. The balance between these two processes during bacterial infection depends on both host and microbial determinants and under the risk of developing cancer. Inhibitor of differentiation (ID/DNA binding) helix-loop-helix proteins are critically related to cell cycle progression, differentiation, and apoptosis. These effects are mediated by inhibiting the DNA binding of basic HLH transcription factors, such as the ubiquitous E47 and tissue-specific factors like myoD. We hypothesised that H pylori could regulate Id expression in gastric epithelial cells following infection. AGS cells (from a poorly differentiated gastric adenocarcinoma) were co-cultured with H pylori 60190 wild type strain (1x108 bacteria/cell) from 2 to 48 hours. RT-PCR analysis revealed down-regulation for Id-1 and Id-3 mRNA levels, which occurred over the first 6 hours of exposure to H pylori. In contrast, Id-2 mRNA levels remained constant. In agreement with transcriptional data, Western blot analysis showed that protein levels were strongly and rapidly downregulated by the bacteria; again Id2 protein levels were unaltered. Culture of AGS cells in presence of H Pylori resulted in the accumulation of cells in the G1 phase of the cell cycle (69% after 24 hours compared with 48% in control cultures), as assessed by FACs analysis. No significant apoptosis was observed. In conclusion, H pylori results in decreased Id-1 and Id-3 expression in AGS cells in vitro, which is associated with arrest of the cells in G1 phase of the cell cycle. These results indicate that H pylori can alter the expression of key regulatory transcription factors controlling gene expression in the cell cycle.

**030 DIRECT VISUALISATION OF CELL SHEDDING FROM THE SMALL INTESTINE OF THE LIVING MOUSE**

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**Introduction:** Epithelial cells arise from stem cells at the base of the crypt and migrate up the crypt/villus axis to the tip of the villus where they shed. The mechanism of cell shedding is unknown but two theories have been proposed. In the first, the shedding process is initiated by the cell undergoing apoptosis, which causes the cell to detach from the basement membrane and neighbouring cells, and thereby be shed into the lumen. In the second, the shedding process is initiated by neighbouring cells extending processes under the cell to be shed, forming tight junctions that extrude the cell into the lumen. Once detached from the basement membrane the cell undergoes apoptosis as a secondary event.
Methods: Mice were anaesthetised with inactin and loop of bowel brought out and opened. The mouse was placed on the stage of a two-photon microscope so the mucosal surface of the bowel could be observed. Nuclei were visualised with Hoechst 33258 1 mg/ml i.p. Caspase 3 activation was monitored with the cell permeant fluorescent dye 10 µM Rh110 (Chromomine). Optical sections were taken of the upper 30 µm of the mouse villi in vivo. Cell shedding was observed from the epithelial monolayer using time lapse imaging. While the cells were within the monolayer no changes in the morphology of the nuclei was observed. However, once shedding was complete cells in the intestinal lumen had condensed nuclei, suggestive of apoptosis. Cell shedding took place at a rate of 3.2 cells/hour/villus ± 3.5 (n = 4 mice). In a minority of cells caspase 3 was found to be activated at the same time as shedding took place. However, the majority of cells were shed without activation of caspase 3. The average rate of the cell moving out of the monolayer into the lumen was 0.83 µm/min ± 0.06, [n = 53 cells]. This is more than twice the rate at which cells migrate up the villus.

Conclusions: The majority of cells are shed without undergoing apoptosis. The observation that cells are shed at a rate greater than the migration rate suggests that cells are actively extruded from the monolayer.

Small bowel free papers
031–036

031 ROLE OF T CELLS IN THE REGULATION OF HUMAN INTESTINAL α DEFENSIN GENE EXPRESSION

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Background: In a 3 year study of an urban African population, we have explored the relationship of intestinal α defensin expression to tropical enteropathy and intestinal infection. Quantification of human defensins (HD) 5 and 6 mRNA revealed marked variation between individuals and with season. There were strong correlations with changes in mucosal architecture and diarrhoeal incidence. This suggests that environmental determinants elicit changes in mucosal α defensin mRNA.

Aims: In view of the role of T cell activation in the pathogenesis of intestinal enteropathy we hypothesise that HD5 and HD6 expression may be modulated by T cells.

Methods: An in vitro organ culture system was developed and small intestinal biopsies from healthy adults undergoing endoscopy were stimulated with staphylococcal enterotoxin B (SEB) over the range 0.1–10 µg/ml for 8 or 24 hours. Biopsies were also cultured for 24 hour with SEB (10 µg/ml) or dexamethasone (10 µM) or both. HD5 and HD6 mRNA was quantified by competitive RT-PCR.

Results: A dose dependent decrease of up to 1.5 log mRNA transcripts/µg total RNA was observed (HD5, p < 0.01; HD6, p = 0.05) with increasing SEB. Dexamethasone abrogated the effect of SEB on mRNA levels, and dexamethasone alone increased mRNA levels (HD5, p < 0.01; HD6, p = 0.05) with increasing SEB. Dexamethasone abrogated the effect of SEB on mRNA levels, and dexamethasone alone increased mRNA levels (HD5, p < 0.01; HD6, p = 0.05) with increasing SEB.

Conclusions: These data suggest that T cell activation downregulates human intestinal α defensin expression and that the effects seen in intestinal enteropathy are at least partly due to interactions with adaptive immune cells.

033 SERUM 7α HYDROXY-4-CHOLESTEN-3-ONE CONCENTRATIONS IN DIFFERENT TYPES OF BILE ACID INDUCED DIARRHOEA

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Introduction and Aims: Bile acid induced diarrhoea can be of three types: type 1: caused by pathology or resection of terminal ileum; type 2: idiopathic bile acid malabsorption (IBAM) due to increased bile acid pool size or rapid ileal transit, rarely a specific bile acid ileal transport defect; and type 3: non-inflammatory secondary to other conditions such as post-cholecystectomy, IBS, diabetes mellitus, bacterial overgrowth, and chronic pancreatitis. Serum concentration of 7α hydroxy-4-cholesten-3-one (7HCO) reflects the rate of bile acid synthesis in man and is elevated in clinical conditions associated with bile acid malabsorption (BAM). Serum 7HCO correlates well with SeHCAT test.

Methods: Serum 7HCO was measured on fasting blood sample using HPLC. Standard 7HCO was a kind gift from Professor I. Bjorkholm, Karolinska Institute, Stockholm. Results were calculated as: test peak area X concentration of standard/standard peak area (ng/ml). Serum 7HCO concentrations > 35 ng/ml were considered to be abnormally raised. A total of 190 patients were recruited into the study. All suffered from watery diarrhoea and were administered medications. Randomised trials are warranted to further establish the role of 7HCO in watery diarrhoea due to bile acid malabsorption. It may provide a safe treatment of this condition as an alternative to cholestyramine and it does not bind to concurrently administered medications.

Results: Thirty one out of forty two patients with ileal Crohn’s disease (including 4 resections) had abnormally high 7HCO (type 1 BAM). The median concentration was 158 ng/ml (range 37–590 ng/ml). Twenty six patients with IBAM (type 2 BAM) had a significantly lower (p < 0.00001) 7HCO concentration (median 67.5; range 39–303 ng/ml) than patients with type 1 BAM. Of patients with IBS, post-cholecystectomy, bacterial overgrowth, and chronic pancreatitis, 16/132 had abnormally elevated 7HCO (type 3 BAM). However, the concentration of 7HCO in type 3 BAM (median 46; range 36–71 ng/ml) was significantly lower than type 2 BAM (p < 0.01).

Conclusions: The three types of BAM stratify according to serum 7HCO type 1 BAM have the highest concentration, and type 3 the lowest concentration. IBAM (type 2) have intermediate values of 7HCO with some overlap with type 1 and type 3.

034 IS THE RISK OF ADULT COELIAC DISEASE CASUALLY RELATED TO CIGARETTE EXPOSURE?

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Introduction and Aim: Previous studies have shown an association between cigarette smoking and the risk of development of adult coeliac disease (CD), but it has yet to be established whether this relationship is causal. The aim of this study was to assess causality using the Bradford-Hill criteria, specifically seeking evidence of a biological gradient.

Method: Matched case control study using a questionnaire to establish a detailed smoking history for 138 incident cases of adult

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CD and 276 age and sex matched controls. Subjects were categorised according to various measures of the duration and intensity of active coeliac exposure prior to diagnosis of the matched case. Conditional logistic regression was used to calculate odds ratios and linear trends.

**Result:** At the time of diagnosis, 10% of cases and 30% of controls were current smokers (odds ratio 0.21, 95% CI 0.11–0.40 for CD in current v never-smokers). The odds of developing CD fell significantly with both increasing total lifetime exposure and exposure to cigarettes over the 15 years prior to diagnosis. However, the strongest relationship was in the number of cigarettes smoked per day at the time of diagnosis (odds ratio 0.15, CI 0.06–0.37, for CD in current heavy v never-smokers). All linear trends were highly statistically significant, and controlling the data for standard of living did not alter the findings.

**Conclusion:** This study strengthens the case for a causal relationship between smoking and CD by demonstrating a strong, temporally appropriate and dose-dependent effect, thus meeting the Bradford-Hill criteria. This suggests that cigarette smoking truly protects against the development of adult CD.

35 COMPLICATIONS OF COELIAC DISEASE – HOW COMMON AND CAN THEY BE PREVENTED?

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**Introduction:** Coeliac disease (CD) is a common condition with wide clinical variation in both severity and type of symptoms. Many complications have been reported to occur but the protective effect of gluten free diet (GFD) remains controversial. The aim of this study was to provide data on the prevalence of complications and assess the effect of strict GFD in a large population with CD.

**Methods:** Consecutive patients attending the coeliac clinic at the Western General Hospital, Edinburgh, were invited to participate. Data were collected from case notes and from questionnaires and entered onto a secure database.

**Results:** Clinical data were obtained from 270 patients, and questionnaires completed by 199. Age at diagnosis was 0.2–88 years (median 41.5 years) with sex ratio of 1M:2.6F. Duration of follow up was 1 month to 68 years (median 6 years). Ninety one per cent reported symptoms of various severity and 9% were asymptomatic, even in retrospect. At diagnosis 75/199 (38%) were anaemic, improving to 30/225 (13%) with treatment; 16% were vitamin B12 deficient at diagnosis; 53% were iron deficient at diagnosis; and 7/32 (22%) had osteoporosis of the hip and 10/24 (42%) of the spine at diagnosis, improving to 15/130 (12%) (p = 0.006) and 34/109 (31%) (p = 0.012) with treatment. Those who described strict compliance to GFD on the questionnaire had significantly higher T scores of the spine compared with those who did not (median 0.018, range 0.007–0.063; p = 0.007). Osteoporosis of the hip and anaemia did not differ in the symptomatic group, but LBW babies did (11/221 pregnancies v 5/24 (p = 0.011)).

**Summary:** Complications occur commonly in coeliac disease. The risk of osteoporosis of the hip and LBW babies may be prevented by strict GFD.

036 LACTOSE MALABSORPTION IN THE ELDERLY

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**Background:** Limited data suggest a high prevalence of lactose malabsorption (LM) in the elderly. The mechanism is uncertain. A significant increase in enterocyte apoptosis raises the possibility that a subtle reduction in mucosal absorptive area, undetectable by standard structural analyses, may be responsible, especially if compensatory enterocyte proliferation is inadequate. Assessment of intestinal absorption of mannitol, taken up transcellularly and hence an index of absorptive area, and intestinal permeability, reflected by urinary lactulose/ mannitol ratios, may resolve this issue.

**Methods:** We studied 20 asymptomatic elderly subjects (median age 76, range 65–94 years) and 20 controls (median age 29, range 21–35 years) with no history of gastrointestinal disease or use of drugs that disturb gut permeability. All were hydrogen producers following ingestion of lactulose. A 50 g lactose breath hydrogen test was performed after dietary preparation and an 8 hour fast. Breath hydrogen was measured by gas chromatography. Lactulose/mannitol ratios were measured by gas-liquid chromatography in urine collected over 6 hours after ingestion of 10 g lactulose and 5 g mannitol. Urinary creatinine levels were measured so that differences in renal function did not confound interpretation of urinary mannitol levels.

**Results:** LM, defined by a rise in breath hydrogen > 20 ppm above baseline, was present in 10/20 (50%) elderly subjects and 0/20 controls. Urinary mannitol/creatinine ratios did not differ significantly in elderly and control subjects (median 111.1, range 17.6–149 v median 92.8, range 45.9–140.8; p = 0.62) or in elderly subjects with and without LM (median 111.1, range 35.6–149 v median 106.7, range 17.6–136; p = 1.0). Urinary lactulose/mannitol ratios were significantly increased in the elderly (median 0.018, range 0.007–0.063) compared to controls (median 0.011, range 0.007–0.025; p = 0.003), but did not differ significantly in elderly subjects with and without LM (median 0.022, range 0.007–0.063 v median 0.014, range 0.011–0.057; p = 0.19).

**Conclusions:** The prevalence of LM in the asymptomatic elderly is high and cannot be explained by any reduction in small intestinal absorptive area. LM in this group is unrelated to disturbed intestinal permeability.

Nutrition free papers 037-041

037 EFFECT OF FLAVOURING ON ISOTONIC SOLUTIONS FOR SHORT BOWEL SYNDROME

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**Background:** Isotonic oral rehydration solutions (IORS) facilitate nutritional management of short bowel syndrome (SBS) and ileostomy dysfunction by reducing stoma output and improving hydration. Maximal intestinal Na+ and water absorption occurs at [Na+] 90–120 mmol/L and is facilitated by glucose. Patient compliance with IORS is poor but can be improved by the addition of flavourings such as fruit juice or squash. Amounts are unspecified and the effect of adding flavouring on the solution biochemistry has not been established.

**Aim:** To determine the effect on [Na+], [glucose] and osmolality, after the addition of fruit juice or squash as flavouring components to IORS.

**Methods:** John Radcliffe Hospital (JRH) prepared IORS and 15 commercial sports/energy drinks were analysed for [Na+], [glucose] and osmolality by standard biochemical techniques. The JRH IORS prepared solutions were: (a) 200 ml no added sugar (NAS) squash + 800 ml H2O + 1 metric teaspoon NaCl; (b) 200 ml regular squash + 800 ml H2O + 1 metric teaspoon NaCl; (c) 200 ml fruit juice + 250 ml H2O + 1 metric teaspoon NaCl; and (d) 1000 ml Lucozade Sport and 1 metric teaspoon NaCl. A variety of sports/energy drinks were analysed.

**Results:** See Table.

**Table**

<table>
<thead>
<tr>
<th>Solution</th>
<th>[Na+] mmol/L</th>
<th>[Glucose] mmol/L</th>
<th>Osmolality mOsm</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>127.6</td>
<td>40.0</td>
<td>279</td>
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<tr>
<td>C</td>
<td>107.1</td>
<td>103.5</td>
<td>704</td>
</tr>
<tr>
<td>D</td>
<td>136.2</td>
<td>162.0</td>
<td>508</td>
</tr>
</tbody>
</table>

**Conclusion:** None of the commercial solutions had adequate [Na+] (range 20–30 mmol/L); they were average hypotonic (rats 335–1031 mmol/L; median 595 mOsm) and had variable, mostly high glucose concentrations (range 10.6–655.7 mmol/L; median 190 mmol/L). Flavouring with fruit juice or squash made IORS hypertonic, therefore rendering them less suitable in managing SBS. All JRH IORS contained adequate [Na+] (> 90 mmol/L) but the addition of 200 ml NAS squash was the only one to remain isosmolar after flavouring.

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**PERCUTANEOUS ENDOSCOPIC GASTROSTOMY SITES INFECTED BY METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS: IMPACT ON OUTCOME**

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**Background:** Methicillin resistant S aureus infection (MRSA) appears to be associated with an increased incidence of colonisation of percutaneous endoscopic gastrostomy (PEG) sites.

**Aim:** We investigated the impact of prior MRSA colonisation on the incidence of symptomatic PEG site wound infection and mortality.

**Method:** Consecutive patients who had PEG tubes inserted recently were identified and their notes studied retrospectively. Presence or absence of MRSA prior to PEG placement was noted. After PEG placement, patients suspected of having wound infection had swabs taken from the site (no routine swabs taken). Mortality within 30 days of PEG placement was determined. Significant wound infection was defined as those requiring antibiotic treatment.

**Results:** Eighty three patients underwent PEG placement; 23 (28%) of these patients had known MRSA infection prior to PEG placement. Of these, 13 (57%) developed symptomatic MRSA colonisation of the PEG site. The remainder of the patients, 60 (73%), had no known prior MRSA infection. In these patients, 9 (15%) developed symptomatic MRSA colonisation of the PEG site. Thus, there was a significantly higher risk of MRSA colonisation of the PEG site if patients had prior MRSA infection (p = 0.00013). Only 4 patients with MRSA colonisation of the PEG site required treatment with antibiotics. Thus the incidence of significant wound infection was 5% of total undergoing PEG placement or 18% of those with MRSA colonisation. The mortality rate associated with the PEG site in those with symptomatic MRSA colonisation of the PEG site was 9% (2 out of 22), although the mortality from non MRSA infected PEGs was 20% (12 out of 61). There was no significant difference, (p = 0.25).

**Conclusion:** Patients with prior MRSA infection had a significantly higher risk of developing symptomatic MRSA infection of the PEG site. However, there was still a significant risk (15%) for patients with no known prior MRSA infection developing MRSA colonisation of the PEG site. MRSA infection of the PEG site did not seem to affect mortality.

**SYNBiotics in Irritable Bowel Syndrome: A Double Blind Prospective Randomised Controlled Trial**


**Introduction:** Alterations in resident GI microflora have been implicated in the pathogenesis of irritable bowel syndrome (IBS) and this provides a theoretical rationale for the use of probiotics in these patients. The aim of this study was to investigate the effects of symbiotics (pre- and probiotics) in this group.

**Methods:** Patients fulfilling the Rome 2 criteria were randomised to receive a symbiotic preparation (oligofructose/Lactobacillus acidophilus, Bifidobacterium Bb12) or placebo for an 8 week period. Frequency of stool and abdominal pain were charted during weeks 0 (pretreatment), and 8, along with linear analogue (100 mm) measures of abdominal pain, flatulence, bloating, and Hospital Anxiety and Depression (HAD) scores. Data from weeks 0 and 8 were treated as "paired," and the difference between the data points calculated for each patient. Non-parametric tests were then applied.

**Results:** A total of 34 patients were randomised (19 placebo, 15 symbiotic). The groups were similar with regards to age (45 ± 17 years placebo, 50 ± 13 years symbiotic) and sex distribution (m:f = 4:15 placebo, 7:8 symbiotic). Both groups of patients showed significant improvement in pain frequency (median reduction three episodes per week), p < 0.05 and severity (median difference 12 mm on analogue score), p < 0.02. Both groups showed significant improvement in HAD score (median improvement 1.3 points), p < 0.05. There were no significant differences between symbiotic and placebo groups in any measured parameter (abdominal pain, flatulence, bloating, frequency of stool, or HAD score).

**Conclusion:** In this group of IBS patients there is no evidence of benefit from 8 weeks of symbiotic treatment. Both symbiotic and placebo groups showed significant clinical improvement, which is likely to represent a placebo effect.

**FATTY ACID COMPOSITION AND FUNCTION OF MONONUCLEAR CELLS IN CROHN’S DISEASE**

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Inflammation in Crohn’s disease (CD) is mediated by mononuclear cells and is associated with increased production of TNFα and prostaglandin E2 (PGE2). In active CD, dietary supplementation with fish oil results in anti-inflammatory effects associated with increases in eicosapentaenoic acid (EPA) and decreases in arachidonic acid (AA) concentrations in plasma. However, in the un-supplemented state the relationship between habitual dietary fat intake, EPA, and AA incorporation into mononuclear cells and TNFα/PGE2 production is uncertain. The fatty acid composition and synthetic function of peripheral blood mononuclear cells (PBMC) were determined in 53 CD patients, stratified into active and inactive disease groups by Crohn’s Disease Activity Index, and age and sex-matched healthy controls. There were no differences between CD and controls in dietary fat or total energy intake. Lower concentrations of AA were noted in active CD (20.2%) vs controls (24.0%) (p < 0.001) and inactive CD (20.2%) vs controls (23.8%) (p < 0.001). Higher concentrations of EPA were noted in active CD (0.7%) and inactive CD (0.8%) vs controls (0.3%) for each control group; p = 0.001). Inactive CD was associated with alterations in the availability of AA and EPA in both active and inactive states. This cannot be simply explained by altered dietary intake but may be an adaptive or pathologic response to the disease process. The anti-inflammatory response to dietary fish oil may reflect a pharmacological effect, and not the correction of a deficiency of EPA. The response of mononuclear cell composition and function to dietary fish oil warrants further investigation.

**SCREENING FOR MALNUTRITION: IMPACT OF THE MALNUTRITION UNIVERSAL SCREENING TOOL (MUST)**

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**Introduction:** Malnutrition is commonly found in hospital in-patients, with a frequency of up to 40%. Intervention studies suggest this is an independent and reversible prognostic factor. The MUST is a validated, simple tool enabling systematic identification of malnutrition.

**Aims:** To establish whether patients were being screened for malnutrition before the introduction of a specific screening tool; then to assess the practicability and effect of introducing the MUST.

**Methods:** All patients on eight wards (general medical, general surgery, care of the elderly, and orthopaedic) at two teaching hospitals were surveyed at one time point. Patients’ medical and nursing notes and bedside charts were examined. Demographic, nutritional status and dietetic referral details were recorded. The audit was repeated 2 months after the MUST was introduced to these eight wards.

**Results:** In the first audit 172 patients were surveyed; mean age 68 years, 90 men, 111 medical/61 surgical, mean length of stay (LOS) 9 days. Sixty four (37%) had weights recorded, 62 (36%) had BMI recorded, and 120 (70%) had comment about appetite made; 55 (31%) patients were referred to the dietetic service, 40% within 2 days of admission. In the second audit 173 patients were surveyed; mean age 66 years, 96 men, 99 medical/74 surgical, mean LOS 13 days; 103 (60%) had weights recorded, 123 (72%) had comment about appetite made; 62 (36%) had a BMI recorded. In the first audit 120 (70%) had comment about appetite made; 55 (31%) patients were referred to the dietetic service, 40% within 2 days of admission. In the second audit 173 patients were surveyed; mean age 66 years, 96 men, 99 medical/74 surgical, mean LOS 13 days; 103 (60%) had weights recorded, 123 (72%) had comment about appetite made; 62 (36%) had a BMI recorded. Comparing the two audits, there was a 70% increase in the number of referrals to the dietetic department and a 40% increase in the number of referrals to the dietetic department.

**Conclusions:** Prior to the introduction of a specific screening tool patients’ weight and BMI were rarely recorded. A pilot introduction of the MUST tool was partially successful and when used increased appropriate dietetic referral rate significantly.
Inflammatory bowel disease free papers 042–052

[042] COMPLEX GENETIC INTERACTIONS REVEALED IN AN IBD GENOME SCAN STRATIFIED BY CROHN’S DISEASE ASSOCIATED VARIANTS


Background and Aims: Genetic studies in inflammatory bowel disease (IBD) have identified multiple susceptibility loci. The significance of these findings depends on verification in independent cohorts. Genetic variants associated with Crohn’s disease have now been identified on chromosomes 5 (IBD5 risk haplotype) and 16 (IBD1 locus, CARD15/NOD2 mutations). These variants now allow stratification of linkage analyses, which will improve the ability to identify other loci, and allow assessment of potential complex interactions between genetic factors. Such gene–gene interactions have been shown to be causal in UC.

Methods: We performed a genome-wide scan of 228 IBD families. Multipoint linkage was assessed using MERLIN in IBD (288 affected relatives pairs), Crohn’s disease (CD, 137 pairs) and ulcerative colitis (UC, 95 pairs) phenotypes. CD analyses were further stratified by common CARD15/NOD2 mutations and the IBD5 haplotype.

Results: We confirmed loci on chromosomes 3q (CD, LOD 2.1; p = 0.0009), 6p (IBD, LOD 2.2; p = 0.0008) and Xp (CD, LOD 2.0; p = 0.0011). Linkage (CD, LOD 2.2; p = 0.0007) was observed 25cM telomeric to CARD15 in CARD15 negative CD affected. The chromosome 16q locus also demonstrated in a Canadian CD population, showed significant genetic heterogeneity with CARD15 (significance test p = 0.002, LOD 2.9; p = 0.0001 in CARD15 negative CD) and epistasis with the IBD5 haplotype (significance test p = 0.02, LOD 2.4; p = 0.0005 in CD IBD5 carriers).

Conclusions: Stratification of a genome scan by Crohn’s disease associated variants demonstrates the complex genetic basis to IBD, with genetic heterogeneity and epistatic interactions between loci. Our data support previous suggestions of a second chromosome 16 locus.

[043] MORTALITY CAUSED BY INFLAMMATORY BOWEL DISEASE IN THE UK: A TWO YEAR SURVEY

S. Dolwani, A.B. Hawthorne. Department of Gastroenterology, University Hospital of Wales, Cardiff, UK (conducted via the BSG-blue card surveillance scheme)

Background and Aims: Previous studies in the United Kingdom have either been regional if population based or entirely based on statistics from the Registrar General’s office. We aimed to ascertain the non-cancer mortality in persons < 75 years of age ascribed to inflammatory bowel disease via a notification system throughout the UK conducted through all members of the BSG from Jan 2000 to Dec 2001.

Methods: All deaths in patients with IBD were notified to the BSG central audit office. Further details and death certificate diagnoses were then requested from the notifying clinician. Subgroup analysis was done according to diagnosis, age, sex, cause of death, duration, site, extent, and operative mortality. These data were then compared with that from the ONS in England and Wales, Scotland, and Northern Ireland.

Results: One hundred and thirty two patients were recorded as having died due to IBD during this period, of which 108 were < 75 years. Of these, 61 had Crohn’s disease, 44 had ulcerative colitis (UC), and 3 had indeterminate colitis. Twenty six patients (24%) died within a year after a diagnosis was made; 36 (33.3%) died within 2 years of diagnosis; 7 (6.5%) had death attributed to medical therapy; and 51 (47.2%) had surgery prior to death. The median time to death after surgery was 7 days. When analysed according to immediate cause (IA on death cert), 23 patients (21.3%) had septicemia, 18 patients (16.7%) colonic perforation, 9 patients (8.3%) multi-organ failure, 8 (7.4%) thromboembolic events (PE), and a similar percentage had pneumonia. There were more female deaths (35 v 22 in Crohn’s compared to UC). Patients aged < 35 years accounted for 25% of all deaths. During the same period the ONS reported 128 deaths due to UC and 240 to Crohn’s disease (which would include cancer related IBD mortality).

Conclusions: Younger patients and those within the first year from diagnosis, as well as those undergoing surgery, account for a significant proportion of all deaths due to IBD in the UK.

[044] COMBINING CLINICAL RISK FACTORS AND GENOTYPE TO PREDICT POSTOPERATIVE RECURRENT OF CROHN’S DISEASE

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Introduction: There is a need to be able to identify patients at highest risk of relapse after surgery for Crohn’s disease, so that preventative treatment can be targeted at those most likely to benefit. Combining clinical risk factors and genotype to predict risk has not previously been explored.

Methods: All 105 patients who had had surgery for ileocaecal Crohn’s disease at the John Radcliffe Hospital, Oxford, on whom DNA had been collected and follow up data obtained were selected. Three endpoints were defined: duration of steroid free remission (EP1), time to clinical relapse (EP2), and time to surgical relapse (EP3). Forty one controls and 57 genetic variants were recorded. Multivariate analysis was performed using the Accelerated Life Model, before decision tree analysis to identify prognostic groups. Owing to the large number of variables, genotypic analysis focused on three mutations of the NOD2 gene and 10 other genes in the HLA region on chromosome 6.

Results: Mean follow up duration was 175 months (range 6–840). Median time (range) to EP1 was 56 (0–540) months; to EP2, 74 (0–810) months; and to EP3, 120 (3–810) months. Perianal disease at index surgery and retinax receptor beta 1 genotype were the only variables associated with shorter times (all p < 0.0004) and heat shock protein 1 genotype with longer times to all three endpoints (p = 0.0145, p < 0.0001, p < 0.0001). Smoking and IkB14 genotype predicted a shorter duration of steroid free remission and time to further surgery, while age > 40 year, male sex, and NOD3D20 genotype predicted a longer duration. Decision tree analysis only predicted steroid free remission: if transmembrane receptor not 4 genotype positive (n = 80), 60% require steroids within 5 years, compared with 24% if not 4 negative.

Conclusions: Smoking and perianal disease are confirmed as predictors of a higher relapse rate after surgery. Genotypes associated with a higher relapse rate are different to those currently associated with disease causation. Patients who are not 4 negative have a 76% chance of prolonged (> 5 years) steroid free remission after surgery. Combining clinical and genotypic factors did not enhance the ability to predict the risk of relapse after ileocaecal resection for Crohn’s disease.

[045] INFLAMMATORY BOWEL DISEASE AND THE RISK OF FRACTURE

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Patients with inflammatory bowel disease (IBD) have an increased risk of low bone mass, the pathogenesis of which is multifactorial. There are limited data on fracture. We therefore conducted a primary care based case-control study to determine the risk and major risk factors of fracture in IBD patients. 231 778 patients with a fracture and 231 778 age and sex matched controls were recruited from the General Practice Research Database. The database has been previously demonstrated to be a representative sample of the general population of England and Wales. Adjusted odds ratios (OR) were estimated from conditional logistic regression. The mean age of cases and controls was 51 years and 52.5% were women. A history of IBD was found in 1134 fracture cases, compared with 896 of the controls (adjusted OR 1.21; 95% CI 1.10 to 1.32). The OR was 1.72 (1.13–2.61) for vertebral fracture and 1.59 (1.14 to 2.23) for hip fracture. The risk of fracture was greater in patients with a history of Crohn’s disease (OR 1.32 [1.13–1.53]) than in patients with ulcerative colitis (OR 1.13 [1.02–1.27]). The risk of fracture in patients with a history of IBD was significantly related to disease severity as assessed by the number of symptoms (OR in IBD patients without symptoms, 1.02 [0.90–1.17]), 1 symptom, 1.66 [1.41–1.96], and ≥2 symptoms, 1.74 [1.43–12.12]). Similarly, severity assessed by medication demonstrated increasing fracture risks compared with untreated patients.
AZATHIOPRINE AND SMOKING STATUS IN CROHN’S DISEASE PREDICT RESPONSE TO INFlixIMAB

I.D.R. Arnott, J. Satrangi. Gastrointestinal Unit, University Department of Medical Sciences, Western General Hospital, Edinburgh

Introduction: Up to 75% of patients given infliximab for Crohn’s disease (CD) will respond. A number of clinical parameters that may predict response have not been proposed but none has been reproduced in an independent cohort. We aimed to identify clinical and laboratory markers of response in patients receiving infliximab at our institution.

Methods: Seventy four well characterised CD patients (42 females, median age 34 years [IQR 23–42.5]) were assessed. Full clinical data was collected prospectively and blood was taken for inflammatory markers, ASCA and ANCA. Eleven had ileal disease, 25 colonic disease, 28 ileocolonic disease and 10 had recurrence following ileostomy. Sixteen had received azathioprine for > 3 months and 5 methotrexate. Single infusions infliximab (5 mg/kg) was given for luminal disease (60 patients) and 3 infusions for fistulating disease (14 patients).

Results: Those who smoked greater than 5 cigarettes per day for > 6 months were less likely to respond to infliximab than those who did not [11/21 v 39/47, χ² = 7.0, p = 0.008, OR 0.22 (CI 0.08 to 0.41)]. Patients on azathioprine for longer that three months at infusion were more likely to respond [15/16 v 35/52, χ² = 4.4, p = 0.014–0.2, OR 3.34 to 10.31]]. Eleven patients (OR 6.190, CI 1.400 to 27.371; p = 0.0251) and rash (χ² = 4.4, p = 0.036, OR 7.31 (CI 3.34 to 10.31)). There was a trend towards better response rates in those with colonic disease (χ² = 2.7, p = 0.09) and worse response rates in those with perianal disease (χ² = 3.7, p = 0.056). Age at diagnosis, previous surgery, sex, pre-infusion disease activity, CRP, and ASCA/ANCA status did not influence response rates in our cohort.

Conclusion: Smoking has a strong adverse effect on response rates to infliximab. Furthermore, patients established on azathioprine for greater than 3 months had greater response rates. Every effort should be made to discourage CD patients from smoking. Ninety two per cent of patients established on azathioprine prior to treatment responded: this has clear implications for clinical practice.

AZATHIOPRINE ACTIVE METABOLITE CONCENTRATIONS IN INFLAMMATORY BOWEL DISEASE

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Introduction: Azathioprine is well established in the treatment of inflammatory bowel disease (IBD). Thioguanine nucleotides (TGNs) are active azathioprine metabolites, elevated TGNs are associated with myelosuppression.

Aim: To investigate TGN metabolite concentrations in a large cohort of IBD patients.

Method: IBD patients on stable dose of azathioprine and thioguanine were studied. Twenty-five had dosage adjustments, 20 due to active IBD, 1 due to infection and 2 due to active colitis (UC, n = 35), 7 due to active IBD (CD, n = 6), and controls with normal colorectal mucosa (n = 25). Fluorescent in situ hybridisation was used to identify E. coli, bifidobacteria, lactobacillus, and bacteroides using RNA probes. Cellular localisation of bacteria was sought immunohistochemically using the phenotypic markers CD68 (macrophages) and CD1a (dendritic cells).

Results: In controls and patients with inactive IBD, all four bacterial species were confined to the mucosal surface. However, individual organisms and clusters of E. coli (but not other species) were seen also in the lamina propria of 7/9 patients with active UC and 4/6 those with active CD (p < 0.0004 from controls and inactive IBD). In patients with active CD, the numbers of macrophages and dendritic cells were increased (p < 0.0001 from controls and inactive IBD). In both active CD and UC patients, the overall numbers of bacteria were increased compared with inactive stages (p < 0.0001 from controls and inactive IBD). In active CD patients, the numbers of E. coli, bifidobacteria, lactobacillus, and bacteroides were increased compared with inactive stages (p < 0.0001 from controls and inactive IBD). In active UC patients, the numbers of bifidobacteria and lactobacillus were increased compared with inactive stages (p < 0.0001 from controls and inactive IBD). In active CD patients, the numbers of E. coli, bifidobacteria, lactobacillus, and bacteroides were increased compared with inactive stages (p < 0.0001 from controls and inactive IBD). In active UC patients, the numbers of bifidobacteria and lactobacillus were increased compared with inactive stages (p < 0.0001 from controls and inactive IBD).
with active IBD. E coli were found adjacent to \( (n = 7) \) and/or internalised by CD68+ macrophages \( (n = 4) \). E coli were not co-localised with CD11a+ dendritic cells in any patients \( (p < 0.00006) \) from macrophages.

**Conclusion:** Their close opposition to, and in some cases internalisation within lamina proprial macrophages in patients with active IBD, suggests that E coli could contribute to the pathogenesis of the disease.

**CROHN’S DISEASE MUCOSA-ASSOCIATED E COLI INDUCE IL-8 RELEASE FROM INTESTINAL EPITHELIAL CELLS AND ADHERE VIA CARBOHYDRATE DEPENDENT MECHANISMS**

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**Introduction:** There is general consensus that intestinal inflammation in IBD is caused by an abnormal response to the intestinal microflora. It is our hypothesis that the altered mucosal glycosylation seen in IBD could allow mucosal recruitment of otherwise non-pathogenic bacteria and thus cause inflammation.

**Methods:** Mucosa-associated bacteria were isolated from colono-scopic biopsies from CD \( (n = 14) \), UC \( (n = 18) \), and control patients \( (IBS and sporadic polyps, n = 28) \) after removal of surface mucus with dithiothreitol. CD ileal-associated E coli were isolated by our French collaborators. Bacteria identified as E coli were screened for possession of at least one virulence factor (e.g., mucin adhesion, invasion, and induction of pro-inflammatory cytokines). We performed agglutination and PCR, to possess an adhesin specific for M blood group antigen. All agglutinating E coli possessed at least one adhesin gene but lacked conventional virulence genes of pathogenic E coli. Of the CD ileal-associated E coli, one strain, LF10, was shown, using both haemagglutination and PCR, to possess an adhesin specific for M blood group antigen. All agglutinating E coli were shown to adhere to both HT29 and I407 cell lines, inducing release of the pro-inflammatory cytokine IL-8 up to 4-fold above baseline levels \( (p < 0.001) \), but not IL-1β.

**Results:** CD is associated with an increased prevalence of mucosally associated E coli, capable of attaching to intestinal cell lines and inducing a pro-inflammatory response. Soluble plantain fibre inhibits E coli attachment and deserves study as a potential prebiotic therapy for Crohn’s disease.

**Abstract 51**

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**5-AMINOSALICYLIC ACIDS AND THE RISK OF RENAL TOXICITY: A LARGE BRITISH EPIDEMIOLOGICAL STUDY**

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The main objective of this study was to evaluate the risk of renal toxicity in patients using aminosalycates (5-ASA). The medical records of GPs in the UK (from the General Practice Research Database) were used to estimate the incidence rates of renal toxicity of adult patients with either a record of inflammatory bowel disease (IBD) or prescription for 5-ASA (eg mesalazine or sulfasalazine) and that of control patients. Each case of renal toxicity was subsequently matched by age, sex, practice, and calendar time to one patient without renal toxicity. 37 984 adult patients with a record of IBD or 5-ASA prescription and a similar number of control patients were included. In the patients without a history of arthropathy, we found that IBD patients using 5-ASA had an increased risk of renal toxicity: the overall incidence was about 1 case per 1000 person-years of treatment (double compared to non-users). The case control analysis revealed the risk of renal disease was related to indicators of IBD severity. It was also increased in current and recent users [ie their last prescription in the 3 to 12 months before the index date] of 5-ASA. Compared to non-users, the odds ratio (OR) for renal events was 1.80 (95% CI 1.22 to 2.60) in current 5-ASA users. This excess risk markedly reduced in current users after adjustment for concomitant disease and drug use (adjusted OR 1.22 [0.69–2.16]). For recent users, the crude OR was 3.96 (2.20–7.13) and adjusted OR 2.80 (1.33–5.91). Users of mesalazine and sulfasalazine had comparable risks (crude ORs 1.66 [0.94–2.96] and 1.93 [1.18–3.14], and adjusted ORs 1.05 [0.47–2.31] and 1.34 [0.68–2.62], respectively). There was no relationship between 5-ASA dose and risk of renal disease. Numbers were too small to compare individual 5-ASA compounds. Users of 5-ASA had an increased risk of renal disease, which may be influenced by the underlying disease severity. There were no differences in risk of renal disease between mesalazine and sulfasalazine.

**Neurogastroenterology/ motility free papers 053–058**

**A CLINICAL INVESTIGATION OF THE EFFECTS OF TEGASEROD TREATMENT REGIME ON THE SYMPTOMS OF IBS-C IN TEGASEROD RESPONSIVE PATIENTS**

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**Background and Aims:** Tegaserod is effective in relieving the symptoms of IBS with constipation (IBS-C), including abdominal discomfort.
BIOFEEDBACK, NOT LAXATIVES, IMPROVES KETAMINE, AN NMDA RECEPTOR ANTAGONIST
SMALL INTESTINAL INFLAMMATION IS ASSOCIATED WITH HUMAN OESOEPHALIC HYPERSENSITIVITY

Methodology:
A randomised, open label, parallel group, multi-centre trial. 519 patients (≥18 years) diagnosed with IBS-C (457 females, 62 males) were treated with tegaserod (4mg twice daily) for 4 weeks. Responders were randomised (1:1) to either continue on tegaserod at the same dose, or to withdraw from treatment for 8 weeks. The absence of recurrence of IBS symptoms was measured at 4 weekly intervals, as derived from the patient's weekly Overall Relief Assessment (ORA).

Results:
274/410 (68%) patients who completed the initial 4 weeks of treatment were responders (experienced relief of symptoms for ≥ 2 weeks). The remaining patients had little or no benefit (n = 131, 32.3%), or were not assessed (n = 5). At the end of the 8 week comparator phase, 90/104 (87%) of those maintained on tegaserod continued in symptomatic remission, judged by ORA scores at the end of week 12, compared with only 61/105 (58%) in whom therapy was withdrawn (p < 0.0001). Adverse events (AEs) were mild or moderate severity. The most frequent AEs in the treatment-continuation arm were diarrhoea (8/130, 6%), reflecting the promotile effect of the drug, and headache (13/130, 10%). In the subjective withdrawal arm, patients reported diarrhoea and 6% (9/141) reported headaches.

Conclusions:
Based on weekly ORA scores, when patients who are responsive to tegaserod were maintained on treatment for 12 weeks, the recurrence of IBS-C symptoms was significantly reduced. Tegaserod treatment was well tolerated.

054 BIOFEEDBACK, NOT LAXATIVES, IMPROVES SYMPTOMS, TRANSIT AND AUTONOMIC TONE IN FUNCTIONAL CONSTIPATION
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Background: Behavioural therapy biofeedback (BF), is an established treatment for patients with functional constipation, allowing avoidance of laxatives in successfully treated patients. Improvement with BF is known to be associated with enhanced autonomic input to the hindgut, as measured by laser Doppler flowmetry (LDF) of rectal mucosal blood flow. It is unknown whether laxatives affect autonomic tone and whole gut transit (WGT).

Methods: Forty-nine consecutive consenting female patients were randomised to receive either BF (n = 27, mean age 46 years, range 23–75) or bisacodyl, 5 to 10 mg as required (n = 22, 41 years, range 22–71). Coeliacs (5/130, 4%). In the subjective withdrawal arm, AEs were measured weekly using radio-opaque markers, slow transit defined as excess gastric volumes and motility were determined by intervention studies using 5HT antagonists.

Results: Subjectively, 19/27 (70%) BF and 6/22 (27%) laxative patients reported improvement, p < 0.01. Nineteen BF patients had increased neuronal excitability, ie central sensitisation [CS]. In somatic tissues the induction of CS in the spinal cord is dependent on the N-methyl-D-aspartate (NMDA) receptor, however, the role of the NMDA receptor in mediating visceral hypersensitivity is unknown.

Aim: To determine if the NMDA receptor antagonist ketamine attenuates CS in a model of human oesophageal hypersensitivity.

Methods:
14 healthy subjects [7 male, age 18–43 years] were studied in a randomised two way double blind placebo controlled crossover study. Pain thresholds (PT) to electrical stimulation were determined in the PO and foot, and then either ketamine (0.075 mg/kg) or placebo (0.9% NaCl) was given as an intravenous bolus. A 30 min infusion of 0.15 M acid was then given in the distal oesophagus together with an intravenous infusion of ketamine (0.005 mg/kg) or placebo (0.9% NaCl) for 30 min. PT in the PO and foot were then repeatedly tested for 120 min post-infusion. PO pH and an attention task was performed throughout.

Results: In all but one subject (excluded from analysis) the pH remained above 5 in the PO during each study. Ketamine attenuated the reduction in PT in the PO in response to acid in the distal oesophagus (Area under curve (AUC): 16.9±3.9 and 12.3±2.6 for ketamine and placebo, respectively, p < 0.002). Ketamine did not affect PT in the foot compared with placebo (AUC 10.8±4.7 and 11.2±5.2, p = 0.5). Ketamine reduced attention scores during the attention task with baseline (Mean 54.4±2.6 and 46.1±4.6, respectively, p < 0.001) but this had ceased 30 min post-infusion (mean 54.9±2.8 and 54.4±2.6, p = 0.27).

Conclusion: The attenuation of PO hypersensitivity by ketamine suggests that the NMDA receptor contributes to the generation of CS in visceral pain. Therefore, NMDA receptor antagonists may have a role in the management of visceral pain hypersensitivity states.

056 POSTPRANDIAL HYPERSEASONINAEMIA AND DELAYED GASTRIC EMPTYING: NEW INSIGHTS INTO POSTPRANDIAL SYMPTOMS IN UNTREATED COELIAC DISEASE
1School of Medical and Surgical Sciences; 2University of Nottingham and Derbyshire Royal Infirmary; 3Magnetic Resonance Centre; 4School of Biomedical Sciences

Background: Anorexia and nausea are common but unexplained features in coeliac disease. We have recently shown that a 5-HT4 agonist delays gastric emptying and induces nausea in healthy subjects. Untreated coeliacs have marked duodenal enterochromaffin cell hyperplasia and we hypothesised that the postprandial dyspepsia and delayed gastric emptying frequently seen in these patients is due to excess serotonin release following a meal.

Methods: Untreated coeliacs (n = 13) and controls (n = 12) received a 500 kcal meal and blood samples were collected during fasting and for 3 hours postprandially. Serotonin was measured in platelet poor plasma using HPLC-EC. The presence of postprandrial dyspepsia was assessed using a questionnaire. On a separate occasion gastric volumes and motility were determined by echoplanar magnetic resonance imaging.

Results: (Mean ±SE) Serotonin rose significantly after the meal, coeliac patients showing a significantly greater postprandial AUC over 3 hours (4386±622) compared with controls (1756±293 nmol/L min, p = 0.001). Peak 5HT levels were also significantly higher in coeliacs (114±26 v 59±27 nmol/L, p < 0.001) and occurred sooner after the meal than in controls (71±16 v 133±9 min, p < 0.01) Coeliacs with significant postprandial dyspepsia (n = 7) had higher postprandial 5HT reseed than those without symptoms (n = 6) (5264±556 v 3361±1089 nmol/L min) this difference was not significant (p = 0.13) Gastric emptying in coeliacs was significantly delayed (72±11 v 40±2 min, p = 0.01) but this did not correlate with serotonin levels (r = 0.29).

Conclusion: Coeliac disease is associated with markedly elevated postprandial serotonin release, postprandial dyspepsia, and delayed gastric emptying. Whether these are causally linked remains to be determined by intervention studies using 5HT antagonists.

057 SMALL INTESTINAL INFLAMMATION IS ASSOCIATED WITH INCREASED ENTEROENDOCRINE CELL NUMBERS AND HYPOPHAGIA
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The mechanisms by which small intestinal infection and inflammation produce symptoms such as anorexia are poorly understood. Upregulation of enteroneuropeptide Y (EEN) cell function is a plausible mechanism,
because regulatory peptides/amines, for example CCK and 5HT, regulate food intake. Trichinella spiralis infection in mice is a well described model of small intestinal inflammation, and has been proposed as an animal model of postinfective functional GI disorders. Effects on feeding and EEC have not been assessed.

Methods: Male NIH mice were infected with 300 T spiralis larvae by oral gavage. Food intake was measured and compared with a control group of naive mice. On days 6, 9, 13, and 20 postinfection (PI), duodenal were fixed and immunostained for 5HT and CCK. Results are expressed as numbers of positive staining EEC per 15 crypt/villus units. To assess the correlation of the mast cell infiltration seen in this model, an anti c-Kit antibody (Ack-2) was administered i.p. to attenuate mast cell responses. A control group received nonspecific IgG.

Results: Six days PI, increased numbers of CCK-positive EEC cells were seen (9.0±0.13) compared to naive mice (6.7±0.7, p = 0.03). This peaked from day 9 (15.3±1.7, p < 0.01) to day 13 (15.0±0.6, p < 0.01) but improved by day 20 (8.5±0.9, p = ns), when inflammation has resolved. Similar changes were seen with 5HT-positive EEC cells, although not significantly increased until day 9 (19.8±2.1, p < 0.01) and day 13 (17.0±0.9, p = 0.01). This again resolved by day 20 (7.2±1.5, p = ns). Food intake dropped from 4.5±0.1 g/mouse/day in naive mice to 3.4±0.5 at day 7, to 2.1±0.8 at day 9, and to 1.2±0.2 at day 11 (all p < 0.05). This normalised by day 14. Studies following Ack-2 showed that hypophagia and increased EEC persist despite effective mast cell attenuation.

Conclusions: Acute small intestinal infection is associated with an increase in EEC cell numbers that coincides with, or contributes to, marked hypophagia. Infiltration by mast cells is not responsible for driving these responses. This represents a potentially important host response to intestinal infection. Both CCK and 5HT influence motility: this may facilitate parasite clearance. CCK may also protect via reduced bacterial translocation and increased IgA secretion. Supported by Wellcome Trust (FC1) and DFP (UWdL).

059 DECREASED POST-PRANDIAL 5 HT IN CONSTIPATION PREDOMINANT IRritable Bowel Syndrome (C-IBS)

S.P. Dunlap, N.S. Coleman, P.E. Blackshaw, A.C. Perkins, G. Singh, C.A. Marsden, R.C. Spiller. Divisions of Gastroenterology, Medical Physics and Neurosciences, University Hospital, Nottingham

Introduction: 5 HT (5-hydroxytryptamine), an important stimulator of intestinal motility and secretions, is stored predominantly within enterochromaffin cells (EC) of the GI tract, which are increased in post-infectious IBS (PI-IBS). Recent reports have associated diarrhoea-predominant IBS with increased 5HT release but whether reduced release plays a role in causing constipation has not been examined.

Aims: To determine the relationship between postprandial plasma serotonin release and colonic transit in CIBS compared with PIIBS and healthy controls.

Methods: 15 CIBS, 15 PIIBS with diarrhoea predominant symptoms, and 15 healthy volunteers recruited through advertisement, underwent serial plasma serotonin measurement after a standard 520 kcal meal for 3 hours. Blood was taken through an 18G cannula into a syringe containing citrate, adenosine, dipyrimadole, and theophylline to inhibit platelet activation. Platelet poor plasma (PPP) and platelet rich plasma (PRP) was assessed for 5 HT using HPLC with electrochemical detection. Colonic transit was measured using marker pellets.

Results: Mean (SEM) colonic transit was prolonged in CIBS (49.4±3.8 h) compared with PIIBS (26.7±4.5) and controls (34.1±4.5) (p = 0.002). The area under the curve (AUC) of PPP serotonin from immediately after the meal to 180 min was lower in CIBS (2593±309 Nmol/L/min) compared with PIIBS (5623±721) and controls (4822±598) (p < 0.001). Although PIIBS showed increased AUC compared with controls, these differences were not significant owing to substantial variability. There was a negative correlation between AUC and transit in all subjects (r = 0.354, p = 0.02). Platelet 5HT was greater in CIBS (652±56.1) compared with PIIBS (PRP = 484±40.7 ng/109 platelets, p = 0.039) but not significantly different from controls (598±536.4).

Conclusions: Reduced 5 HT release may be an important contributor to slow intestinal transit in CIBS.

060 A SYSTEMATIC REVIEW AND ECONOMIC ANALYSIS OF THE COST-EFFECTIVENESS OF PROTON PUMP INHIBITOR THERAPY IN NON-ULCER DYSPEPSIA

P. Mooyeed1,2, B. Delaney1. 1Gastroenterology Unit, City Hospital, Birmingham, UK; 2Dept of Academic Primary Care and General Practice, Birmingham University, Birmingham B15 2TT

Introduction: Proton pump inhibitor (PPI) therapy is an established treatment for gastro-oesophageal reflux disease, but their efficacy in non-ulcer dyspepsia (NUD) is controversial. Randomised controlled trials (RCTs) have given conflicting results so we have conducted a rigorous Cochrane systematic review of the literature and evaluated the cost effectiveness of this strategy.

Methods: The Cochrane Controlled Trials Register, Medline, EMBASE, and CINAHL electronic databases were searched for RCTs evaluating PPIs in NUD. Experts in the field and pharmaceutical companies were contacted for information on any unpublished RCTs. A single investigator reviewed papers generated from this search according to predefined eligibility and validity criteria. Outcomes were dichotomised into dyspepsia minimal/resolved versus some/worse. The results were entered into a Markov model (Tree Age version 4.0) that compared costs and effects of PPI with antacid therapy over a 12 month period from a health service perspective. Full dose PPI was assumed to cost 22.75, low dose PPI 12.43, antacid 2.48/month, and a GP visit 18. Monte Carlo simulations of 5000 patients were performed using the 95% CI of the meta-analysis data to give stochastic estimates of cost effectiveness.

Results: Seven RCTs evaluating 3031 patients for 2–8 weeks were eligible for the review. PPI therapy was significantly superior to placebo in treating NUD (relative risk (RR) of remaining dyspeptic = 0.86; 95% CI = 0.80–0.93, p < 0.001, random effects model). There was significant heterogeneity between the studies. The number
needed to treat to cure one case of dyspepsia = 9 (95% CI = 6 to 26). Six RCTs evaluating 2032 patients compared high versus low dose PPI with no statistical difference in curing NUD symptoms (RR = 0.98; 95% CI = 0.92 to 1.05). The Markov model suggested full dose PPI cost 60/month free from dyspepsia (95% CI = 42–112) while half dose PPI cost 29/month free of dyspepsia (95% CI = 19–55).

Conclusions: PPI is mildly effective in NUD and the economic model suggests low dose PPI is cost-effective in NUD.

061 PLASMA GHRELIN FOLLOWING CURE OF HELICOBACTER PYLORI

D. Freshwater, H.S. Randeva, P. O’Hare, C.U. Nwokolo. University Hospitals Coventry and Warwickshire NHS Trust and Biomedical Research Institute, University of Warwick, UK

Background: In the Western world, the incidence of oesophageal adenocarcinoma has increased over the past 30 years, coinciding with a decrease in the prevalence of H pylori. Trends of increasing oesophageal adenocarcinoma can be linked causally to increasing gastroesophageal reflux disease (GERD), which can be linked to an increasingly obese population. However, there is no plausible biological mechanism of association between H pylori, obesity, and GERD. Ghrelin, a peptide produced in the stomach that regulates appetite, food intake, and body composition, is studied in H pylori positive asymptomatic subjects.

Methods: Plasma ghrelin, leptin, and gastrin were measured for 6 h after an overnight fast, before and after cure of H pylori in 10 subjects. 24 h intragastric acidity was also assessed.

Results: After cure median (95% CIs) integrated plasma ghrelin increased from 1160.5 (765.5–1451) pg/ml/h to 1910.4 (1675.6–2395.6) pg/ml/h (p = 0.002 Wilcoxon Rank Sum Test), a 75% increase. This was associated with a 14% increase in 24 h intragastric acidity (p = 0.006). There was a significant positive correlation between plasma ghrelin and intragastric acidity (r = 0.44, p = 0.05, Spearman rank correlation) and no significant change in leptin or gastrin.

Conclusions: After H pylori cure, plasma ghrelin increases profoundly in asymptomatic subjects. This could lead to increased appetite and weight gain and contribute to the increasing obesity seen in Western populations where H pylori prevalence is low. This plausible biological mechanism links H pylori, through increasing obesity and dyspepsia, to an increase in oesophageal adenocarcinoma observed in the Western world.

062 PCR DETECTION OF CAG PATHOGENICITY ISLAND GENES DOES NOT ACCURATELY PREDICT FUNCTIONALITY OF CAG ENCODED PROTEINS

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H pylori associated disease is more common in patients infected with CagA+ strains. CagA is one of 31 proteins encoded on the cag pathogenicity island (Pal). CagA itself is translocated into host cells via a syringe like structure comprising other cag encoded proteins. Here it becomes tyrosine phosphorylated and causes proliferative cell signal-ling and cytoskeletal changes. Interaction of the cag syringe itself with epithelial cells results in induction of proinflammatory cytokines, and/or secrete IL-8. Of the remaining 6 strains none induced IL-8 secretion. The degree of cagA phosphorylation induced and the amount of translocated cagA were not related to the level of IL-8 secretion induced. Six strains that possessed cagA did not produce cagA protein. Four strains predicted to lack a complete cag Pal by PCR analysis induced both cagA phosphorylation and IL-8 production, and one strain predicted to possess an intact Pal by PCR did not induce cagA phosphorylation or IL-8 production.

Conclusion: PCR analysis of selected cag Pal genes cannot reliably predict whether the Pal is functional, either in terms of cagA translocation and phosphorylation or IL-8 induction in epithelial cells. PCR analysis is therefore unlikely to be as accurate as these phenotypic assays in measuring strain virulence.

063 EVOLUTION OF THE HELICOBACTER PYLORI VACA TOXIN BY RECOMBINATION IN VIVO

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Introduction: The H pylori vacuolating cytotoxin, Vaca, varies between strains, with a decrease in the prevalence of Vaca+ strains being correlated with a decrease in the prevalence of H pylori in Western populations where the prevalence is low. This plausibly represents an adaptation process for survival in the changing gastric environment. Changing H pylori virulence within an individual stomach has important implications for pathogenicity and for vaccine development.

Conclusions: After H pylori cure, plasma ghrelin increases profoundly in asymptomatic subjects. This could lead to increased appetite and weight gain and contribute to the increasing obesity seen in Western populations where H pylori prevalence is low. This plausible biological mechanism links H pylori, through increasing obesity and dyspepsia, to an increase in oesophageal adenocarcinoma observed in the Western world.

064 A SYSTEMATIC REVIEW OF HELICOBACTER PYLORI ERADICATION THERAPY IN DUODENAL AND GASTRIC ULCER HEALING AND MAINTENANCE

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Introduction: H pylori eradication (HE) therapy is regarded as the treatment of choice for duodenal (DU) and gastric ulcer (GU). Surprisingly there have been few systematic reviews on the efficacy of this approach both for acute healing and maintenance.

Conclusions: We have demonstrated evolution, by homologous recombination, of the toxin gene, vacA, and hence of toxin phenotype within an individual stomach. From our vacA sequence data, it appears most likely that the less pathogenic strain is the result of this evolution process. Evolution of Vaca in vivo might represent an adaptation process for survival in the changing gastric environment. Changing H pylori virulence within an individual stomach has important implications for pathogenicity and for vaccine development.

Abstract 64

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>RCTs</th>
<th>Patients</th>
<th>RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>HE+UHD vs UHD for DU healing</td>
<td>31</td>
<td>3654</td>
<td>0.62 (0.540–0.72)</td>
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<tr>
<td>HE vs placebo for DU healing</td>
<td>2</td>
<td>207</td>
<td>0.37 (0.260–0.53)</td>
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<tr>
<td>HE+UHD vs UHD for GU healing</td>
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<td>1123</td>
<td>1.11 (0.841–1.46)</td>
</tr>
<tr>
<td>HE vs placebo for GU maintenance</td>
<td>25</td>
<td>2372</td>
<td>0.21 (0.160–0.28)</td>
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<tr>
<td>HE+UHD vs UHD for GU maintenance</td>
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<td>246</td>
<td>0.68 (0.381–1.24)</td>
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<tr>
<td>HE vs placebo for GU maintenance</td>
<td>9</td>
<td>831</td>
<td>0.27 (0.170–0.45)</td>
</tr>
</tbody>
</table>
therapies were ulcer healing drugs (UHD) or placebo/no therapy. Experts in the field and pharmaceutical companies were contacted for information on any unpublished RCTs. Articles were included on predefined eligibility and validity criteria.

**Results:** 82 articles were reviewed, 57 were eligible, and data was extractable in 52 papers. The results are given in the table in terms of relative risk (RR) of ulcer unhealed/relapsed. Where statistically significant heterogeneity (p < 0.2) existed (denoted by *) a random effects model was used (see Table).

The pooled relapse rate for DU recurrence in those allocated to no treatment over 12–52 weeks was 60% compared with 14% in the HE group. The corresponding figures for GU patients were 45% and 12%. Meta-regression was performed to evaluate factors that might explain the heterogeneity in the DU and GU maintenance meta-analyses. Eradication rate was not a significant factor in this model with only concealment of allocation an independent predictor of trial outcome.

**Conclusions:** HE is an effective therapy to prevent DU and GU recurrence although the efficacy of this may be overestimated and there is variability in study results not explained by efficacy of eradication. HE has additional benefit to UHD in healing DU (but not GU) patients.

---

**Methods:** Gastric biopsies were taken at endoscopy from *H pylori* infected (n = 17) and uninfected (n = 16) patients, and *MMP-7* expression examined by immunohistochemistry (paraffin-embedded sections), ELISA (R&D systems), and Real Time PCR. *H pylori* strains were cultured and PCR-typed for cagA, cagE, and vacA. For immunohistochemistry, slides were examined by two blinded observers and staining intensity was graded 0–4. Results were compared by Mann Whitney U test (immunohist) and t test (ELISA, Real Time PCR).

**Results:** Epithelial cells from *H pylori* infected patients stained more intensely for *MMP-7* than uninfected patients both in antrum and corpus. This was most marked superficially in the antrum (median Hp+ 2, Hp− 1, p < 0.05) and in the proliferative zone in the corpus (median Hp+ 3, Hp− 2, p < 0.05). There was also a significant increase in *MMP-7* staining inflammatory cells in infected patients. ELISA confirmed these results with a threefold increase in infected patients (Hp+ 0.182 ± Hp− 0.059, p = 0.009). Real Time PCR demonstrated upregulation of *MMP-7* at RNA level (antrum Hp+ 0.038 v Hp− 0.008, p = 0.007). It was not possible to correlate changes with strain type due to small numbers of agents.

**Conclusion:** This study demonstrates increased expression of *MMP-7* in vivo in nonmalignant gastric epithelial cells colonised by *H pylori*. We speculate that upregulation of *MMP-7* in *H pylori* gastritis may play a role in *H pylori* induced gastric carcinogenesis.

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**Background and Aims:** Recent in vitro and animal model studies have identified a number of epithelial peptides with antimicrobial and gastroprotective activities. To investigate their relevance to human peptic ulcer disease, we assessed gastric epithelial secretory leukocyte proteinase inhibitor (SLPI) and human beta defensins, HBD1, HBD2, and HBD5 in a range of peptic disorders.

**Methods:** Gastric biopsies were taken from 52 patients, median age of 55 years, including 31 males and 8 smokers. Expression of SLPI, HBD1, HBD2, and HBD5 mRNA was determined using real time quantitative PCR. Histological assessment was carried out on biopsies from the same anatomical regions. The activity of gastritis was graded on a 0–3 scale, 0 being normal and 3 severe. Specimens carried code numbers for blind assessment.

**Results:** The antrum gastric had an median SLPI level of 0.93 and HBD1 of 0.42, compared with 0.13 (p = 0.001) and 0.08 (p = 0.002) respectively, in the gastric body. The antral histological scores correlated positively with HBD2 expression (r = 0.69; p < 0.001) and negatively with SLPI (r = −0.47; p = 0.006), particularly in the absence of aspirin. Patients with *H pylori* gastritis, gastric, or duodenal ulcers had lower expression of HBD1 and greater expression of HBD2, and HBD5 in a range of peptic disorders.

**Methods:** Four (2m, 2f) healthy volunteers received naproxen 500 mg base daily, for 2 days. Blood (2f) received no active drug. Antral biopsies [4] were taken by endoscopy before and following (3, 12, and 48 h) treatment. Total RNA was extracted from 2 of the biopsies with RNeasy® mini kits and 2 were used for histology. The expression of ∼8000 genes were assessed by cDNA microarray. After normalisation the expression of 1258 genes were significantly altered by naproxen as judged by ANOVA (p < 0.05). Data in brackets are maximum percent increase compared to control.

**Results:** Scrutiny of the microarray data identified increased transcription of genes coding for the following proteins at 3 h: caspase 1 (29%), and 7 (21%), E2F dimmerization partner 2 (18%), at 12 h: caspase 3 (35%), poly (ADP-ribose) synthase (33%), NFkB (14.5%), methyl CpG binding domain protein 4 (33%), APC (20x), DNA protein kinase (43%), damage specific DNA binding protein 2 (24%), cell division cycle 25A (17%), checkpoint kinase 2 (47%), cyclin dependent kinase (CDK) 6 (20%), cyclin H (33%); and at 48 h: caspase 9 (31%), xeroderma pigmentosa group A (22%), mothers against decapentaplegic homologue 6 (30%), CDK 7(40%), CDK associated protein 1 (37%). Histological assessment found no inflammatory changes in the gastric mucosa correlated to drug treatment.

**Conclusion:** These transcriptional changes suggest naproxen not only causes apoptosis but also DNA double-strand breaks, stimulates DNA repair responses and checkpoint cell cycle arrest. This preliminary analysis of an in vivo human experiment is consistent with the in vitro findings of others. The data also allow identification of previously unrecognized changes in gene expression that may be related to the anticancer properties of NSAIDs.

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**Introduction:** We have previously reported the use of secretin MRCP to quantify pancreatic function. We have now studied a group of normal patients and patients with chronic pancreatitis.

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**GASTRIC EPITHELIAL CELLS IN VIVO WITH UPREGULATION OF MATRILYSIN (MMP-7) IN GASTRIC EPITHELIAL CELLS IN VIVO**

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**Methods:** We now examined both the protein and RNA level, and that this is more marked for *H pylori* strains with an intact cag pathogenicity island. We have previously reported the use of secretin MRCP in an in vivo human experiment is consistent with DNA repair responses and checkpoint cell cycle arrest. This preliminary analysis of an in vivo human experiment is consistent with the in vitro findings of others. The data also allow identification of previously unrecognized changes in gene expression that may be related to the anticancer properties of NSAIDs.

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**HELICOBACTER PYLORI INFECTION IS ASSOCIATED WITH UPPREGULATION OF MATRILYSIN (MMP-7) IN GASTRIC EPITHELIAL CELLS IN VIVO**

J.R. Bebb1, F. Awiles1, N.H. Andrews1, A. Zaitoun1, J.C. Atherton1.

**Introduction:** To investigate their relevance to human peptic ulcer disease, we assessed gastric epithelial secretory leukocyte proteinase inhibitor (SLPI) and human beta defensins, HBD1, HBD2, and HBD5 in a range of peptic disorders.

**Background:** *H pylori* infection is associated with duodenal ulceration and peptic ulceration. It can also be modulated by low dose aspirin particularly in subjects infected with *H pylori*.

**Results:** The pooled relapse rate for DU recurrence in those allocated to no treatment over 12–52 weeks was 60% compared with 14% in the HE group. The corresponding figures for GU patients were 45% and 12%. Meta-regression was performed to evaluate factors that might explain the heterogeneity in the DU and GU maintenance meta-analyses. Eradication rate was not a significant factor in this model with only concealment of allocation an independent predictor of trial outcome.

**Conclusions:** HE is an effective therapy to prevent DU and GU recurrence although the efficacy of this may be overestimated and there is variability in study results not explained by efficacy of eradication. HE has additional benefit to UHD in healing DU (but not GU) patients.
Methods: 62 patients referred with suspected or known pancreatic pathology underwent SSFSE MRCP both before and after 0.1 ml/kg IV secretin. The sequence with identical positioning and receiver gain was performed prior to secretin and at 2 min intervals post-secretin to a mean of 7 min. All patients also underwent parenchymal pancreatic imaging with a coronal triplane and axial 11W sequence. The pancreatic flow rate was calculated as the change in signal intensity over time within a ROI that encompassed not only the pancreas but the small bowel. A voxel containing 100% water was used to correct for variations in receiver gain between individuals. 63 patients had concurrent CT scans. Using the Cambridge classification patients were divided into mild, moderate, and severe chronic pancreatitis.

Results: There were 31 patients with a normal pancreas. The mean flow rate was 8.0 ml/min +/- 2.6. 31 patients had evidence of chronic pancreatitis, 6 mild, 6 moderate, and 19 severe chronic pancreatitis. Mean flow rates were; mild pancreatitis 6.9 +/- 1.7, moderate 6.0 +/- 1.7, and severe 5.9 +/- 2.9. This was statistically significant from the normal group.

Conclusion: Significantly different flow rates were found in patients with severe chronic pancreatitis compared with normals. Further, there appeared to be a trend down through the different levels of severity of chronic pancreatitis. Changes in flow rates in a given individual should provide useful information and a trend down on sequential measurements may prove to be an early indicator for pancreatic disease.

Oesophageal free papers 070–075

ENDOSCOPIC GASTROPALATION FOR THE TREATMENT OF PAEDIATIC GASTRO-OSOPHAGEAL REFUX DISEASE

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1Centre for Paediatric Gastroenterology, Royal Free Hospital, London,
2Royal London Hospital, London

The aim of this work is to assess the safety and efficacy of endoscopic gastropalation (EG) (BARD Endocinch© device) for the treatment of GORD in children and adolescents. 20 patients (13 cerebral palsy, 8 male, median (range) age 12.8 years (6.1–17.7), weight 46 kg (16.5–75)) with symptoms of GORD dependent/refractory wt PPIs for > 12 months underwent EG. Median follow up: 15 months. Exclusion criteria were age > 17 years, dysphagia, obesity (BMI > 99th centile), previous upper GI surgery, and hiatus hernia > 2 cm. Preprocedure assessment included symptom scoring, upper GI endoscopy, upper oesophageal manometry [in (4), liquid/solid phase gastric scintiscan, 24 hour oesophageal pH, and completed reflux quality of life (QOLRAD) questionnaire. Postprocedure symptomatology, QOL and adverse events were assessed at 1, 3, 6, and 12 months. Repeat 24 h pH was performed at 15 months (16 patients). All occurred under general anaesthesia as is standard practice in paediatric endoscopy. The median duration of the procedure for 3 plications (3 pairs of sutures) was 65 min. The median heartburn score improvement (daily heartburn frequency x severity [0–10]) was 25%. Procedure and follow up complications were mild, 6 (0.58%) non-fatal life-threatening complications, which is significantly more (p < 0.01) than in open 15 (0.13%). Five patients died in laparoscopic (mortality 0.08%) and 10 in open fundoplication (mortality 0.17%, p = n.s.). Laparoscopic fundoplication had 35 (0.58%) non-fatal life-threatening complications, which is significantly more (p < 0.01) than in open 15 (0.25%). Inclusion criteria were: age > 17 years, symptoms of GORD for > 12 months, failed antireflux surgery with/without re-operation, incarceration of the intestine after previous surgery, and aggressive lifestyle. The current mortality of open fundoplication is relatively low (0.13%), but still, almost every 200 patient suffers from life-threatening and/or fatal complications. There is no significant difference in the mortality between laparoscopic and open fundoplication, but laparoscopic fundoplication is associated with significantly more life-threatening complications. These facts must be considered both when planning operations and when informing patients.
saliva dilutes and neutralises the remaining acid in the oesophagus. However, this novel idea needs further investigation.

**Aim:** This study was designed to assess the effect of chewing gum on postprandial GOR. The objective was to compare postprandial pH on the same patient on two occasions by keeping the experimental conditions identical.

**Method:** A standard refluxogenic meal was devised with 60% fat using a computer program [comp.eat]. 21 subjects with symptoms of GOR were chosen. Each subject had standard manometry followed by the insertion of the pH catheter. Subjects were given the refluxogenic meal on the first and the second day for lunch having starved for 4 h prior to eating the meal on both occasions. They were randomly selected to chew a piece of gum for half an hour after eating the meal on either the first or the second day. pH was measured for 2 h during the postprandial period on both occasions under the same conditions. Percentage time pH below 4 was compared for the two postprandial periods.

**Results:** The mean (sd) and median (IQ range) values for the percentage time pH below 4 during the postprandial period without chewing gum were 9.2(8.9) and 5.8(2–13.5) respectively and with chewing gum 4.7(5.4) and 3.6(0.6–6.8). This difference was statistically significant (p = 0.005).

**Discussion:** Chewing gum significantly reduced postprandial reflux in those by multiple biopsies, CT and EUS. Oesophagectomy was considered first line therapy for high grade dysplasia (HGD) in Barrett’s oesophagus but has considerable morbidity and mortality. Photodynamic therapy (PDT) using 5-aminolaevulinic acid (ALA) offers a minimally-invasive method for mucosal ablation of HGD. No published studies have attempted to optimise treatment conditions. Our aim was to confirm safety and determine the effect of light dose and treatment regime on outcome.

**Methods:** With ethical approval, 22 patients with HGD (Vienna category 4) were treated from 1998. HGD was confirmed and carcinoma excluded by multiple biopsies, CT and EUS. Oesophagectomy was inappropriate because of co-morbidity or patient refusal. Patients received 60 mg/kg ALA orally (DUSA Pharmaceuticals Inc.) At endoscopy 4–6 h later, laser light (wavelength 633 nm) was delivered by diffuser fibre through an oesophageal balloon or silicone bolster at a dose of 500, 750 or 1000/cm diffuser fibre. Follow up was by endoscopy and multiple biopsies after 1, 3, 6, 9 and 12 months. PDT was repeated up to three times if HGD persisted.

**Results:** Overall, 12/22 (55%) patients are clear of HGD, after a median follow up of 18 months. However, 9/12 (75%) patients treated with 1000 J are clear v 3/10 with lower light-doses (500–750 J) (p < 0.02). Two 1000 J treatments scheduled 4 weeks apart appears the most effective treatment regime.

**Conclusions:** Photodynamic therapy using ALA is a safe initial approach to HGD in Barrett’s oesophagus. Intensive therapy with two 1000 J/cm treatments 4 weeks apart appears the most effective treatment regime.
DOES SIZE MATTER, OR, WHERE SHOULD DECREASED BONE MINERAL DENSITY AT DIAGNOSIS IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE

N.M. Croft, J.H. Olatunji, M.O. Savage, I.R. Sanderson. Departments of Adult and Paediatric Gastroenterology and Paediatric Endocrinology, Barts and the London, Queen Mary’s School of Medicine and Dentistry, London, UK

Introduction: Significantly reduced bone mineral density (BMD) has been reported in cross sectional studies of children with established inflammatory bowel disease (IBD). In this study we have examined the bone mineral density within 3 months of diagnosis in children with IBD.

Methods: Children with IBD underwent dual-energy x ray absorptiometry (DEXA) of the whole body (BMD WB) and lumbar spine (BMD LS) within 3 months from diagnosis. The data were matched for age, sex, and race and expressed as standard deviation scores (SDS). Bone age was recorded ( Tanner-Whitehouse) and the BMD adjusted accordingly. CD and UC/IC group data were compared using the Mann-Whitney U test. Osteopenia is defined as BMD SDS between −1.0 and −2.5, osteoporosis < −2.5.

Results: 21 children (8 male and 13 female), median age 12.8 years, have been studied. 14 had Crohn’s disease (CD), 6 ulcerative colitis (UC), and 1 indeterminate colitis (IC). Bone age was delayed (> 2 years) in 1 and advanced (> 2 years) in 2 children. Median body mass index Z score was −1.08, significantly lower in CD vs UC (−0.97 vs 1.0). Height for age Z score was −0.06. BMD was reduced both in the whole body (median SDS –1.08) and lumbar spine (−1.38). There was a trend to these being worse in the CD group (BMD WB: CD −1.35 vs UC/IC: −0.46, p = 0.2; BMD LS, −1.95 vs −1.0, p = 0.5). BMD WB SDS was < −1 in 52% of the 21 subjects (osteopenia in 39% and osteoporosis in 13%), and for BMD LS was 66% (osteopenia 42%, osteoporosis 24%). Using BMD not corrected for bone age for the whole body 25% had a BMD score < −1 (osteopenia 25%, osteoporosis 0%) and lumbar spine 38% (osteopenia 28% and osteoporosis 10%). There was no significantly increased frequency in these abnormalities in the CD group over the UC group.

Conclusions: These data demonstrate reduced bone mineral density at diagnosis in a high proportion of children with IBD. As peak BMD is not reached until early adulthood evidence based strategies to manage low BMD must be clarified for the paediatric population.

Plenary free papers 076–079

076 DOES SIZE MATTER, OR, WHERE SHOULD OESOPHAGO-GASTRIC CANCER BE MANAGED?

A.M. Thompson, K.P. Park. For the Scottish Audit of Gastric and Oesophageal Cancer, Department of Surgery and Molecular Oncology, Ninewells Hospital, Dundee DD1 9SY, UK

The Scottish Audit of Gastric and Oesophageal Cancer prospectively collected population based data on 3293 cancers diagnosed over a 2 year period with a minimum 1 year follow up. One aim of the project was to examine whether hospital size was related to outcome. The 53 contributing hospitals were divided by caseload, with small hospitals having significantly less delay in diagnosis than larger institutions (p = 0.001). However, this did not significantly improve subsequent survival (see Table 1).

<table>
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<th>Abstract 076 Table 1</th>
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<tr>
<td>Number of cases presenting per year:</td>
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<tr>
<td>Delay in diagnosis &gt; 4 weeks</td>
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<tr>
<td>1 year survival</td>
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There was no statistically significant difference in postoperative mortality for either gastric or oesophageal cancer by hospital size (Table 2).

<table>
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<th>Abstract 076 Table 2</th>
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<tbody>
<tr>
<td>Number of operations per year:</td>
</tr>
<tr>
<td>Oesophageal mortality</td>
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<tr>
<td>Gastric mortality</td>
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</table>

Overall survival was 32% at 1 year (54% for surgical patients) and 17% at 2 years (33% for surgical patients). The factors adversely affecting survival by multivariate analysis in the surgical patients were American Society of Anaesthesiologists grade 4 [Hazard Ratio 2.35, CIs 1.00 to 1.81, p = 0.047] or 5 [HR 2.86, CI 1.40 to 4.27, p = 0.001] and margin involvement by tumour (HR 1.97 CI 1.32 to 2.96, p = 0.001). Conversely, non-smokers [HR 0.78, CI 0.64 to 0.94, p = 0.01], patients with functional cancers [HR 0.7, CI 0.51 to 0.95, p = 0.021], and those with a history of H pylori infection [HR 0.79, CI 0.63 to 0.99, p = 0.04] did better. Following univariate, case mix adjusted and multivariate analysis, there was no difference in survival according to the size of the hospital of presentation or hospital of surgery. In combination with data emerging from elsewhere, the guidance on the organisation of oesophago-gastric cancer services in the UK should be reviewed.

077 DECREASED BONE MINERAL DENSITY AT DIAGNOSIS IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE

N.M. Croft, J.H. Olatunji, M.O. Savage, I.R. Sanderson. Departments of Adult and Paediatric Gastroenterology and Paediatric Endocrinology, Barts and the London, Queen Mary’s School of Medicine and Dentistry, London, UK

Introduction: Significantly reduced bone mineral density (BMD) has been reported in cross sectional studies of children with established inflammatory bowel disease (IBD). In this study we have examined the bone mineral density within 3 months of diagnosis in children with IBD.

Methods: Children with IBD underwent dual-energy x ray absorptiometry (DEXA) of the whole body (BMD WB) and lumbar spine (BMD LS) within 3 months from diagnosis. The data were matched for age, sex, and race and expressed as standard deviation scores (SDS). Bone age was recorded ( Tanner-Whitehouse) and the BMD adjusted accordingly. CD and UC/IC group data were compared using the Mann-Whitney U test. Osteopenia is defined as BMD SDS between −1.0 and −2.5, osteoporosis < −2.5.

Results: 21 children (8 male and 13 female), median age 12.8 years, have been studied. 14 had Crohn’s disease (CD), 6 ulcerative colitis (UC), and 1 indeterminate colitis (IC). Bone age was delayed (> 2 years) in 1 and advanced (> 2 years) in 2 children. Median body mass index Z score was −1.08, significantly lower in CD vs UC (−0.97 vs 1.0). Height for age Z score was −0.06. BMD was reduced both in the whole body (median SDS –1.08) and lumbar spine (−1.38). There was a trend to these being worse in the CD group (BMD WB: CD −1.35 vs UC/IC: −0.46, p = 0.2; BMD LS, −1.95 vs −1.0, p = 0.5). BMD WB SDS was < −1 in 52% of the 21 subjects (osteopenia in 39% and osteoporosis in 13%), and for BMD LS was 66% (osteopenia 42%, osteoporosis 24%). Using BMD not corrected for bone age for the whole body 25% had a BMD score < −1 (osteopenia 25%, osteoporosis 0%) and lumbar spine 38% (osteopenia 28% and osteoporosis in 10%). There was no significantly increased frequency in these abnormalities in the CD group over the UC group.

Conclusions: These data demonstrate reduced bone mineral density at diagnosis in a high proportion of children with IBD. As peak BMD is not reached until early adulthood evidence based strategies to manage low BMD must be clarified for the paediatric population.

078 ANATOMICAL CLUSTERING OF TYPE II FLAT AND DEPRESSED COLORECTAL LESIONS: RELATIONSHIP BETWEEN DYSPLASIA, NEOPLASIA, AND MORPHOLOGY SUBTYPE

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Introduction: Current data suggest that more than 30% of all adenomatous colorectal lesions are of flat morphology (Japanese Research Society Classification type II - JRSC). Reporting of anatomical preponderance has however been inconsistent in Western cohorts. Malignant potential in this group is significant. The optimal approach to diagnosis, management and eventual screening in the UK will be influenced by anatomical distribution.

<table>
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<th>Abstract 78</th>
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<tr>
<td>JRSC Class</td>
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Aim: To evaluate the anatomical distribution of JRSC type II colorectal lesions in the UK and establish if any association exists between site and dysplastic/neoplastic transformation.

Subjects and Methods: Total colonoscopy was performed on 600 consecutive patients, by a single endoscopist using the Olympus...
Hepatic inflammation is an important determinant of portal pressure in alcoholic liver disease


Background: A hyperdynamic circulation and elevated portal pressure are established features of cirrhosis. Furthermore, in patients with alcoholic cirrhosis with superadded inflammation, defined on biopsy as alcoholic hepatitis (AH), an inflammatory cytokine cascade perpetuates further injury. We hypothesise that this additional hepatic inflammation in these patients is central to further deterioration in their portal haemodynamics.

Methods: 10 patients with cirrhosis and superadded inflammation on biopsy, fulfilling histological criteria for AH, (5 male; age 49.5 (34–69); discriminant function [DF] 36.8 ± 9.6) were compared with 13 patients with only alcoholic cirrhosis (12 male; age 51 (40–62); DF 17.4 ± 5.5). Cardiovascular haemodynamics (cardiac output [CO] and mean arterial pressure) and systemic vascular resistance [SVR] using a Swan-Ganz catheter, and mean arterial pressure) and wedged hepatic venous pressure gradient [HVPG] were assessed in both groups using standard techniques, during routine clinical assessment, in accordance with local ethics approval. Clinical and biochemical profiles were also assessed. IL-6 and IL-8 plasma levels were assessed via commercially available ELISAs.

Results: The patients fulfilling AH biopsy criteria had significantly elevated white blood cell counts (13.7 ± 2.7 v 7.8 ± 0.9; p < 0.05), C-reactive protein (36.0 ± 5 v 18.9 ± 3.8; p < 0.05) and systemic inflammatory response syndrome scores (1.4 ± 0.3 v 0.2 ± 0.1; p < 0.01) compared with patients with alcoholic cirrhosis alone (AC). Significant differences in haemodynamics were noted between the two groups, following nonparametric analysis (Mann-Whitney, *p < 0.05; **p < 0.01). The measured pro-inflammatory cytokines, IL-6 and IL-8, also showed substantial increases in the AH group compared to AC (p < 0.05 in each case).

Conclusions: This study demonstrates a significant difference in portal and systemic haemodynamics between patients with alcoholic cirrhosis and those with additional hepatic inflammation, highlighting the important contribution of inflammation to the development of portal hypertension in these patients and the potential benefit to portal pressure from future anti-inflammatory treatments.

Gastrointestinal physiology

Does Bethanechol Provoocation Testing (BPT) predict symptom relief after cholecystectomy for acalculous biliary pain?

A. Smythe, A.W. Majeed, R. Ahmed, M. Fitzhenry, A.G. Johnson. Division of Clinical Sciences South, University of Sheffield, UK

Introduction and Aims: We have previously shown that cholecystokinin provocation testing does not predict symptomatic benefit from cholecystectomy in patients with acalculous biliary pain (ABP). Bethanechol is a muscarinic agent, which stimulates the gall bladder in vitro. The aim of this study was to evaluate the value of BPT in patients with acalculous biliary pain as a predictor of symptom relief after cholecystectomy.

Methods: 51 patients with ABP were given saline and bethanechol (0.5 µg/kg) in a dose 0.50 µg/kg to provoke biliary pain (blinded). If pain was reproduced with bethanechol, patients were classed as BPT+ve. If pain was not reproduced with either saline or bethanechol, patients were classed as BPT−ve. If pain was reproduced with saline, bethanechol was not given and patients were analysed separately. Percentage gall bladder emptying was monitored with serial ultrasonography. All patients were offered cholecystectomy irrespective of the outcome of the BPT and symptoms were reassessed at 6 months.

Results: 20 patients were BPT+ve and 24 patients were BPT−ve. Percentage gall bladder emptying (mean±SD) was similar in both groups (BPT+ve: 30±16%, BPT−ve: 32±16%, p = 0.7). 17/20 BPT+ve patients underwent cholecystectomy of whom 9 (53%) remained asymptomatic 6 months after operation. 11/24 BPT−ve patients underwent cholecystectomy and 6 (54%) remained symptomatic. 2/20 BPT+ve did not undergo cholecystectomy and were subsequently lost to follow up. 9/24 BPT−ve did not undergo cholecystectomy, of these 7 patients had spontaneous reduction in symptoms at 6 months. Of 7 patients positive for saline, five underwent cholecystectomy and two remained symptomatic.

Conclusion: Bethanechol provocation of gall bladder symptoms in patients with ABP does not predict symptom relief at 6 months after cholecystectomy.

Oesophageal manometry in children with feeding difficulties


23 Children aged between 11 months and 15.5 years were seen in our clinic within the period October 01 2001–2002. They presented with feeding difficulties that required oesophageal manometry, among other diagnostic investigations. The commonest symptoms were dysphagia for solids, regurgitation, and vomiting, in order of frequency. Lower Oesophageal Sphincter (LOS) pressure and body motility were measured using a standard eight channel, water perfused adult catheter (3.9 mm diameter) or a 2.3 mm catheter purpose designed for paediatric use (Mediplast). LOS pressure and oesophageal body motility were measured using a Flexiog 4000 recording system. Nine out of 23 patients had a hypertensive LOS (pressure > 26 mm Hg). These patients with hypertensive LOS but without achalasia often had regurgitation and vomiting as major presenting symptoms. Only 2 out of 23 patients had achalasia and only one of the two had a hypertensive LOS. Non-specific motility disorder (7/23), in which there were few peristaltic waves with a majority of simultaneous contractions, was the commonest cause of dysphagia. Of significance was a subgroup (4/23) with a partially relaxing LOS (residual pressure 6–11 mm Hg) but who did not have achalasia. This group had varied symptoms such as vomiting, regurgitation, and dysphagia for solids. A large hiatus hernia (7 cm) was the only finding in an adolescent girl with unexplained vomiting, normal oesophageal body motility, and "normal" OGD.

In summary, children with feeding problems who present with regurgitation, vomiting, and dysphagia for solids are most likely to have a hypertensive LOS or non-specific oesophageal dysmotility rather than achalasia. Unexplained vomiting with normal LOS function and body motility may be due to hiatus hernia, which could be missed during OGD. In conclusion, oesophageal manometry is an essential diagnostic tool in the investigation of upper gastrointestinal manifestations. From our experience, it is best suited to children aged over six years, as in younger children, manometry can be difficult because of non-compliance, and other diagnostic tests for detecting oesophageal dysmotility may be preferred.

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<tbody>
<tr>
<td>AC</td>
<td>15 (6–24)</td>
<td>6.2 (3.5–11.2)</td>
<td>1265 (536–1806)</td>
<td>86 (71–102)</td>
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084–097

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**082 ANTIREFLUX SURGERY IN BARRETT’S OESOPHAGUS: SYMPTOMATIC VERSUS PHYSIOLOGICAL OUTCOME**

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**Background:** The appropriate management of Barrett’s disease remains controversial. We report the long term outcome of anti-reflux surgery in Barrett’s patients in a tertiary referral centre.

**Methods:** Between 1985 and 2001, 67 patients with Barrett’s oesophagus underwent Nissen Fundaplication. Follow up via questionnaire (n = 58), endoscopy/histology (n = 57) and 24 h pH monitoring (n = 41) were examined.

**Results:** At a median follow up of 59 months, 95% (55/58) of patients considered the surgery either excellent/good. The median DeMeester score reduced from 69.5(2–309) before to 6.1(0–222) after surgery (p < 0.001). Lower oesophageal sphincter pressure increased from 7(3–27) mm Hg before to 15(3–40) mm Hg afterwards (p < 0.001). Six patients (10%) had developed recurrent symptoms. 17/41(41%) patients had abnormal post-operative DeMeester scores (> 15) of whom 11 had a reduction in their DeMeester scores but were still outside the normal range. Six out of 8 patients with preoperative dysplasia showed evidence of regression. Dysplasia developed after surgery in 2 patients. Two patients developed adenocarcinoma within Barrett’s 4 and 7 years postoperatively, respectively. These 4 patients had abnormal postoperative acid scores.

**Conclusions:** Nissen Fundaplication provides excellent long lasting relief of symptoms in Barrett’s patients. Postoperative 24 h pH studies establish that acid reflux has been abolished. Abnormal postoperative studies may be associated with dysplasia and adenocarcinoma in the long term and emphasises the need for long term follow up.

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**083 REFLUX EXPOSURE UNITS— A NEW WAY OF EVALUATING OESOPHAGEAL PH MEASUREMENTS?**

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**Background and Aims:** Although considered the “gold standard” for assessing gastro-oesophageal acid reflux, evidence suggests a poor correlation between pH measurements and the degree of oesophagitis seen during endoscopy. The current pH features examined, described as exposure, focus on the time the measured pH falls below 4. Importantly, these measures may not take into account distension of the oesophageal lumen. This study examined the diameter of the oesophageal lumen, its effect on mucosal folds and the effect that these may have on acid exposure at the mucosa.

**Methods:** The diameters of the oesophageal lumen of 25 patients under investigation for oesophageal disorders were studied using a video barium swallow. The widest luminal diameter was measured for each subject for a series of five controlled swallows and the results critically examined with regard to the usual measure of acid exposure.

**Results:** The results showed the lumen diameter varies widely from 0.9 to 3.8 cm. No difference in maximum luminal diameter was found between successful and failed swallows (student “r” p > 0.05). In addition, results from endoscopy show oesophagitis often occur at the tips of the mucosal folds creating linear longitudinal patterns of erythema. Changes in lumen diameters have also been previously shown to affect the different degrees of mucosal folding. These results suggest that individual patients may have varying areas of mucosa exposed to luminal content. As a result of these considerations a new Acid Exposure Unit was developed to take into account not only the time of exposure but also pH and the area of mucosa exposed.

**Conclusion:** In conclusion the range of luminal diameters measured and the developed exposure units highlight that the current measures of oesophageal pH exposure, which do not include the area of mucosa exposed, may explain why only a poor correlation is found between pH measurements and the degree of oesophagitis seen during endoscopy.

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**084 INFORMED CONSENT FOR ENDOSCOPY: AN OBSERVATIONAL STUDY**

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**Background:** The amount and type of information that patients require about risk in order to consent to endoscopic procedures has never been established.

**Aims:** To evaluate the amount of information patients undergoing endoscopic procedures require regarding risk.

**Methods:** Patients were given written and verbal information about the nature, incidence, and consequences of complications, then asked how common each complication would have to be before requiring information for informed consent.

**Results:** 150 colonoscopy and 150 gastroscopy patients were studied. 24–32% of gastroscopy and 31–43% of colonoscopy patients wanted to be informed of one or more complications irrespective of frequency. 19% of gastroscopy and 14% of colonoscopy patients wanted to know about all possible complications. This was unrelated to the severity of the complication. Among gastroscopy patients, 17–25% did not want to be informed of one or more complications, no matter how serious or frequent they were, and, again, this was unrelated to the severity. In the colonoscopy patients only 2–17% did not want to be informed of one or more complications. Significantly fewer [0.7%] colonoscopy patients required no information about any complications, compared to gastroscopy patients [10%, p < 0.001]. In both groups many more required information about serious complications than minor complications when the complications occurred with a risk rate < 1/1000 (p < 0.001).

**Conclusions:** Up to a fifth of patients want to be informed of all possible complications. Consent for colonoscopy requires greater risk disclosure. Patient’s threshold for information on major complications is much lower than for minor ones. Serious complications likely to occur in >1/1000 cases should be disclosed to all patients.

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**085 ASSESSING RESECTION MARGINS USING HIGH MAGNIFICATION CHROMOSCOPY FOR “EN-BLOCK” COLORECTAL ENDOSCOPIC MUCOSAL RESECTION OF FLAT LESIONS: A USEFUL TOOL FOR PREDICTING REMNANT TISSUE**

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**Introduction:** EMR in parallel with high resolution chromoscopic colonoscopy (HRCC) may permit safer and more accurate resection practice. Residual tumour or a disrupted, incomplete resection interface can be difficult to detect with conventional endoscopic techniques.

**Aim:** To evaluate the efficacy of HRCC in predicting complete horizontal and vertical resection margins for flat lesions less than 10 mm diameter.

**Subjects and Methods:** Total colonoscopy was performed on 600 consecutive patients using the Olympus CF240Z endoscope from 01/02 to 09/02 by a single endoscopist. 196 lesions were evaluated using HRCC pre- and post-EMR, using locally applied 0.5% indigo carmine (IC). The crypt appearance of all lesions was graded according to the modified Kudo class. Those demonstrable of a type V(n) or V(a)/IIIs were excluded due to the high risk of submucosal-massive invasion, and lesions failing to “lift” symmetrically at EMR. Lesions with a Kudo I crypt were excluded as these were also also additionally excluded (hyperplastic). Resection was performed en-block with submucosal lift using 0.5% IC and an Olympus barbed snare. Resection margins were then reassessed with a second dye spray around the circumferential horizontal and vertical border. Type I/II crypt was used as evidence of complete resection endoscopically. Histological confirmation was obtained on all specimens.

**Results:** See Table. Percentage agreement between HRCC and actual histological verification of vertical and horizontal clearance was calculated using the Kappa statistic, κ = 0.78 [excellent agreement, 95% CI].

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**Conclusion:** Prospective evaluation of resection margins using HRCC proves it is a useful tool for predicting excision completeness post-EMR.

### Abstract 85

<table>
<thead>
<tr>
<th>Endoscopic Margin</th>
<th>Histological Margin</th>
<th>Complete</th>
<th>Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>92</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>09</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

N = 184 (12 lesions excluded on above criteria)

**Background:** Focal submucosal invasive colorectal cancers (localised to the upper third of the submucosa, ie sm1) can be managed by endoscopic mucosal resection (EMR) as local lymph node metastasis (LLNM) are rare. Morphologically, these lesions are usually flat, depressed, or mixed – Japanese Research Society Classification (JRSC) Ia/b/c. In deeper vertical submucosal invasion (ie sm2/3) LLNM rates exceed 10–15%. EMR within this group can be complicated with perforation and non-curative resection. It is thus essential to differentiate accurately focal sm1 disease from submucosal sm2/3 disease.

**Aim:** To evaluate the relationship between the Kudo type Vn (A–C) crypt pattern and submucosal invasion depth for flat type (JRSC type II) colorectal lesions.

**Methods:** 600 consecutive patients were colonoscopy, by a single endoscopist using the Olympus CF240Z, from 01/02 to 09/02. Kudo type V pits were identified using 0.5% crystal violet (CV) applied directly to the lesion with a steel tipped catheter. Type V pits were graded into class Va or Vn as per the modified Kudo class. Vn pits were identified using 0.5% crystal violet (CV) applied directly to the lesion with a steel tipped catheter. Type V pits were identified using 0.5% crystal violet (CV) applied directly to the lesion with a steel tipped catheter.

**Results:** 47 JRSC class II lesions had a type Vn (pit) pattern (see Table).

<table>
<thead>
<tr>
<th>Dominant Pit Morphology</th>
<th>Invasive depth</th>
<th>No. of lesions</th>
<th>% lesions with sm2+ invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vn (A)</td>
<td>10/47 (21.3%)</td>
<td>08</td>
<td>02</td>
</tr>
<tr>
<td>Vn (B)</td>
<td>28/47 (59.6%)</td>
<td>09</td>
<td>19</td>
</tr>
<tr>
<td>Vn (C)</td>
<td>09/47 (19.1%)</td>
<td>00</td>
<td>09</td>
</tr>
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</table>

**Conclusions:** High resolution chromoscopy is a predictor of invasive depth. The safety of EMR can be greatly enhanced using this technique.

### Abstract 86

**Background:** In patients with PSC, the optimal management of the minority who develop dominant biliary strictures remains uncertain. Several studies suggest surgical benefit of endoscopic dilatation +/- stent insertion compared with expectant management alone, but they have generally reported only short term follow up.

**Aim:** To review the endoscopic management of PSC in a tertiary referral centre, and to assess the impact of intervention on outcome.

**Methods:** Cases were identified via endoscopy, pathology and clinical databases, from 1984–2000. The numbers of ERCPs,
interventions, length of endoscopic follow up, and outcome, were compared in patients with and without dominant strictures.

**Results:** Of 161 patients identified with PSC, 131 [85M, 46F; mean age 55 years, range 14–86 years] underwent 382 ERCPs during the study period (3.4% of 11,326 ERCPs). Interventions and endoscopic follow up in the patients are shown in the table.

**Abstract 89**

<table>
<thead>
<tr>
<th>Patients (pts)</th>
<th>71</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCP per pt mean (range)</td>
<td>4.5 (1-18)</td>
<td>1.5 (1-7)</td>
</tr>
<tr>
<td>Interventions per pt</td>
<td>3.6 (1-18)</td>
<td>0.6 [0-4]</td>
</tr>
<tr>
<td>Pts with follow-up ERCP</td>
<td>51 (72%)</td>
<td>20 (33%)</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>37 (1-192)</td>
<td>28 (1-120)</td>
</tr>
</tbody>
</table>

Of stricture interventions performed, stent insertion alone was performed in >65% of cases, dilatation alone in <25% of cases.

**Discussion:** This single center experience indicates that patients with dominant strictures due to PSC can be successfully managed long term with endoscopic therapy. Ongoing prospective follow-up will allow the effects of biliary interventions on clinical outcome to be assessed in detail.

**090 A PROSPECTIVE SINGLE BLIND STUDY COMPARING CAPSULE ENTEROSCOPY WITH PUSH ENTEROSCOPY AND SMALL BOWEL ENEMA IN OBSCURE GASTROINTESTINAL BLEEDING**


**Background:** Obstruct GI bleeding remains a clinical problem in up to 10% of patients with anaemia with the small bowel as the most possible source of bleeding. Wireless capsule endoscopy has not been evaluated in comparison with the established methods of small bowel examination, enteroscopy, and small bowel enema in anaemic patients.

**Aim:** To compare prospectively the diagnostic yield of capsule enteroscopy with push enteroscopy and small bowel enema.

**Method:** Patients with obscure GI bleeding with negative upper GI endoscopy and colonoscopy were studied. Each examination was performed and reported independently by physician or radiologist.

**Results:** Preliminary data from the first 9 enrolled patients are presented. Mean age was 63.5 years (range 58–79) and male to female ratio was 1:2. Comorbidity existed in 5/9 (55.5%) patients with polycystic kidneys [1], previous gastric operation for peptic disease [2], right hemicolecotomy [1], and cardiac valve replacement [2]. Push enteroscopy discovered a definite bleeding source in 4/9 patients and a possible source in one. Capsule enteroscopy found a definite bleeding source in 7/9 patients and a possible cause in one. Six of them had a definite lesion beyond the reachable area of the enteroscope. Other findings not related with bleeding source were found in one patient in each method. None of the patients had abnormal small bowel enema findings. The diagnostic yield of push enteroscopy was 44.4% in comparison to capsule enteroscopy, which was 77.7%. Additional information within the small intestine was obtained using the capsule enteroscopy in 66.6% of the patients.

**Conclusion:** This prospective single blind study shows for first time that capsule enteroscopy detects more lesions than push enteroscopy or small bowel enema in patients with obscure GI bleeding. It can also diagnose intestinal bleeding source beyond the reach of push enteroscopy in a substantial larger number of patients.

**091 EVALUATING MRC AGAINST ERCP IN THE ASSESSMENT OF BILE DUCT STONES**

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**Aim:** To evaluate magnetic resonance cholangiography (MRC) in the detection of bile duct stones.

**Methods:** The study was performed over 2 years. Patients presenting with biliary symptoms who were assessed as having a low to medium probability of bile duct stones according to predefined criteria had an MRC. In general patients who had positive MRC had an endoscopic retrograde cholangiogram (ERC) while patients who had a negative MRC did not have further biliary imaging. MRC and ERC data were gathered prospectively. At completion of the study the patients who had both procedures were compared for presence of stones on each modality. A rigorous retrospective case notes review was carried out for all those who had a negative MRC to spot subsequent admissions related to probable biliary disease, biliary symptoms in new referral or follow up clinic letters and mortality.

**Results:** 229, 133, and 27 patients had ERCP, MRC, and both, respectively. MRC was positive in 30. ERCP was scheduled for these patients and performed in 24. In the remainder ERCP was not performed for the following reasons: 2 declined, 2 cancelled, 1 ERCP failed, and 1 had surgery. The positive predictive value of MRC was 91.7%. Three patients with a negative MRC had a subsequent ERCP (for clinical indications) and all were negative. The number of patients with a negative MRC later admitted with biliary disease was 6. Five had a cholecystectomy for gall stones, [3 emergency, 2 elective] and 1 declined to have follow up. One had pancreatitis while awaiting surgery. None of the patients who underwent surgery had bile stones at operation. Five patients had persistent or recurrent symptoms; 1 was found to have pancreas divisum and 4 patients continue to have upper abdominal pain which appears muscular in origin. Further investigation. 3 patients have died due to unrelated causes. The complications of ERCP were pancreatitis in 4 cases out of 229 [2 mild, 2 moderate], a minor bleed in 1 case [no transfusion required]. There were no complications in the MRC group.

**Conclusion:** This study demonstrates that MRC has a high positive predictive value in the assessment of the presence of bile duct stones. Patients having a negative MRC rarely develop subsequent symptoms in relation to bile duct stones.

**092 PATIENT TOLERABILITY OF VIRTUAL COLONOSCOPY IN COMPARISON TO CONVENTIONAL COLONOSCOPY AND BARIUM ENEMA**

S. Moreea1, A. Singhal1, C.G. Beckett, C.L. Kay2. Department of Gastroenterology; 2Department of Radiology, Bradford Royal Infirmary, Bradford BD9 6RJ

**Aim:** To evaluate the discomfort associated with bowel cleansing and the degree of discomfort/abdominal pain in patients having a virtual colonoscopy (VC), conventional colonoscopy (CC) and barium enema (BE) and to determine patient preference between VC and CC.

**Methods:** Patients referred for CC were recruited to have a VC prior to their CC. A separate group of patients having a BE or CC alone were also recruited. Using a 100 point visual analogue scale, patients were asked to rate the following after the individual procedure: discomfort caused by the bowel preparation (Kleanprep for VC/CC and picosulphate for BE), discomfort and abdominal pain during the procedure. They were asked about the amount of discomfort/pain during the procedure, whether they would have the procedure again, their preferred procedure, and the length of time they were prepared to wait for their preferred procedure. On the visual analogue scale 0 meant no discomfort/pain and 100 was severe discomfort/pain. Conscious sedation was used for CC.

**Results:** 33 patients had both a VC and CC, 32 patients had CC alone [total number of CCs: 65] and 61 patients had a BE. Discomfort of bowel cleaning was rated for VC/CC: 49/100, and for BE: 22/100. Mean procedure discomfort was VC: 34/100, CC: 25/100, and BE: 30/100. Mean procedure pain was VC: 37/100, CC: 22/100, and BE: 23/100. Lack of respect was reported in 9% of VCs, 4.6% of CCs, and none of the BEs. 9%, 12%, and 11% of patients would not have a repeat VC, CC, and BE, respectively. 27/33 patients in the VC/CC arm of the study returned a 24 h questionnaire: 11 preferred CC and 13 preferred VC and 3 had no preference. 54% of patients were prepared to wait for 4 weeks or more to have their preferred procedure.

**Conclusion:** Bowel cleansing for VC/CC was more uncomfortable than the actual procedure and that for BE (picosulphate) was less uncomfortable than that of VC/CC (Kleanprep). Patients reported more pain with VC than with either CC or BE. The greater relative comfort of CC v VC may be partly due to the effect of conscious sedation but other factors may be involved as unsedated patients reported less pain with BE v VC. Patients would wait 4 weeks for their preferred test.
**THE "TWO WEEK RULE" (2WR) DIRECTIVE : GOOD OR BAD POLITICS FOR PATIENTS?**

A. Douglass, A. Agarwal, R.G. Wilson, P.A. Cann. Endoscopy Centre, James Cook University Hospital, Middlesbrough

Introduction: The 2wr directive for GI malignancies, suspected by GPs, purports to enhance and accelerate diagnosis and care. The imperative is to “see” the patient within 2 weeks, whereas the relevant first key clinical step is to confirm or refute the diagnosis for all potential cases. This is optimised by fast tracking to definitive investigations—usually endoscopy. If resources do not allow for this within 2 weeks, urgent clinic slots are taken up mostly just to explain the need for that test. No evidence base shows this approach as helpful overall and perhaps it disadvantages a significant proportion of patients.

Aims and Objectives: We determined the potential number of 2wr referrals out of all colorectal referrals received (catchment 300 K). We also established the proportion of actual colorectal cancer (CRC) cases that would not have fulfilled the national 2wr criteria.

Methods: All (medical and surgical—clinic and open access) referrals to a 10 week period and all CRC cases diagnosed in a 1 year period were reviewed.

Results: Referral audit: 773 referrals total (86 excluded—insufficient data in referral). 248 fulfilled the 2wr criteria and were referred via open access colonoscopy (87) and clinic (161), representing 34% and 32% of all such referrals, respectively. Only 83 were actually referred by 2wr—a further 18 were assigned other degrees of urgency by the GP. 248 in 8 weeks is ~30/week. If 20 min is allowed per 2wr clinic slot, this amounts to 10 h/week even before diagnosis is organised for most. (The impact for upper GI cases could be similar). CRC Audit: 178 CRC cases total, 48 presented acutely. 33 (25% of non-acute) did not fulfil 2wr criteria (Dukes A and B 53%), the remainder did (A and B 52%).

Conclusions: Many CRC cases do not fulfil 2wr referral criteria but have similar staging. If the 2wr was strictly adhered to in primary care, these face potential disadvantage in timely treatment. Furthermore, clinic time spent on achieving 2wr targets might be better spent on improving or providing fast track definitive investigation, managing diagnosed cancer cases or the majority of our patients without cancer.

**PROSPECTIVE COMPARISON OF ENDOSCOPIC ULTRASOUND GUIDED 22G FINE NEEDLE ASPIRATION (EUS-FNA) WITH 19G TRUCUT NEEDLE BIOPSY (EUS-TNB)**

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Background: EUS-FNA of mediastinal and gastrointestinal mass lesions is sensitive for diagnosing malignancy and has a low complication rate. However, EUS-FNA ideally requires an on-site cytopathologist to ensure adequate sampling, and the diagnosis of certain neoplasms is difficult based on cytology alone. A 19G trucut needle (Quick-Core, Wilson-Cook) has been recently developed for mediastinal mass biopsies. We compared the efficacy of this needle (Quick-Core, Wilson-Cook) has been recently developed for mediastinal mass biopsies. A 19G trucut needle (Quick-Core, Wilson-Cook) has been recently developed for mediastinal mass biopsies. EUS-FNA and EUS-TNB in patients with suspected mediastinal or gastrointestinal mass lesions.

Methods: Over a 10 week period, 12 patients (10M, 2F; mean age 68 year, range 43–82 year) underwent combined 22G EUS-FNA (median 3 passes, range 1–4) and 19G EUS-TNB (2 passes, range 1–3) of suspected mediastinal (n = 2) or pancreaticobiliary mass lesions (transgastric approach in 4, transduodenal in 6). Pathologic samples were assessed independently by two pathologists, neither of whom attended the EUS. Patients were contacted 24–48 h later to assess complications.

Results: The median size of the lesions biopsied was 2 cm (range 0.5–7 cm). The final diagnoses were benign disease in 6 and malignancy in 6 (adenocarcinoma in 4, lymphoma in 1, gastrinoma in 1). In two patients, EUS-TNB allowed additional characterisation of the tumour not provided by cytology. There were two false negative results for EUS-FNA (1 ‘highly suspicious’, 1 inadequate), and two needle failures during attempted transduodenal EUS-TNB, but the accuracy of the combined tests in detecting malignancy was 100%. One patient reported mild abdominal discomfort for < 24 h after the procedure.

Conclusions: Combined EUS-FNA and EUS-TNB appears to be safe and to have a high diagnostic yield. EUS-TNB from the second part of the duodenum is associated with a high technical failure rate.

**OUTPATIENT ENDOSCOPY FOR PATIENTS PRESENTING WITH MINOR UPPER GI BLEEDING**

G. Mulholland, J.A.H. Forrest. Stobhill Hospital, Glasgow, UK

Introduction and Aim: Acute upper GI bleeding (UGIB) accounts for approximately 8% of acute medical admissions and such patients are routinely admitted for observation and diagnostic endoscopy. This study aimed to assess the safety and outcome of rapid access outpatient endoscopy for patients presenting with minor upper GI bleeding (Rockall score zero).

Study Design: Over a 3 year period patients presenting with UGIB who had a pre-endoscopy Rockall score of zero were identified in A&E. They were discharged home with an appointment for an OP endoscopy.

Results: 64 patients were referred from A&E; 42 M and 21 F, mean age 37.8 (range 19–79). 42 endoscopies were performed, there being 20 DNAs and 2 inappropriate referrals (vomiting alone). 51 patients presented with haematemesis, 4 with melaena, and 7 with both. 8 patients had taken aspirin or an NSAID and 24 excess alcohol. Of the 20 DNAs 14 had misused alcohol. At endoscopy 14 patients had oesophagitis, 8 a peptic ulcer, 4 gastritis, 4 duodenitis, and 1 oesophageal varices. 7 patients had dual pathology and 18 patients had oesophagitis, 8 a peptic ulcer, 4 gastritis, 4 duodenitis, and 1 oesophageal varices. 7 patients had dual pathology and 18 patients had oesophagitis. H. pylori was positive in 16 of 34 patients tested. Average Hb (n = 24) was 14.3 (range 11.3–16.8). Average interval between presentation and endoscopy was 14 days (range 1–77). No patient had recurrent bleeding.

Conclusion: The study showed it to be safe practice to discharge patients from A&E with minor UGIB and a pre endoscopy Rockall score of zero and to perform OP endoscopy. The high DNA rate (31%) reflected the significant number of patients who misused alcohol. 57% of those attending for endoscopy had significant pathology; oesophagitis being the most common abnormality. The number of A&E referrals with UGIB for OP endoscopy was significantly less than expected; probably because SHOs were unhappy to discharge such patients home.
A PROSPECTIVE RANDOMISED COMPARISON OF 10 FR AND 7 FR BIPOLAR ELECTROCAUTERIAL CATHETER IN COMBINATION WITH ADRENALINE INJECTION IN THE ENDOSCOPIC TREATMENT OF BLEEDING PEPITIC ULCERS

Background and Aims: Our study sought to compare the efficacy of bipolar electrocautery (gold probe) with 10 Fr (Group A) versus 7 Fr (Group B) catheter following adrenaline injection in the treatment of bleeding peptic ulcers. To the best of our knowledge, this is the only prospective, randomised study in humans.

Methods: 77 consecutive patients with endoscopic evidence of peptic ulcer with active bleeding or a non-bleeding visible vessel were randomly assigned to one of the above protocols. 39 patients (31 males, 8 females, mean age 62 years) were included in group A and 38 (28 males, 10 females, mean age 61 years) in group B.

Results: The initial haemostasis rate, rebleeding rate, duration of hospital stay, volume of blood transfused, number of operations needed, and number of deaths were not significantly different between the two groups. The mean number of electrocauterations and the subsequent mean duration of electrocauterations were significantly higher in group B patients (7.0±3.3, 14.1±7.6 seconds, respectively) compared with those of group A (4.6±2.6, 9.3±5.3 sec, p < 0.01). Multivariate stepwise logistic regression analysis revealed that among sex, age, location of bleeding, ulcer size, endoscopic severity of bleeding, and the size of the gold probe, the endoscopic severity of the bleeding, the small size of the gold probe, and the increased ulcer size were the only factors significantly associated with an increased number of electrocauterations (χ² = 31.1, p < 0.01, χ² = 23.9, p < 0.01 and χ² = 13.4, p < 0.01, respectively).

Conclusions: Our data suggest that the use of the large size gold probe was significantly associated with a decreased number of electrocauterations resulting in the reduction of electrocautery duration.

Colorectal free papers 098–107

SHOULD DIGITAL RECTAL EXAMINATION STILL BE PART OF THE PHYSICAL EXAMINATION OF PATIENTS WITH COLONIC SYMPTOMS?

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Background: It is an unchallenged axiom that digital rectal examination (DRE) is an essential part of the physical examination of patients with colonic symptoms. However, there is no evidence demonstrating that routine unsedated, unprepared DRE at the initial consultation is useful in patients in whom colonoscopy is indicated.

Aims: To assess the value of DRE in patients presenting to gastroenterologists with colonic symptoms.

Methods: Consecutive patients presenting to gastroenterologists with colonic symptoms, in whom a colonoscopy was later performed, were studied. Patients with perianal pain or tenesmus and those in whom DRE was done for indications other than routine were excluded. Endoscopic findings were evaluated. Rectal cancers were recorded as distal (within 7 cm of the anal verge and potentially palpable on unprepared DRE) or proximal (beyond 7 cm).

Results: In 4834 patients undergoing colonoscopy, 166 cancers were diagnosed, of which 68 (41%) were rectal cancer (23 distal, 45 proximal). Anaemia was a more frequent indication in those with colonic cancers (p < 0.001). A qualitative questionnaire revealed unanimous patient and doctor preference for DRE at the time of colonoscopy rather than unsedated, unprepared DRE. In a presumptive analysis of usefulness, a 75% sensitivity of DRE for distal cancers was assumed. 280 DREs, therefore, would be required to detect one distal cancer in this cohort, with the outcome of this being a possibly reduced waiting time to colonoscopy.

Conclusion: Routine DRE was not sensitive for the diagnosis of colorectal cancer. It was unpopular with patients and doctors and would not alter management in more than 0.4% of patients. In those with a positive DRE, the maximum benefit would be to shorten the interval to colonoscopy. In practice, valuable time spent performing DRE may be better spent in the endoscopy suite reducing colonoscopy waiting times.

DO CALCIUM ANTAGONISTS PROTECT AGAINST PERFORATED COLORECTAL DIVERTICULAR DISEASE? A CASE-CONTROL STUDY

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Background: Perforated colorectal diverticular disease (PCDD) may result from a combination of high intracolonic pressures, secondary to excessive colonic segmentation, and impairment of the mucosal barrier. Calcium channel blockers and antimuscarinic drugs, which reduce colonic contractility and tone, could potentially protect against perforation. The aim of this study was to test this hypothesis using a case-control design.

Methods: All cases of acute PCDD were identified over a 5 year period in two hospitals in Norfolk, UK. Each case was matched for age, sex, and date of admission to two controls groups: (a) patients undergoing colectomy surgery and (b) patients with basal cell carcinoma. Data on drug use prior to hospital admission were obtained from medical and nursing records and compared between cases and controls.

Results: 120 cases of PCDD were identified and matched to 240 controls in each group. A statistically significant protective association was seen between calcium channel blocker use and PCDD using both control groups (see table). No association was found with antimuscarinic drugs.

Conclusions: This study has shown for the first time that a protective association exists between calcium channel blockers and PCDD. Further studies are required to confirm this association but calcium channel blockers may represent a potential preventive therapy in PCDD.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds ratio (95% Confidence Interval)</th>
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<tr>
<td>Anti-muscarinics</td>
<td>1.33 (0.64–2.80)</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>0.41 (0.18–0.93)</td>
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<tr>
<td>Dermatology Controls</td>
<td>0.36 (0.16–0.82)</td>
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<tr>
<td>Ophthalmology Controls</td>
<td>1.19 (0.59–2.43)</td>
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PATIENT SUITABILITY FOR NURSE LED FOLLOW UP: A PROSPECTIVE AUDIT

R. Christie, E.V. Robinson, E. Rassy, A.F. Horgan (introduced by N. Thompson). Department of Colorectal Surgery, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Trust, Newcastle-upon-Tyne, NE7 7DN, UK

Government’s targets, including the 2 week cancer rule, derived from the New NHS: modern and dependable (1997) document have resulted in increased pressure on already stretched resources within the NHS. Managing increasing referrals within a shorter timeframe has therefore become more difficult. Following endoscopic investigations, the waiting time for outpatient review appointments for patients with colorectal conditions within many UK trusts is up to 3 months. This delay has an impact on the patients’ experience, quality, and access to colorectal services. A prospective audit of 122 patients attending outpatient review appointments, identified the method of referral and the reason for review. This was broken down further as patients were allocated as to whether it would have been suitable for them to be reviewed by a nurse, either via nurse led clinic or by telephone. Patient satisfaction of current practice was assessed by means of a questionnaire.

78/122 suitable for nurse led follow up; 40 telephone follow up, 33 nurse led clinic; 49 patients discharged for hospital care following review appointment.

We have therefore shown that the majority of patients (64%) referred with colorectal symptoms are suitable for nurse led follow up. We therefore intend to set up a nurse led follow up service that...
ultimately will provide a more efficient colorectal service, with improved utilisation of resources.

**101 PRIMARY RESTORATIVE PROCTOCOLECTOMY FOR FAMILIAL ADENOMATOUS POLYPOSIS**
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**Introduction:** Some surgeons favour colectomy and ileoanal pouch (RPC) as prophylactic surgery in familial adenomatous polyposis (FAP), citing the absent risk of rectal cancer and avoidance of further surgery. However, the disadvantages of early postoperative complications, particularly sepsis, late pouch dysfunction, and reduced fertility should all be considered.

**Aims:** To investigate the long term outcome in a cohort of FAP patients undergoing primary RPC.

**Methods:** All patients undergoing prophylactic colectomy between January 1980 and December 2001 were identified from a single polyposis register. Cases where the primary operation was colectomy with construction of an ileoanal pouch were included, case notes and the registry database being examined to determine outcome.

**Results:** Primary RPC was performed in 59 of 285 patients (21%). Follow-up was complete for 58 patients (98%) and for an average of 8 years and 8 months (6 months to 20 years and 7 months). There were 34 males and 25 females, average age at surgery 32 years and 1 month (range 10 years 10 months). 20 patients (35%) suffered at least one early postoperative complication including pelvic sepsis (9), anastomotic leak (3), prolonged small bowel obstruction (4), postoperative haemorrhage (2), pulmonary complications (4), early pouchitis (1), and wound breakdown (1). Five patients required subsequent pouch excision, one for carcinoma, three for pouch evacuation problems and one for chronic pelvic sepsis; all had suffered early postoperative complications. In only one case was revision surgery successful, the remainder being managed with an end ileostomy. Four patients died during follow up, three of these from colorectal carcinoma.

**Conclusion:** Pouch surgery is not without complications. Failed pouch surgery has resulted in an ileostomy in 4% of patients. The choice of primary surgery for FAP remains difficult.

**102 SCREENING FOR IRON DEFICIENCY AMONG SUBJECTS AGED 55–74 YEARS IN PRIMARY CARE: A PILOT STUDY**
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**Background:** Most patients with proximal colonic cancer have iron deficiency anaemia at presentation. Therefore, measurement of serum iron and stores could prove a potential adjunct to faecal occult blood testing (FOBT) in screening and early detection of colorectal neoplasia.

**Methods:** From a general practice serving 6677 in November 2000 we identified 1351 subjects aged 55–74 years. Of these 86 were excluded (comorbidity, previous colorectal cancer or inflammatory bowel disease and/or already undergoing endoscopic surveillance and/or investigation of established iron deficiency during the previous 3 years). Thus, 1240 subjects were mailed to explain the study and invite them to the surgery. After obtaining consent, blood was taken for serum iron, iron saturation, and ferritin. Those with iron saturation < 10% and/or ferritin < 15 µg/l were invited to see their GP for history and physical examination, plus FOBT, blood count and coeliac serology, and offered hospital referral for consultation, gastroscopy and colonoscopy.

**Results:** There were 23 subjects who had recently died or moved away. Of the remaining 1217 subjects 570 (47%) have so far come forward for venepuncture. Iron deficiency was detected in 26 of these (5%), of whom 24 agreed to hospital referral and 18 consented to endoscopic investigation. One had a large sessile adenoma requiring right hemicolecotmy and another had 5 pedunculated sigmoid polyps. One patient was found to have coeliac disease. Erosive oesophagitis, gastric erosions, and angiodysplasia were each found in two patients. Just before the study 2 patients from the practice (aged 56 and 73) were diagnosed with iron deficiency anaemia due to colorectal cancer, both of whom would have been detected by the study had it started 3 months sooner.

**Conclusions:** Screening middle aged and older subjects for iron deficiency in primary care is feasible, and is accepted by 47%, which compares favourably with studies using FOBT. Clinically significant pathology in addition to colorectal neoplasia can be detected. Larger studies of population screening in parallel with FOBT are indicated.

**103 THE PREVALENCE OF IRON DEFICIENCY AMONG PATIENTS PRESENTING WITH COLORECTAL CANCER**
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**Background:** Retrospective studies suggest that up to half of patients with colorectal cancer (CRC) have iron deficiency anaemia at presentation. Iron deficiency (ID) is likely to precede anaemia by several months, hence measurement of serum iron and ferritin could have a role in screening and early diagnosis of CRC.

**Aims:** To examine prospectively the prevalence of ID among patients presenting with colorectal cancer.

**Methods:** All new patients with CRC presenting to our unit over a 12 month period were invited to participate. Blood was taken at diagnosis or prior to surgery. Criteria for anaemia were Hb < 12.5 g/dl for men and 11.5 g/dl for women with coexistent ID. ID was defined as serum ferritin < 15 µg/l and/or iron saturation < 14%. Right-sided lesions were defined as those proximal to the splenic flexure. We excluded patients with recurrent cancer or co-existing inflammatory bowel disease.

**Results:** During the study period 157 patients presented with new onset CRC, of whom we were able to study 130. Established iron deficiency anaemia was present in 54 (42%) at presentation and a further 23 (18%) were found to be iron deficient without anaemia. 53 patients (40%) had normal iron status at diagnosis. Iron deficiency was more common among patients with right-sided CRC than those with left-sided and rectal tumours ($x^2 = 13$, $p < 0.001$).

**Conclusions:** Four-fifths of patients presenting with CRC proximal to the splenic flexure are iron deficient at presentation. Measurement of iron status could assist in the early diagnosis of CRC and might also have a role in selecting healthy subjects for screening by colonoscopy.

**104 DISTRIBUTION OF COLORECTAL CANCERS AND ADENOMAS IN A SCREENED POPULATION**
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The Nottingham trial of faecal occult blood (FOBT) screening, randomised 152 850 individuals between the ages of 45 and 74, with the identification of 1551 cancers and 1497 individuals with at least one adenoma, within the screened group. The distribution of colorectal cancers was 37% (576) in the rectum, 31% (484) in the left colon and 32% (491) proximal to or including the splenic flexure (right-sided lesions). Rectal cancers among males remained high (43%) compared with females (29%), while 39% (261) of female cancers were right-sided. Of those who had adenomas detected by colonoscopy, 80% (1201) had only one adenoma. Considering only the distribution of the right colonic polychrome of each individual, 91% (1158) were found distal to the splenic flexure. This is the first time a screening study has identified a right-sided shift in colorectal cancer distribution. This trend has been noted by other recent papers but not within a screening programme. This shift has important implications for any screening modality if a national screening programme is to be considered.
TRUNCATING AND MISSENSE GERM LINE MUTATIONS IN MYH ARE A FREQUENT CAUSE OF A SPECIFIC MULTIPLE COLORECTAL ADENOMA PHENOTYPE


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Background: Compound heterozygosity for missense variants of the base excision repair (BER) gene MYH has been linked to inheritance of multiple colorectal adenomas or carcinoma in a small UK family. Colorectal adenomas from affected individuals displayed an excess of somatic G:C→T:A transversions in the adenomatous polyposis coli (APC) gene, consistent with a BER defect.

Methods: 157 unrelated UK patients with multiple (3 to 115) colorectal adenomas were screened for germ line mutations in MYH and subsets were screened for the related BER genes, MTH1 and OGG1. Adenomas from patients harbouring pathogenic MYH germ line mutations were tested for somatic APC mutations and loss of heterozygosity at MYH. Clinicopathological and molecular data were compared between patients with and without MYH mutations.

Results: Twenty-four (9%) patients harboured germ line MYH variants, with 8 (5%) having biallelic, pathogenic mutations. Both nonsense and protein truncating MYH mutations were found. Missense variants Y16SC and G382D were the most frequent alterations observed. Patients with biallelic MYH mutations had more polyps than carriers of single mutations or MYH wild-type patients (medians, 55 vs 3 vs 7, respectively; p < 0.01). Four out of 28 (29%) patients with 15 to 115 adenomas had biallelic MYH mutations. All somatic APC mutations identified in such patients were the expected somatic G:C→T:A transversions. No clearly pathogenic MTH1 or OGG1 germ line mutations were identified.

Conclusions: The data provide strong evidence to show that individuals with two allelic MYH mutations are predisposed to a multiple adenoma phenotype. Progression to colorectal carcinoma occurs in some cases.

AETIOLOGY OF COLORECTAL CANCER AND RELEVANCE OF MONOGENIC INHERITANCE

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Although many factors contribute to the development of colorectal tumours, the only clearly identified aetiological factors include inheritance (lynch syndrome (HNPPC) and familial polyposis (FAP)), inflammatory bowel diseases (ulcerative colitis and Crohn's disease, IBD), papillomavirus and AIDS (HIV).

Purpose: To find our what proportion of colorectal malignancies can be attributed to each of these specific factors.

Patients and Methods: Data of a colorectal cancer registry have been analysed, over a period of 15 years, during which nearly 2500 cases were recorded. In patients with clinical suspicion of hereditary tumours, microsatellite instability was assessed, and in positive families constitutional mutations of the main mismatch repair genes (hMLH1, hMSH2, hMSH6) were evaluated by single strand conformation polymorphism and sequencing.

Results: IBD, FAP, and AIDS were rare causes of colorectal cancer (3, 3 and 1 cases, respectively). Anal squamous carcinoma (attributed to papillomavirus infection) developed in 27 patients (1.0%). In 34 patients (from 34 families) a clinical diagnosis of HNPPC could be established (2.4% of the total). Altogether, cases with a known aetiology (N = 92) accounted for only 3.7% of all patients. Microsatellite instability was found in 15 HNPPC families, while germ line mutations in one of the mismatch repair genes were detected in 6 families (12 patients, 0.5% of the total). Microsatellite positive families, regardless of the mutational status, were clinically similar, thus suggesting an involvement of the mismatch repair system even when mutations were not detected.

Conclusion: The study suggests that the aetiology of colorectal neoplasms remains elusive in the large majority of cases. Among specific causes, HNPPC represents by far the most frequent. However, by using a population-based approach, constitutional mutations of the main genes responsible for HNPPC can be detected in only 20% of the cases.

INVESTIGATING THE ROLE FOR NORADRENALINE IN NEUROGENIC RESPONSES OF THE SHEEP INTERNAL ANAL SPHINCTER


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Introduction: Nitric oxide (NO) is the principal inhibitory neurotransmitter in the internal anal sphincter (IAS) of humans and sheep with noradrenaline (NA) responsible for causing neurogenic contractions via α adrenoceptors following inhibition of NO synthesis. Previous work using isolated IAS muscle from sheep has surprisingly shown that noradrenaline, an α adrenoceptor antagonist, fails to enhance neurogenic relaxations under control conditions. This study aims to further investigate the nature of neurogenic responses of the sheep IAS.

Methods: Using an established sheep IAS model, strips of internal sphincter were placed in isolated organ baths. The neurogenic responses to NA 1 Hz and 10 Hz stimulation [300 mA pulse strength, 0.3 ms pulse width, 30 s every 180 s] in the presence and absence of 3 μM phentolamine were tested.

Results: There was no significant difference in the magnitude of the neurogenic relaxations observed following stimulation at 1 Hz or 10 Hz and the addition of 3 μM phentolamine failed to enhance these responses at either frequency. The time taken for the neurogenic relaxations to return to 50% of the initial tone was significantly longer with 1 Hz (34.6 ± 0.6 sec) compared with 10 Hz (25.8 ± 1.9 sec, n = 24, p < 0.05). Phentolamine had no effect on the duration of these responses at 1 Hz but significantly prolonged the responses at 10 Hz (32.1 ± 1.5 sec, n = 24, p < 0.05).

Conclusion: Based on the effects of phentolamine, NA is released at 10 Hz but not 1 Hz. NA does not alter the magnitude of the neurogenic relaxations, but limits the time course of the response. Phentolamine, an α adrenoceptor antagonist, increased the time course of the neurogenic relaxations and therefore preserved the effects of neuronal NO. These findings raise the possibility that topical α adrenoceptor antagonists may be useful, either with or without a direct acting relaxant, in instances of excessive adrenergic tone (e.g. anal fissures).

Further reading:

108 CCK2 RECEPTOR AS A THERAPEUTIC TARGET FOR NEUROENDOCRINE TUMOURS

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Aim: To investigate the role of gastrin and the CCK2 gastrin receptor in the proliferation of neuroendocrine tumour cell lines.

Methods: CRI-G1, NHCH727, RIN 5F, and SHP 77 neuroendocrine tumour cells were studied. CCK2 receptor was detected in cell lysates by immunoblotting using an antibody [antGnR1] raised against the C-terminal sequence of the receptor. For uptake studies, cells were cultured in chamber well slides. The cells were incubated with either gastrin 7 coupled to rhodol green dye or antiGRE1 labelled against the C-terminal sequence of the receptor. For uptake studies, cells were cultured in chamber well slides. The cells were incubated with either gastrin 7 coupled to rhodol green dye or antiGRE1 labelled with Alexa Fluor 546 dye for 1 h at 37°C. After fixation, cells were counterstained for apoptosis with either gastrin 7 coupled to rhodol green dye or antiGRE1 labelled with Alexa Fluor 546 dye for 1 h at 37°C. After fixation, cells were counterstained for apoptosis with antiGRE1 antibody were subsequently counterstained for apoptosis using the TUNEL method (ApopTag FITC kit). Proliferation studies were performed by incubating cells alone or with CCK2 antagonist PD 135 at 10-4 M for 96 h followed by measurement of cell number using the MTT assay.

Results: Immunoreactivity to CCK2 was detected in all cell lines. A 122KD band was seen at in all 4 cell lines with an additional 186 kd...
band seen only in the CRI G1 and RIN 5F cells. Uptake of rhodamine green labelled gastrin 7 and of Alexa Fluor 546 labelled anti-GR1 antibody was seen in all 4 cell lines with the fluorescence being most prominent in the SHP 77 cells. ApopTag FITC staining revealed a coincidence of antibody uptake and apoptosis in the latter cell line. PD135 at a concentration of 10−4 M gave inhibition of proliferation in all 4 cell lines (87–95% reduction compared to controls).

Conclusions: We present evidence for the existence of CCK2 receptor in NET cell lines. We have demonstrated uptake of gastrin peptide and antibody by tumour cells and a role for CCK2 in proliferation. These results suggest that the gastrin pathway could be a potential target for treatment in neuroendocrine tumours.

109 ADHERENT E COLI FROM COLON CANCER TISSUE INCLUDE ISOLATES CAPABLE OF INDUCING IL-8 RELEASE AND COX2 EXPRESSION

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Introduction: A previous study by Swidsinski et al demonstrated the presence of intracellular E coli in both the carcinoma and in the macroscopically normal tissue of colon cancer patients. It is our hypothesis that these altered mucosal glycosaccharides seen in colon cancer and pre-cancerous polyps may function as receptors for adhesions of otherwise non-pathogenic bacteria, promoting mucosal recruitment and intestinal inflammation.

Methods: Mucosally associated and intraepithelial bacteria from adenomas and macroscopically normal colorectal mucosa of patients with colon cancer (n = 21) were isolated after removal of superficial mucus followed by the gentamicin protection assay. Bacteria identified as E coli were screened for agglutination of human red blood cells and characterised for genotype/phenotype using PCR. E coli were also assessed for attachment/invasion to intestinal cells and for their ability to induce release pro-inflammatory cytokines.

Results: 71% (15/21) of tumour tissue specimens were positive for mucosa associated bacteria compared with 57% (12/21) of macroscopically normal tissue. Using a panel of glycocjugates, all agglutinating E coli attached to both HT29 and I407 cell lines, with invasion only in I407 cells. Agglutinating E coli induced IL-8 release, up to 5 times above basal levels (p < 0.01).

Conclusions: These results support the hypothesis that altered mucosal glycosylation in colon cancer causes alterations in mucosa associated flora, leading to recruitment of non-pathogenic bacteria, which may then result in inflammation. This could be relevant to the progression from dysplastic polyps to invasive cancer. Soluble plantain fibre inhibits adherence of these E coli and further studies are warranted to assess its possible role in tumour prevention.


110 EXPRESSION OF MACROPHAGE MIGRATION INHIBITORY FACTOR IN INTESTINAL ADENOMAS

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Background: The cytokine macrophage migration inhibitory factor (MIF) is expressed in normal human colorectal mucosa and promotes tumour growth in several experimental cancer models.

Aims: The aim of this study was to investigate MIF expression and activity in human sporadic colorectal adenomas and in intestinal adenomas from the Apcmin/− mouse model of familial adenomatous polyposis.

Methods: Immunohistochemistry was performed on archival formalin-fixed, paraffin-embedded human sporadic colorectal adenomas (n = 56), and on small and large intestine of Apcmin/− mice and wild-type littermates. Human MIF protein levels were analysed in fresh paired colorectal adenoma and normal mucosal samples by ELISA (n = 16) and by Western blot analysis (n = 8). A p-hydroxyphenylpyruvate (HPP) tautomerase assay was used to measure specific MIF activity in paired fresh tissue (n = 20).

Results: In human colorectal tissue, immunohistochernistry and Western blot analysis both demonstrated increased MIF protein levels in adenomas compared with paired normal colorectal mucosa. MIF was localised to both epithelial (particularly at the apical membrane) and stromal cells in adenomas. The ELISA demonstrated a mean 1.9-fold increase (95% CI 1.1 to 2.7) in immunoreactive MIF in adenomas compared with paired normal mucosa. The HPP tautomerase assay revealed a mean 1.5-fold increase (95% CI 1.2 to 1.7) in MIF activity in adenomas. Immunohistochemical analysis of Apcmin/− mouse intestine revealed a similar pattern of protein localisation in adenomas and histologically normal mucosa, with prominent MIF protein expression in dysplastic epithelial cells in adenomas.

Conclusions: MIF protein levels are increased in human sporadic colorectal adenomas and in intestinal adenomas from the Apcmin/− mouse. The precise role of MIF in epithelial and stromal cell compartments of adenomas during the early stages of intestinal tumorigenesis is currently being investigated.

111 TOP DOWN OR BOTTOM UP MORPHOGENESIS OF COLORECTAL ADENOMAS: COMPETING MANAGEMENT STRATEGIES IN THE ORIGINS OF COLORECTAL NEOPLASIA

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Introduction: The adenoma-carcinoma sequence is well established. Understanding the molecular pathology of the adenoma is therefore important. There is great controversy within the field. The Vogelstein group champion the “top down” theory: colorectal adenomas arise and grow across the mucosal surface, and down into the crypts, whereas other studies, including our own, propose “bottom up” spread.

Methods: Serial sections of 40 small (∼3 mm) sporadic colorectal adenomas were stained with H&E, and for MB-1 and β catenin. 11 early adenomas were Feulgen stained and microdissected. In addition, we examined the flat mucosa of 3 patients who had undergone colectomies for familial adenomatous polyposis (FAP) and also specimens from an XO/XY individual with FAP, the latter using in situ hybridisation for the Y chromosome.

Results: In the earliest sporadic adenomas there were crypts entirely filled with adenomatous epithelium, which showed proliferative activity and nuclear localisation of catenin. There was a sharp cut off between crypt epithelial cells showing nuclear β catenin and surface cells with no membrane staining. In slightly larger lesions, Wnt-dependent spread from the mucosal surface was seen. In advanced adenomas spread foci were seen, proliferation equally distributed throughout. In FAP tissue, numerous isolated monocryptal adenomas, which were clonal in origin, were seen. Examination of adenomas in the XO/XY individual showed no instances of XY or XO adenomatous epithelium growing down into crypts of the other geno-type.

Conclusions: Both sporadic and FAP adenomas start as an unirradiated adenomas, and grow initially by crypt fission—a “bottom up” pattern. Later, in sporadic adenomas, there is evidence of growth down into adjacent crypts—“top down”.

112 THE PREVENTION OF COLORECTAL CANCER BY COLONOSCOPIC SURVEILLANCE IN INDIVIDUALS WITH A FAMILY HISTORY OF COLORECTAL CANCER

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Background: Surveillance by colonoscopy has been recommended for individuals with a significant family history of colorectal cancer. We report results of 2983 surveillance colonoscopies in 1519 individuals.
METHODS: Families were classified into four groups: hereditary non-polyposis colorectal cancer (HNPCC = Amsterdam Criteria positive), and those with 1, 2, or 3 affected first-degree relatives. Colorectal cancer was observed in all 3 groups. The two affected relatives had colorectal cancer incidence and mortality during over 11,000 person-years of follow up were compared to those expected in the absence of surveillance.

RESULTS: Advanced colorectal cancer was most frequent in HNPCC (6.5% on initial colonoscopy). In non-HNPCC, it was infrequent (1.2%) under age 45 (even when a relative had developed cancer under age 45 years) and on follow up if advanced neoplasia was absent initially (1.3%). After adjusting for the relative risk based on family history and age, there was a highly significant reduction in colorectal cancer incidence in non-HNPCC (58.5% in HNPCC) and mortality (91% in non-HNPCC, 80% in HNPCC).

CONCLUSIONS: HNPCC family members require surveillance with short intervals. Those with a lesser family history do not require surveillance under age 45 years, and if advanced neoplasia is absent on initial colonoscopy, surveillance intervals may be lengthened. Colonoscopic surveillance reduces the risk of colorectal cancer in those with a strong family history.

LOSS OF TRANSFORMING GROWTH FACTOR-α REDUCES TUMOUR INITIATION BUT DOES NOT AFFECT TUMOUR PROMOTION

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Background: TGF-α may be the main ligand for the EGF receptor in the gut and thus plays an important role in maintaining the integrity of the gastrointestinal tract. TGF-α null mice show some changes in the morphology of the colon and also have an increased susceptibility to colitis. TGF-α expression is increased in humans with adenomas and autocrine stimulation of the EGF-receptor by TGF-α has been linked to the growth of adenomatous cell lines.

Aims: To determine if TGF-α knock out leads to altered susceptibility to carcinogen induced colonic tumours.

Methods: TGF-α null mice and appropriate wild type mice were either injected with saline or dimethylhydrazine (DMH) for 16 weeks. Two weeks after the last injection they were given BrdU and vincristine and then autopsied. Polyp number, cell proliferation, and crypt fission were then assayed.

Results: Small bowel weight was significantly greater in the TGF-α null mice (p < 0.001), but colon weight was not changed. DMH had no effect on small bowel weight but significantly increased colon weight and cell proliferation (p < 0.001). There was a small but non-significant reduction in poly number (7.1 ± 0.6 WT/KO) but the number of aberrant crypt foci was reduced from 97.5 ± 0.6 WT/KO to 53.2 ± 4.1 (p < 0.001) in the null mice.

Discussion: TGF-α knock out mice had half the number of aberrant crypt foci in wild type mice, but polypt number was not altered, suggesting that TGF-α is involved in the initiation rather than the promotional stages of carcinogenesis.

SEVERITY OF DYSPLASIA IN COLONIC POLYPS AND NOT LESION SIZE IS DIFFERENTIALLY ASSOCIATED WITH ELEVATED FAECAL CALPROTECTIN—A COMPARATIVE STUDY WITH FAECAL α1ANTITRYPSIN

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Introduction: Levels of both calprotectin (Cal) and α1antitrypsin (α1at) have been shown previously to be elevated in colorectal neoplastic disease. There are, however, little data on either their comparative performance as markers of neoplasia or their discriminatory function as markers of dysplastic change within polyps.

Aim: To assess the sensitivity of faecal Cal and α1at levels in patients with severely dysplastic colorectal polyps.

Method and Results: A prospective study of 137 patients (male:female 69:73, median age 68 years, range 24–86) undergoing colonoscopy was made. 44 patients underwent a normal colonoscopy with a median faecal calprotectin of 4 µg/g (range: 1–367) and α1at of 44 µg/g (2–168). 28 patients had one or more large (> 1 cm) polyps (2 right colon, 2 left colon and 3 sessile polyps) but neither Cal (13 ± 0.6 µg/g, 1–397, p = 0.1) nor α1at (51 µg/g, 9–296, p = 0.6) was significantly raised. 8 patients had one or more estimated small (< 1 cm) polyps at colonoscopy (2 right colon, 5 left colon and 1 both sides of colon); again neither faecal Cal (median 2 µg/g, 1–15 µg/g, p = 0.5) nor α1at levels (44 µg/g, p = 0.39) were significantly higher than the normals. 11 adenocarcinomas (10 left colon, 1 right colon) and 31 adenomas (24 left colon, 5 right colon and 1 both sides) were reported. Significant differences in Cal values were found between adenocarcinoma (44 µg/g, 12–397) and adenoma (3.5 µg/g (1–94 µg/g) p = 0.0002) and metaplasia (n = 16, median 5.5 µg/g (1–45 µg/g) p = 0.0009). A significant higher was found to be associated with either severely dysplastic adenomas (71 ± 46 µg/g; p = 0.53), or the normal group (71 ± 45 µg/g; p = 0.38). In the severely dysplastic adenomas (n = 15), significantly higher Cal (8 µg/g, 1–48) was found than in those with only little dysplasia (n = 17, 1 µg/g, 1–10 µg/g, p < 0.05). α1at was not different in either group (p = 0.33). Using ROC analysis, at a Cal level of 8 µg/g, sensitivities for carcinoma, 100%, severely dysplastic adenomas, 54%, and adenomas with little dysplasia, 25%, were achieved.

Conclusion: Faecal calprotectin and not faecal α1at is significantly higher in those patients with adenocarcinoma or severely dysplastic adenomas by contrast to adenomas with little dysplasia, irrespective of polypt size or location.

THE ACCURACY OF EUS, HCT AND PET IN RE-STAGING OESOPHAGEAL CANCER FOLLOWING CHEMOTHERAPY

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The best approach to re-staging oesophageal cancer following chemotherapy is unknown. Potential limitations exist for all imaging modalities: hCT and EUS cannot differentiate between viable tumour and inflammation, whereas although PET scanning may detect remnant malignancy, it lacks spatial resolution. The purpose of this study was to compare the accuracy of CT, EUS, and PET scanning in the assessment of oesophageal tumour response to chemotheraphy using pathological correlation. Initial results are presented.

12 oesophageal cancer cases underwent CT, EUS, and FDG-PET before and after 3 cycles of ECF chemotherapy. The follow up FDG-PET was performed at least 4 weeks after the end of the ECF and 8 weeks after the E/C. Quantitative PET data using standard uptake values (SUV) were measured. Results were compared with surgical pathological findings. Baseline EUS gave initial T stage as T4 in 2, T3 in 9 and T12 in 1 patient. Ten patients were staged as N1 and 2 as N2. CT and EUS concurred in all the patients for nodal status with CT understaging the T1 stage in 3 patients. PET identified all the tumours but was unable to T stage accurately and identified only 5 of the N1 patients.

1 Patients underwent oesophagectomy. The two remaining cases did not undergo surgery due to early death and disease progression. Of the 10 surgical patients, only 2 had responded. CT identified one of the responders correctly, overstaged the other and understaged 3/8 of the non-responders. EUS significantly overstaged one of the responders (1/2) and understaged 4/7 of the non-responders, particularly the N stage. Quantitative PET measurement of the reduction in tumour uptake was significantly different between the responders (77% ± 26%) and the non-responders (39% ± 22%), but FDG-PET underestimated nodal disease in 4 patients. Qualitative assessment alone using FDG-PET was unreliable as 2 non-responders were labelled responders.

Neither CT nor EUS could accurately predict response following chemotherapy. FDG-PET could differentiate responders from non-responders based on the reduction in uptake values and was better at identifying liver metastases than CT. No single imaging modality conferred, however, adequate accuracy in assessing oesophageal tumour response to chemotherapy.

HGF/MET INDUCES DOWNREGULATION OF E-CADHERIN AND INCREASES TCF/BETA-CATENIN SIGNALING IN OESOPHAGEAL ADENOCARCINOMA

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Background: The development of oesophageal adenocarcinoma is characterised by progression along the Barrett’s metaplasia–dysplasia–carcinoma sequence. The HGF receptor, Met, shows raised expression in a cohort of patients with severely dysplastic colonic polyps.
increased expression along this sequence and patients with carcinomas that overexpress Met exhibit poorer short term survival. The perturbation of cadherin/catenin complexes has been shown in oesophageal adenocarcinoma with downregulation of E-cadherin a common finding. We sought to investigate a link between Met activation and cadherin/catenin biology.

Aims: To investigate the effect of Met activation on E-cadherin expression and on Beta-catenin nuclear signalling in oesophageal cells.

Methods: Two cell lines that express Met (OE33, SEG1) and a cell line that does not (TE7) were incubated with HGF at doses ranging from 1 ng/ml to 500 ng/ml. At set time points from 30 min to 24 h, mRNA and protein were harvested. Real time PCR was used to assess levels of E-cadherin mRNA. Western blot was used to assess levels of E-cadherin protein. Levels of nuclear TCF/Beta-catenin signalling were assessed following transient transfection with a TCF/luciferase reporter construct. An ELISA was used to measure levels of HGF in the culture media at different time points to detect any endogenous synthesis of HGF by the cell lines themselves.

Results: OE33 and SEG1 showed a 37% and 69% reduction in E-cadherin mRNA following 30 min stimulation with HGF at 100 ng/ml (p < 0.01). This minimum dose was reduced by altering the amount of cell serum supplemented in the culture media. Reduced E-cadherin protein expression was seen. OE33 showed a two-fold increase in the relative levels of luciferase activity following HGF stimulation (p < 0.01). TE7 (which lacks the Met receptor) showed no response.

Conclusions: Met activation induces downregulation of E-cadherin and increases nuclear TCF/Beta-catenin signalling. Thus Met activation may impair cell adhesion and play a role in regulating gene transcription.

117 SURVEY OF CURRENT CLINICAL PRACTICE IN THE DIAGNOSIS, MANAGEMENT AND SURVEILLANCE OF BARRETT’S METAPLASIA: A UK NATIONAL SURVEY

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Introduction: Barrett’s metaplasia (BM) is the precursor lesion for oesophageal adenocarcinoma, a tumour with a rising incidence and a uniformly poor prognosis. In spite of the recognition of this fact and the almost exponential increase in clinical and basic science research, much uncertainty remains as to the optimum management of Barrett’s disease, 1/3 for all patients, but 2/3 only for those with long stand-

Methods: In order to assess the current situation in the UK an anonymous questionnaire was sent to members of the BSG asking for details of their current practice.

Results: Of 401 questionnaires sent, 228 were returned (57%), indicating no differences in practice. Of the responders, 50% routinely consider screening in patients with gastro-oesophageal reflux disease, 1/3 for all patients, but 2/3 only for those with long standing reflux disease. Fifty-five percent will diagnose BM using histological criteria by the presence of intestinal metaplasia anywhere in oesophagus. Although the majority (90%) consider surveying patients with known BM using a 4-quadrant protocol, there is considerable variation in the frequency and implementation. Endoscopy intervals also vary in patients with low grade dysplasia. Although there is greater agreement in management of patients with high grade dysplasia (HGD), with the majority considering surgery for suitable patients, there was considerable variation in access to pathological expertise and utilisation of this expertise in cases of HGD. The majority supported the idea of clinical trials in BM, particularly into the value of surveillance.

Conclusion: This survey indicates a wide variation in the management of BM in the UK. This is likely to reflect the lack of good evidence to base a protocol over another and in certain cases a lack of clinical resources, particularly in pathology. There is a clear need for a more robust evidence base on which to base management and direct resources by a large randomised multicentre intervention and surveillance study.

118 MANAGEMENT OF HIGH GRADE DYSPLASIA (HGD) IN BARRETT’S OESOPHAGUS: A RETROSPECTIVE 10 YEAR REVIEW

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Background: Management of HGD in Barrett’s remains controversial.

Aim: To review management and outcome of HGD from three hospitals in one district.

Methods: Case record study. Patients with dysplasia identified from pathology database. All HGD verified by at least two upper GI pathologists and those with coincident adenocarcinoma (AC) with HGD excluded.

Results: 99 cases of dysplasia identified; 36 had HGD arising in Barrett’s mucosa, M/F 31/5, mean age 67 (range 24-95). 9/36 (25%) were identified during Barrett’s surveillance. 7 had no further interventions due to age and comorbidity. On repeat endoscopy and biopsy of the remaining 29 (usually within 3 months), 9 had intramu-

cosal AC and are not further considered. Of the remaining 20, 16 had persisting HGD and 4 became and remained negative for dysplasia (mean follow up 17.2 months). Of the 16 with persisting HGD, 8 had oesophagectomy of which 6 had AC on operative histol-

ogy. At a mean follow up of 18.7 months, 6 patients were disease free. There were no immediate (30 day) postoperative deaths; 3 died (2–47 months after surgery), 2 of unrelated causes and one of meta-

stasis. 5 were treated with argon ablation of which 2 had nodules and/or ulcers in the Barrett’s segment. In 4/5 the Barrett’s segment was ablated; absence of HGD was confirmed histologically in 2 (both originally had HGD in “flat” mucosa) who remained disease free (mean FU 10 months); 2/5 developed metastatic AC of whom 1 has died. The final 3/16 continued to have surveillance: 2 developed AC (1 death) and 1 died of an unrelated cause. In summary: 15 of 36 patients were disease free. There were no immediate (30 day) postoperative deaths; 3 died (2–47 months after surgery), 2 of unrelated causes and one of meta-

stasis. 5 were treated with argon ablation of which 2 had nodules and/or ulcers in the Barrett’s segment. In 4/5 the Barrett’s segment was ablated; absence of HGD was confirmed histologically in 2 (both originally had HGD in “flat” mucosa) who remained disease free (mean FU 10 months); 2/5 developed metastatic AC of whom 1 has died. The final 3/16 continued to have surveillance: 2 developed AC (1 death) and 1 died of an unrelated cause. In summary: 15 of 36 (42%) of patients with biopsy proven HGD, have underlying AC either on resection or on early rebiopsy. A further 4 developed AC during surveillance (median 17 months, range 4–64). A small proportion of HGD regresses (4/36–11%).

Conclusions: Oesophagectomy remains the treatment of choice in HGD because a high proportion have coincident AC. Argon ablation can be effective in a proportion of those unfit for surgery but may be less successful if the Barrett’s segment contains nodules/ulcers.

119 NOVEL P53 MUTATIONS BUT LACK OF A MUTATIONAL FINGERPRINT IN HUMAN INTRAHEPATIC CHOLANGIOCARCINOMA

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Background: Cholangiocarcinoma (CCa) may arise from cholangiocyte DNA damage due to genotoxic compounds in bile. We have previously shown that human biliary tissue is exposed to genotoxic agents, as evidenced by the presence of DNA adducts. The correlation of DNA lesions along a target gene with a known “muta-

tional signature” induced by an environmental carcinogen is a means of linking cause and effect in human cancer. The tumour suppressor gene p53 is known to have “hotspots” for particular chemical carcino-

gens. Previous studies of p53 mutation in CCa have focused on exons 5–8, potentially missing gene alterations at other sites. This study examined the link between environmental carcinogens and CCa, by analysing CCa DNA for complete p53 mutational signatures.

Methods: Entire p53 cDNA (all exons) from 31 intrahepatic CCa patients were screened by single strand conformational polymorph-

ism. Exons exhibiting aberrant bands were fully sequenced. Muta-

tions were compared to known p53 mutations in CCa, and to mutations induced by environmental mutagens, as described in p53 databases.

Results and Conclusions: Five non-silent p53 mutations were found, including an exon 5 missense and a nonsense mutation, both previously reported. Three frame-shifts (2 deletions and 1 insertion) in exons 4, 5, and 6, and two intron mutations were discovered, none of which have been previously reported. No predominant mutational signature was seen. This may be due to host or environmental differ-

ces in study populations, lack of data outside exons 5–8, bias in mutation reporting or because non-coding regions or other genes are involved. Further epidemiological and molecular studies are required to establish risk factors and elucidate genotoxic and host mechanisms in cholangiocarcinoma.
**Plenary posters 120–149**

**120** FLAT AND DEPRESSED COLORECTAL LESIONS HAVE A HIGH MALIGNANT POTENTIAL IN THE UK: A PROSPECTIVE STUDY USING HIGH RESOLUTION CHROMOSCOPIC COLONOSCOPY

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**Introduction:** Flat and depressed colorectal (CR) lesions are well described in Japanese and now western European cohorts. Studies assessing their malignant potential have shown high variability. Detection using conventional colonoscopy can be difficult. High resolution chromoscopic colonoscopy (HRCC) may facilitate detection of such lesions and allow histological characteristics to be predicted in vivo.

**Aim:** To evaluate the efficacy of HRCC in predicting the malignant potential of flat CR lesions.

**Subjects and Methods:** Total colonoscopy was performed on 600 consecutive patients, by a single endoscopist using the Olympus CF240Z endoscope from 01/02 to 09/02. Locally applied 0.5% indigo carmine (IC) was used to facilitate crypt pattern appearance of such lesions. JRSC class, N, Mean size, Dominant and Benign were used. "mild/mod dysplasia" was defined as a score of ≤ 55, and "severe dysplasia" was defined as a score of > 55. Histological analysis was obtained on all specimens. Lesions > 20mm diameter, had evidence of lymph node metastases and/or extensive metastases at the time of diagnosis. One patient had no record of lymph node spread but died 53 days after diagnosis. Of the 2 patients presenting with simple dyspepsia and found to have upper GI cancers, 6 were found to have lymph node metastases and/or extensive metastases at the time of diagnosis. Each of these 6 patients died from their cancer between 3 and 26 months from diagnosis. One patient had no record of lymph node spread but died 53 days after diagnosis. Of the 2 patients presenting with simple dyspepsia and found to have upper GI cancers, 6 were found to have lymph node metastases.

**Results:** Of the 106 cancer cases identified only 23.5% (24) had simple dyspepsia without evidence of lymph node spread, 1 died 57 days post-diagnosis from post-gastroectomy complications. Only 1 patient presenting with simple dyspepsia and found to have cancer remains alive at 5 years follow up.

**Conclusion:** A policy of endoscoping patients ≥ 55 years with simple dyspepsia will reduce death from upper GI cancers by less than 1% in our population.

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**121** ENDOSCOPY PATIENTS WITH UNCOMPANDED DYSPHESIA OVER AGE 55 HAS MINIMAL IMPACT ON MORTALITY FROM UPPER GASTROINTESTINAL CANCER

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Most guidelines recommend endoscoping patients over 55 years of age with uncomplicated dyspepsia. This rationale is based on the assumption that an upper gastrointestinal (GI) cancer may be detected at a curable stage in such patients.

**Aim:** To determine the proportion of upper GI cancers that present with uncomplicated dyspepsia in patients ≥ 55 years and determine the proportion of these upper GI cancers that are curable.

**Method:** We reviewed the case notes of patients within a catchment area of the North Glasgow Trust, population of approximately 300,000, who were ≥ 55 years age, diagnosed with an upper GI cancer between October 1995 and December 1998 inclusive. These patients were identified by the West of Scotland Cancer Registry. Presenting symptoms were taken to be those recorded at the time of referral for initial investigation.

**Results:** Of the 106 cancer cases identified only 23.5% (24) had dyspepsia (complicated or uncomplicated) as their predominant symptom. Only 8.5% (9) of patients presented with uncomplicated dyspepsia. Of those 9 patients presenting with uncomplicated dyspepsia and found to have upper GI cancer, 6 were found to have lymph node metastases and/or extensive metastases at the time of diagnosis. Each of these 6 patients died from their cancer between 3 and 26 months from diagnosis. One patient had no record of lymph node spread but died 53 days after diagnosis. Of the 2 patients presenting with simple dyspepsia and found to have upper GI cancers, 6 were found to have lymph node metastases.

**Conclusion:** A policy of endoscoping patients ≥ 55 years with simple dyspepsia will reduce death from upper GI cancers by less than 1% in our population.

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**122** CAN AN INTENSIVE, STRUCTURED TRAINING WEEK IMPROVE COLONOSCOPY PERFORMANCE?

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**Introduction:** We developed a structured colonoscopy training course aimed at improving technique of trainees with intermediate colonoscopy skills.

**Methods:** 12 specialist registrars (8 surgeons, 4 physicians) attended for a week of comprehensive colonoscopy training and assessment in 3 main areas: core knowledge; two teaching videos; and a CD Rom on colonoscopy/basic polypectomy technique were watched by each trainee. Knowledge was assessed using 2 purpose designed, multiple choice question (MCQ) papers shown to be of equal difficulty. Simulator (hand skills): a mean of 24 (16–31) computer simulator cases were performed. A standardised simulated test case (SSTC) was used to score performance. Clinical skills were taught during 5 training lists by two experts. A mean number of 21 (14–26) clinical cases were performed by each trainee throughout the week. Structured subjective scores using 100 point visual analogue scales were made by both trainers. All assessments were made at the start and end of the week.

**Results:** Eight had performed < 200 cases previously, 4 had performed more than this. The MCQ score significantly increased: mean score 54.8% v 64% (n = 8; p = 0.008). Structured subjective scoring demonstrated an improvement in clinical skill: overall subjective pre- and post-scores 59.6 v 70.8 (p = 0.0004). Mean total time taken to complete the SSTC improved significantly from 1631 secs pre-training v 1163 secs post-training (p = 0.02). There were no perforations or haemorrhages during the SSTCs and only one vasovagal episode.

**Discussion:** We believe that training must be shown to be effective in achieving its goals. We have demonstrated that a week of structured intensive training can result in an improvement in colonoscopy clinical skills and core knowledge in moderately experienced trainees.
Patients and Methods: Between June 1989 and June 2002, 24 patients (15 female) underwent an endoscopic retrograde cholangiopancreatogram (ERCP) following suspected biliary trauma sustained during hepatobiliary surgery. Mean age was 54 years (range 29–79). Symptoms were of right upper quadrant pain (n = 16), fever (n = 1), jaundice (n = 3), or none (n = 4).

Results: At ERCP 14 patients were found to have a leak in the biliary tree and underwent a papillary sphincterotomy and single stent insertion (mean duration = 92 days). 7 had strictures: 2 patients with Bismuth type I strictures required stenting only once and 5 patients with type II or III strictures required multiple stent changes (mean = 3). Symptoms resolved when the stents were finally removed. Three patients had both a biliary leak and a stricture (Bismuth type I in all cases). All 3 required multiple stent changes. 2 out of the 24 (8%) required subsequent surgical intervention in a tertiary referral centre. A patient with a leak and stricture was referred for hepatobiliary surgery. Ten patients with 2 strictures was referred for surgery 11 days after ERCP due to continuing symptoms. Complications noted were stent migration (n = 2), ascending cholangitis (n = 1), and acute pancreatitis (n = 2).

Conclusion: Postoperative complications of biliary surgery may be managed by therapeutic ERCP effectively and safely in the district general hospital setting. Bile duct leaks and uncomplicated Bismuth type I strictures may both be treated effectively by a single stent for 3 months. Type II and III strictures may require a limited number of stent changes. Patients with multiple strictures or a combination of leak and a stricture may be more difficult to treat endoscopically.

124 ONE STOP INVESTIGATION OF IRON DEFICIENCY ANAEMIA. THE WAY AHEAD?
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Adults with iron deficiency anaemia require GI tract investigation. Traditionally gastroscopy (FOG) and barium enema (DCBE) are used, with colonoscopy (FOC) if DCBE is normal. Primary FOC is not used traditionally gastroscopy (FOG) and barium enema (DCBE) are used, with colonoscopy (FOC) if DCBE is normal. Primary FOC is not used traditionally gastroscopy (FOG) and barium enema (DCBE) are used, with colonoscopy (FOC) if DCBE is normal. Primary FOC is not used traditionally gastroscopy (FOG) and barium enema (DCBE) are used, with colonoscopy (FOC) if DCBE is normal. Primary FOC is not used.

Findings:

Abstract 124

Findings: (%)
Colon cancer 7 (11.1)
Idiopathic BD 2 (3.2)
Colon lymphoma 1 (1.6)
Gastric carcinoma 2 (3.2)
Peptic ulceration 3 (4.5)
Coeliac disease 1 (1.6)
Oesophageal varices 1 (1.6)
Total 17 (27.0)

Investigation of iron deficiency anaemia by FOG and FOC at one sitting is safe and effective. Significant pathology was found in 17 (27%) patients and 21 (35%) were returned to their general practitioner after the examination. This cohort of patients are at high risk of having malignant disease and need expeditious investigation. This approach allows prompt, complete investigation and discharge of many patients directly to primary care with the reassurance that no significant abnormality has been found.


125 PERFORMANCE AT SCREENING FLEXIBLE SIGMOIDOSCOPY: A NEW VIDEO ASSESSMENT TOOL

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Background: Adenoma detection rates (ADR) at screening flexible sigmoidoscopy (FS) are known to be variable. No existing objective method for scoring endoscopy performance exists.

Methods: To develop a video assessment tool that evaluates performance in FS for potential screening purposes, the main objective being confidence that no lesions are missed during an examination (exam).

Methods: Eight experiments using video footage from a selection of 2000 cases from the UK Flexible Sigmoidoscopy Trial were performed. 5 experienced endoscopists independently scored, on average 5 exams from different endoscopists with varying ADRs. All experiments tested inter-observer variability (IOV), experiments 7 and 8 tested correlation of scores with ADR (validity) by looking at several cases from an individual endoscopist back-to-back. Cases were selected and extubations edited together by independent reviewers. Variables assessed were: Bowel mucosa NOT visualised, Confidence NO lesion missed; Time spent viewing mucosa; re-examination of poorly viewed areas; Suctioning of fluid; Luminal distension; lower rectal exam; and overall quality of exam. Experiments 1–3 used Visual Analogue Scales (VAS), replaced in experiments 4–8 (due to high IOV) by grades A–E (A = excellent, B = good, C = needs improving, D = not good enough, E = unacceptable).

Results: The A-E system produced less variability and more validity in predicting overall quality of exam. In experiments 7 and 8 the endoscopist with highest ADR was ranked as most technically proficient. In experiment 8 there was 100% agreement in ‘Overall’ score given for 2 of 3 endoscopists when 5 cases from each were viewed back-to-back. For the third, all scorers agreed that the endoscopist needed to improve their technique (Grades C or D).

Conclusions: An objective performance score for screening FS based on video footage is possible. There is less inter-observer variability when 5 cases from an individual endoscopist are viewed back-to-back and then scored. Further validation is being performed in a larger sample.

126 THE EFFECTS OF LONG TERM CHRONIC HELICOBACTER PYLORI INFECTION ON GASTRIC GROWTH FACTOR EXPRESSION IN THE MONGOLIAN GERBIL

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Introduction: Chronic H pylori infection in the Mongolian gerbil has been demonstrated to result in gastric cancer. To gain a greater understanding of the mechanisms involved, this study investigated the effects of infection on gastric expression of growth factors.

Methods: Male Mongolian gerbils were orally infected three times with H pylori SST1 strain. Infected gerbils (n = 20) and controls (n = 17) were sacrificed at 36 and 62 weeks post-infection (p.i.). Gastric mucosa was snap frozen for analysis of growth factor transcripts by RT-PCR. Cross-species PCR and sequencing was used to identify gerbil transcripts for heparin-binding epidermal growth factor (HB-EGF) and transforming growth factor alpha (TGFα). The ratio of growth factors to β-actin was determined by computer image analysis. In addition, HB-EGF localisation was detected by immunohistochemistry.

Results: All infected gerbils had chronic gastritis, with more severe pathology and corpus atrophy observed in the 62 week infected animals. Uninfected control exhibited age-related increase in transcripts of both HB-EGF (36 week 1.1 ± 0.9 v 62 week 2.1 ± 0.17, p < 0.01) and TGFα (36 week 1.57 ± 0.195 v 62 week 2.28 ± 0.13, p < 0.02). H pylori infection was associated with significantly (p < 0.01) decreased TGFα transcripts at 62 weeks p.i. In infected gerbils HB-EGF also increased with age, but levels were not significantly different to controls. Immunolocalisation showed HB-EGF was present in parietal cells in controls. In contrast, in 62 week H pylori infected corpus with atrophy HB-EGF was localised in gastric epithelial cells.

Conclusions: In the gerbil there are age related increases in gastric growth factor expression. Gastric TGFα but not HB-EGF, was decreased in long term chronic H pylori infection. In H pylori induced corpus atrophy, the presence of HB-EGF in the gastric epithelial cells may play an important role in epithelial hyperplasia.


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IDENTIFICATION OF RISK FACTORS FOR THE DEVELOPMENT OF OESOPHAGO-GASTRIC CANCERS IN SCOTLAND

E. Fernandes, A.G.K. Li, H. Rashid, K.G.M. Park on behalf of the SAGOC Steering Group Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK

Background: The early detection and treatment of oesophageal and gastric cancer offers the only chance of an improved outcome. However, the relatively low incidence of these tumours renders screening programmes uneconomical and unpractical.

Aim: To target groups of patient who are at increased risk of developing gastric and oesophageal cancer and identity risks factors for this disease.

Methods: Data from the Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) were prospectively collected from 3293 patients with oesophageal and gastric cancer from 1997 to 1999. χ² analysis was performed between the risk factors for each tumour type.

Results: The population study included cancers of the oesophagus (45%), gastro-oesophageal junction (16%), and stomach (39%). Of the oesophageal tumours, 51% were oesophageal adenocarcinoma (OAC) and 39% squamous cell carcinomas (SCC). Significantly high rates of tobacco and alcohol consumption were seen in patients with SCCs. 14% of patients with OAC had pre-existing Barrett's oesophagus, which was present in 4.3% of the tumours of the OG junction, 0.9% of SCCs and 0.9% of gastric tumours. A history of GOR was present in 16% of the total study group. Conversely, 27% of patients with OAC had history of GOR compared with 20% of junctional tumours, 13% of SCCs, and 12% of gastric cancers.

Conclusion: These data indicate the relative importance of known risk factors in the development of upper gastrointestinal cancers in Scotland. While each of these may be proportionally common within the general population, a targeted screening algorithm based upon a combination of such factors could be developed to direct investigation of patients.

HEPATIC MANIFESTATIONS OF THE ANTIPHOSPHOLIPID SYNDROME

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Background and Aims: Antiphospholipid syndrome (APS) is increasingly recognised to have a wide range of clinical manifestations, although involvement from this disorder within the liver or its vasculature is poorly identified.

Patients and Methods: 49 consecutive patients with a liver disorder investigated between 1994 and 2002 who fulfilled the diagnostic criteria for APS were studied. Patients were followed up for a median of 10 months (range 6–94 months).

Results: Of the 49 cases, 21 were male, 28 female. Median age at presentation was 42 (range 17–67). 29 patients were north European (60%), 5 (10%) Mediterranean, 8 (16%) Afro-Caribbean, and 5 (10%) Asian. 36 patients had primary APS (80%), 7 had APS associated with SLE (14%) and 3 associated with other autoimmunity diseases (6%). 3 patients had “equivocal” APS. A diagnosis of APS had been made in only 2 of 49 (4%) symptomatic cases prior to referral. A wide range of clinical and pathological findings involving the liver parenchyma and its vascular compartments were identified. 6 (12%) had either thrombosis or arthritis of the hepatic arterial tree. Portal-mesenteric thrombosis was present in 13 cases (27%) and nodular regenerative hyperplasia in 7 (14%). In 9 patients, Budd Chiari syndrome (6), veno-occlusive disease (2) or congestion secondary to right ventricular failure (1) was diagnosed. Autoimmune hepatitis was diagnosed in 9 patients. Associated non-hepatic clinical manifestations included vasculitis (10 (20%)), thromboses (8 (16%)) and unexplained myocardial dysfunction (5 (10%)). Anticardiolipin antibodies were detected in 48 of 49 (98%) and lupus anticoagulant in 14 of 36 (39%) of the patients tested. Complement C4 levels were low in 22 of 32 (67%) patients tested. 7 of 49 (14%) had SLE, 11 underwent transplant. 8 of 49 (16%) had lupus anticoagulant and 14 of 36 (39%) of the patients tested. Complement C4 levels were low in 22 of 32 (67%) patients tested. 7 of 49 (14%) had SLE, 11 underwent transplant.

Conclusion: The antiphospholipid syndrome has multiple hepatological manifestations and should be actively excluded in arterial, vascular and venous vaso-occlusive complications. This newly identified association with autoimmune hepatitis has rarely been reported.

TRANSJUGULAR LIVER BIOPSY: SAFETY, ADEQUACY AND CLINICAL IMPACT IN A NON-TRANSPLANT CENTRE

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Introduction: Histological examination of liver tissue is the gold standard for diagnosing and staging liver disease. We assessed the safety, efficacy, and clinical impact of transjugular liver biopsy (TJb) in a non-transplant centre.

Methods: 180 consecutive biopsies were performed using an automated transjugular cutting biopsy needle with a maximum core length of 25 mm and diameter of 2.2 mm. Mean patient age was 54.2 ± 13.8 (17–89) of whom 114 were male.

Results: Indications for TJb were pleatet count < 100 × 10⁹/l (49%), INR > 1.4 (41%), bilirubin > 100 μmol/l (35%), tense ascites (23%) or other (17%). 44% had two or more indications. Minor transient complications occurred in 11 cases only (5 hypotension, 4 pain, 2 fever). Biopsy sample was adequate for histological diagnosis in 93%, inadequate in 4%, and technically unsuccessful in 2%. Mean biopsy size was 14.8 ± 0.6 (5–35) mm. Adequacy and length did not differ between cirrhotic and non-cirrhotic biopsies. In 63% of cases, alcoholic liver disease was the presumed diagnosis before biopsy. TJb had a clinical impact in 78%; changed diagnosis in 38% (drug induced liver injury 11, haemochromatosis 8, normal liver 6, cryptogenic cirrhosis 5, other 3); and changed stage in 40%. The likelihood of a change in diagnosis was greater in the non-cirrhotic 21/64 compared with the cirrhotic 35/116 (Chi test; p = 0.001). In addition, a change in diagnosis was less common in those with a presumptive diagnosis of alcoholic liver disease 25/113 compared with those without 44/67 (Chi test; p = 0.001).

Conclusions: Transjugular liver biopsy is a safe procedure in high risk patients in a non-transplant centre. It provides adequate tissue samples in the vast majority irrespective of the presence or absence of cirrhosis. It has a clinical impact in 78% leading to an unsuspected diagnosis in 38%.

UP-REGULATION OF TOLL-LIKE RECEPTOR EXPRESSION IN CHRONIC HEPATITIS C: CORRELATION WITH CIRCULATING PRO-INFLAMMATORY CYTOKINE LEVELS AND HEPATIC NECRO-INFLAMMATORY ACTIVITY

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Background: Innate immunity to microbial pathogens, leading to the production of pro-inflammatory cytokines such as tumour necrosis factor [TNF-α], occurs as a result of activation of toll-like receptors (TLRs). Expression of TLRs has not been investigated in chronic hepatitis C (CHC). This is important as TNF-α may contribute to liver damage in this disorder.

Methods: We studied 16 hepatitis C virus RNA-positive patients (genotype 1, n = 11; 2, n = 2; 3, n = 3) with CHC (median Ishak histological activity score 4, range 2–7; median stage 2, range 1–4) and raised serum ALT levels (median 109, range 35–350 U/l; normal 15–45 U/l) and 32 healthy controls. TLR2 and TLR4 expression on CD14+ve peripheral blood mononuclear cells (PBMCs) was measured by flow cytometry. Serum TNF-α levels were measured by ELISA (R&D Systems, USA).

Results: TLR2 expression on PBMCs (expressed as a ratio to results in controls) was significantly increased in patients with CHC (median 1.18, range 0.77–2.41, p = 0.001). TLR4 expression was also significantly increased in this group (median 1.25, range 0.94–1.66, p < 0.0005). Serum TNF-α levels were significantly higher in CHC patients (median 2.3, range 0.8–9.3 pg/ml) than controls (median 1.9, range 0.8–3.4 pg/ml) and were correlated significantly with BMPC expression of TLR2 (r = 0.58, p < 0.0005) but not TLR4 (r = 0.01, p = 0.96). In CHC patients, serum ALT levels were correlated significantly with TLR2 expression (r = 0.74, p = 0.001) and TNF-α levels (r = 0.53, p = 0.05).

Conclusions: Up regulation of PBMC expression of TLR2 and TLR4 occurs in CHC. Cell signalling via TLR2, in particular, may contribute to both increased circulating TNF-α levels and liver damage in this disorder. These findings provide novel insight into the pathogenesis of CHC.
**131 IMPAIRED TOLL-LIKE RECEPTOR EXPRESSION IN CHRONIC HEPATITIS B**

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**Background:** Mechanisms by which hepatitis B virus (HBV) establishes persistent infection remain unclear. In particular, expression of toll-like receptors (TLRs), increasingly recognised as critically involved in the innate immune response to bacterial and viral pathogens, has not been investigated.

**Methods:** Eighteen non-cirrhotic patients with chronic hepatitis B and on-going viral replication (HBV DNA > 200 000 genomes/mL, n = 12 and 200–10 000 genomes/mL, n = 6; Cobas Amplicor HBV MonitorTM Test, USA) and 32 healthy control subjects were studied. TLR2 and TLR4 expression on CD14+ve peripheral blood mononuclear cells (PBMCs) was measured by flow cytometry using anti-CD14 (Becton Dickinson) and anti-TLR2 and anti-TLR4 (eBioscience, USA) monoclonal antibodies. TLR expression was re-assessed in 5 patients in whom HBV DNA fell from > 200 000 to < 200 genomes/mL following treatment with lamivudine. In vitro TLR2 expression by PBMCs was measured in 5 control subjects at baseline and following stimulation for 20 h by partially purified recombinant HBV.

**Results:** TLR2 expression (expressed as a ratio to control results) was significantly reduced in chronic hepatitis B patients with HBV DNA > 200 000 genomes/mL (median: 0.63; range: 0.05–1.52) compared with controls (p = 0.001) and those with HBV DNA 200–10 000 genomes/mL (median: 0.98; range: 0.94–1.17, p = 0.04). TLR4 expression did not differ significantly between the 3 groups. TLR2 expression normalised in each of the 5 lamivudine-treated chronic hepatitis B patients in whom HBV DNA became undetectable. In vitro expression of TLR2 fell in a concentration dependent manner following exposure to recombinant HBV.

**Conclusions:** HBV downregulates expression of TLR2 on PBMCs. This virus induced defect in innate immunity may contribute to the development of persistent infection.

**132 MOLECULAR PROFILES OF PANCREATIC ADENOCARCINOMA**

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In order to expand our understanding of the molecular changes underlying the complex pathology of pancreatic malignancy, global gene expression profiling of pancreatic adenocarcinoma compared to normal pancreatic tissue was performed. Human cDNA arrays comprising 9932 elements were interrogated with fluorescently labelled normal and adenocarcinoma samples using a reference control design, so that a pool of normal pancreatic tissues was always labelled with direct incorporation of Cy3 dCTP, while test samples (nine tumours, three normal pancreata and three cell lines) were always labelled with Cy5 dCTP. The enrichment with tumour cells was performed by manual trimming of the frozen blocks controlled by frequent microscopical examination of H&E stained sections. This resulted in enrichment of the specimens to at least 80% of tumour cells. The data were analysed for differential gene expression, which was confirmed by serial analysis of gene expression (SAGE), digital differential display (DDD) analysis, and immunohistochemistry for selected cases. The array data were filtered to produce a total of 75 genes significantly upregulated or downregulated in pancreatic adenocarcinoma. Two of those showing the highest differential were members of the S100 family of Ca binding proteins (S100P and S100A6) and were selected for additional studies by immunohistochemistry. As neither of them is expressed in normal pancreatic tissues, they could represent potential markers for pancreatic carcinogenesis.

**133 PS3 DEPENDENT DIFFERENTIAL EXPRESSION ANALYSIS OF ETOPOSIDE INDUCED STRESS IN THE MURINE SMALL INTESTINE**

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**Background and Aims:** Etoposide (VP16) induced stress in the mouse small intestine displays a dose and time dependent apoptotic response. Apoptosis only occurs in the stem cell compartment of the crypts and is Bax and p21 independent, but p53 dependent. Apoptosis is absent in the villi. We exploited the differential response to VP16 along crypt-villus axis to identify novel p53 dependent genes that are either pro-apoptotic or protective against cell death.

**Methods:** cDNA array analysis was performed in the p53 +/+ and p53−/− mouse total epithelium of the small intestine (10 mg/kg VP16 exposure for 4.5 h). Data were analysed using GeneSpring software (Silicon Genetics), which generated a list of >2-fold p53 dependent gene expression changes. Laser capture microdissection (LCM) was used to isolate pure crypt and pure villus epithelial cell populations, and real time PCR (QPCR) performed to detect differential gene expression along the crypt-villus axis. Protein expression analysis was analysed by Western blot and immunohistochemistry techniques.

**Results:** Proliferin 2 (PS2) and baculoviral IAP repeat 3 (BIRC3) were identified as VP16 induced p53 dependent genes by array analysis. Western blot analysis of total epithelium showed an upregulation of PS2 and BIRC3 protein levels in a p53-dependent manner. QPCR analysis of LCM isolated p53-wildtype crypts and villi revealed a differential gene expression of PS2 along the crypt-villus axis: a decrease of gene expression in the crypts, but an increase in the villus. Our initial histopathological observations support these data. BIRC3 expression was downregulated in both the crypt and villus.

**Conclusions:** BIRC3 does not appear to regulate apoptosis in intestinal epithelium. The differential mRNA expression of PS2 along the crypt-villus axis may indicate a pro-apoptotic role for low PS2 expression in the crypts, while providing apoptotic protection in the villus following VP16-induced stress.

**134 DYSREGULATION OF MYC NETWORK PROTEINS IN BARRETT’S METAPLASIA**

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Barrett’s metaplasia is a premalignant lesion predisposing to oesophageal adenocarcinoma. Patients with Barrett’s metaplasia have an approximate 0.5–2% annual risk of developing adenocarcinoma, 30–125 times the risk seen in the general population. Barrett’s metaplasia is associated with severe gastro-oesophageal reflux disease and there is increasing evidence that the reflux of bile acids is likely to be important in malignant development. We have previously demonstrated that c-Myc is upregulated in the malignant progression of Barrett’s metaplasia, and using in vitro cell models shown that bile acids can induce c-Myc. However, because c-Myc alone is unable to transactivate genes associated with mitogenic and oncogenic functions we sought to characterise the other essential c-Myc network proteins, namely Mad-1 and Max in this malignant process.

By use of microarrays on RNA extracted from Barrett’s patients (n = 4) we have identified the c-Myc antagonist Mad-1 as downregulated. These data were verified by quantitative real time PCR and have shown that in 19/20 Barrett’s metaplasia samples there was Mad-1 repression. By Western blotting we were able to demonstrate that repression also occurred at the level of protein. Furthermore, Mad-1 expression was also modulated in cell culture experiments. Thus our data would suggest that in the malignant progression of this disease an imbalance in the c-Myc regulatory system exists, with c-Myc being over-expressed while the c-Myc antagonist Mad-1 repressed. Furthermore, with increasing evidence that components of the refluxate can modulate these proteins this may provide a useful tool for identifying Barrett’s patients at greatest risk of developing adenocarcinoma, leading to an impact on surveillance programmes and patient health-care.
LOW BAT-26 AND BAT-25 POLYMORPHISM (PM) RATES IN A UK POPULATION SAMPLE: ROUTINE COLORECTAL CANCER (CRC) ANALYSIS FOR MSI IS POSSIBLE

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Background: Microsatellite instability (MSI) is a change in length of a simple repeat sequence (microsatellite (MS)) in tumour DNA compared to normal. It is a non-specific marker of a mismatch repair defect. It occurs in hereditary non-polyposis CRC (HNPCC) and in a proportion of sporadic CRCs. MSI-CRCs have distinctive clinicopathological features, behaviour, and response to chemotherapy. A panel of five MS markers is recommended for analysis of MSI in tumours, but this requires normal DNA for comparison. The use of mononucleotide markers alone (e.g. Bat-25) has been suggested as a simple screen for MSI without the need for normal DNA. Germline PMs in mononucleotide markers occur, and without normal DNA, may be misinterpreted as MSI. The PM rates vary according to the population studied (13–18% in African-Americans). The PM rates in the UK are not known.

Methods: A population based sample of germline DNAs (prepared from blood) from 789 individuals from one centre of the UK flexible sigmoidoscopy screening trial was analysed. Blood DNA was amplified at Bat-25 and Bat-26 loci by polymerase chain reaction (PCR) using fluorescent labelled primers. Products were electrophoresed on 5% denaturing polyacrylamide gels on an ABI 377 sequencer and analysed using GENASWICH Genotyping software. Two independent observers read the traces. Any DNAs thought to be polymorphic were re-PCRd to confirm.

Results: Results were available in 787. Four (0.5%) were polymorphic at both Bat-25, 1 (0.1%) at Bat-26 and 0 at both loci.

Conclusions: There is a low rate of Bat-25 and Bat-26 PMs in this UK sample. If MSI analysis was conducted on tumour DNA without matched normal tissue, about 0.6% would be incorrectly classified as MSI-positive. Bat-26 is the better marker to screen tumours for MSI as it has the lowest PM rate. MSI-positive tumours should be confirmed by comparison with normal DNA, although analysis for MSI at both Bat-25 and Bat-26 is probably sufficient.

RELATIONSHIP BETWEEN HELICOBACTER PYLORI AND COX2 EXPRESSION IN PATIENTS WITH GORD

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Background: The factors involved in the progression of GORD to Barrett’s oesophagus, and then to oesophageal adenocarcinoma are still unclear, however, gastric and bile reflux, cytokines (IL-18, TNF-α), and inflammatory mediators eg PGs are known to play a role. COX2 activity has been shown to effect cell turnover in oesophageal cancer. Previous studies have also shown that COX2 is induced by H pylori in the stomach.

Aim: To study COX2 expression in patients with reflux symptoms and Barrett’s oesophagus, and correlate this with their helicobacter status.

Method: 53 patients with reflux symptoms, 35 Barrett’s patients and 20 non-reflux control patients were recruited. For purpose of analysis we divided the reflux group into GORD and NERD, 33 and 20 respectively. During an upper GI endoscopy, biopsies were taken from the oesophagus, the gastric body and antrum of each patient. CLO test, ELISA and histopathology were used to assess the H pylori status. COX2 estimation was carried out by ELISA on the oesophageal and antral biopsies.

Results: COX2 was expressed more in Barrett’s (mean value 412 ng/ul) than in GORD patients (mean value of 312 ng/ul) (p < 0.005) this difference was more evident in patients with dysplasia. COX2 expression was higher in GORD patients than NERD (mean value of 245 ng/ul) (p < 0.005), whereas control group expressed minimal expression. COX2 was expressed more in Barrett’s (mean value of 187.5 ng/ul). When comparing these results with H pylori status, COX2 expression was greater in oesophageal biopsies for both reflux and Barrett’s in H pylori +ve (370 ng/ul, and 450 ng/ul, respectively) than H pylori –ve patients (237 ng/ul and 392 ng/ul, repsectively). In H pylori +ve patients COX2 was expressed at a greater level in the oesophageal biopsies compared with antral biopsies (450 ng/ul vs 240ng/ul), for H pylori –ve patients this trend was less marked.

DYSPHAGIA AND THE 2 WEEK RULE: A HARD ACT TO SWALLOW?

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Background: Guidelines from the DOH guarantee a specialist sees everyone with suspected cancer within 2 weeks of urgent GP referral. Symptom guidelines for suspected upper GI cancers were distributed.

Aims: To evaluate the symptom guidelines for identifying oesophageal cancer. To assess delays in the patient pathway by comparing time from urgent referral to first hospital appointment (endoscopy or outpatients), before and after the guidelines were introduced, and waiting times to first endoscopy in those with benign and malignant dysphagia.

Methods: Patients with oesophageal cancer were identified from PAS and endoscopy, for the 1 year before and after the guidelines were introduced. A sample of age/sex matched patients with benign dysphagia was identified for comparison. Case notes were reviewed.

Results: 44 subjects with oesophageal cancer were identified, 21 before and 23 after guidelines introduced. 8 had ‘curative’ surgery. Symptom guidelines would have missed 3/23 GP referrals presenting with anaemia, haematemesis and weight loss without dyspepsia. Since guidelines, referrals to endoscopy with dysphagia (excluding outpatient visits) increased from 12 to 13 per month, the percentage seen within 14 days dropping from 56 to 46%. The wait to first endoscopy has increased from 13 days range 1–73 to 120 days (range 2–120). Non-urgent referrals with cancer also showed an increase in wait to first consultation from mean 27 (4–50) to 36 days (23–46), the percentage seen within 14 days rising from 50 to 64%. The wait to first endoscopy has increased from mean 27 (4–50) to 65 (3–107) days. Waiting times have also increased for benign dysphagia.

Conclusions: Identifying delays in the patient pathway may improve the service to patients. However, introducing the 2 week rule is unlikely to have a significant effect on outcome, and may delay diagnosis in those with early, asymptomatic disease, who are not referred urgently.

SALIVARY FLOW RATE AND BUFFERING CAPACITY: A COMPARISON BETWEEN PATIENTS WITH REFLUX SYMPTOMS AND CONTROLS

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Introduction: Heartburn and regurgitation are known to be reliable indicators of gastro-oesophageal reflux (GOR). Saliva has been shown to prevent GOR damage, by diluting and buffering the gastric acid and also by initiating primary peristalsis. The aim was to assess salivary flow rate and buffering capacity of stimulated saliva in patients complaining of GOR symptoms compared with a group of controls without GOR symptoms.

Method: 47 patients (mean age 44) referred with GORD symptoms and 30 age matched controls (mean age 41) were studied. Patients voided stools were scored for 4 h. Saliva was stimulated by chewing a piece of paraffin wax. Salivary flow rate was calculated as time taken to collect 3 ml of saliva. The salivary buffering capacity was assessed by mixing 1 ml of saliva with a standard buffer solution to analyse the final pH. All saliva was collected mid-morning. All patients then proceeded to have manometry and ambulatory 24 h pH tests.

Results: 57.6% of patients were diagnosed with reflux disease. 65.9% had symptoms associated with reflux and 56% had a symptom index [percentage of symptom associated with reflux] > 50%. The median and range for saliva buffering capacity were significantly lower for patients than controls (p = 0.0004). There was no significant difference in the salivary flow rate between patients and controls.

Conclusions: Pathological reflux and symptoms associated with GORD were common in this group of patients. The causes of GORD disease and symptoms are multifactorial, however, the poor buffering
capacity of saliva may be one of the important factors for the presence of GOR symptoms and disease.

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#### NEOENDOCRINE TUMOURS OF GUT, LIVER, AND PANCREAS: OVERALL SURVIVAL IN A LARGE COHORT

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**Introduction:** Neuroendocrine tumours constitute a heterogeneous group of neoplasms, which originate from neuroendocrine cells in the gut, pancreatic islet cells, respiratory epithelium, thyroid, and pituitary glands. They are rare tumours, hence series tend to be small from individual centres. These are slow growing tumours for which many expensive therapies exist. It is important to assess background survival rates to compare to treated groups.

**Aim:** To determine the 3, 5, and 10 year survival in all the patients followed up in the carcinoid clinics at King’s College and North Hampshire Hospitals.

**Method:** We carried out a retrospective analysis of the notes and computer database of the carcinoid and neuroendocrine tumour clinics at both hospitals.

**Results:** There were 212 patients on the database. 49 were excluded due to incomplete data. 163 were analysed with an average age of 54.61 years. There were 79 (48.5%) male and 84 (51.5%) female. There were 19 (11.7%) pancreatic islet cell neuroendoctrine tumours, 7 (4.3%) fore gut, 66 (40.5%) midgut, 3 (1.8%) hindgut, 9 (5.5%) lung, 52 (31.9%) unknown primary, and 7 (4.3%) pancreatic islet cell neuroendocrine tumours, 7 (4.3%) fore gut, 66 (40.5%) midgut, 3 (1.8%) hindgut, 9 (5.5%) lung, 52 (31.9%) unknown primary, and 7 (4.3%) unknown primary.

**Conclusion:** Neuroendocrine tumours have a good overall prognosis compared to other gastrointestinal malignancies. Those with lung and midgut primaries showed the best prognosis, whereas those with an unknown primary the worst. Trials of new therapies are rarely randomised but survival data need to be compared with these figures to demonstrate efficacy.

### Abstract 140

#### THE CO-EXPRESSION OF CYTOKINES AND P-CADHERIN IN INFAMED BARRETT’S METAPLASIA

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**Introduction:** Barrett’s metaplasia is a known premalignant lesion associated with a chronic inflammatory cell infiltrate. Recently work from our and other groups have identified some of the important inflammatory cytokines expressed, but their association along the metaplasia-dysplasia-adenocarcinoma sequence has not been fully elucidated. In particular it has been shown that the pro-inflammatory cytokine tumour necrosis factor alpha (TNFα) may downregulate E-cadherin (the prime epithelial cell-cell adhesion molecule) expression with consequential effects on differentiation and migration. However, ulceration in established Barrett’s metaplasia is very rare and it has been postulated that upregulation of other cell-cell adhesion molecules may help to prevent loss of tissue integrity.

**Aim:** To assess the co-expression of cytokines and P-cadherin (the cadherin most associated with proliferating and migrating cells) along the metaplasia-dysplasia-adenocarcinoma sequence.

**Methods and Results:** We assessed expression of P-cadherin and interferon gamma (IFNγ) by routine immunocytochemistry and Western blotting on 10 patients from each of the following tissue types: normal oesophagus; reflux oesophagitis; Barrett’s metaplasia; Barrett’s dysplasia; oesophageal adenocarcinoma; lymph node adenocarcinoma. P-cadherin expression was upregulated along the metaplasia-dysplasia-adenocarcinoma sequence being expressed in predominantly proliferating cells. Similarly IFNγ was upregulated in the same tissues and was significantly correlated with P-cadherin expression. IFNγ was expressed in both the inflammatory and epithelial cells.

**Conclusions:** This data lends further support to the notion that cytokines may regulate cadherin expression in the remodelling of epithelial cells arising in the background of chronic mucosal inflammation. In addition this correlation is currently being tested in functional assays in order to assess the mechanism of cytokine regulation of cadherin transcription and translation.
and 4 h (30 min intervals) after a standard carbohydrate meal (457 kcal) in 39 patients (aged 19–52 yrs) with high P/O (studied either during the luteal phase of the menstrual cycle or while taking combined P/O oral contraception) and in 11 aged matched patients (aged 22–45 years) with low P/O levels (menses). S-HT concentration was measured by reverse-phase high performance liquid chromatography with fluorometric detection. In addition, symptomatology (0–4: 4 = severe) was assessed throughout the study.

Results: Under fasting conditions there was no difference in PDP S-HT concentration between patients with a high (5.41 ng/ml, [mean]) and low (4.98 ng/ml): difference high low (95%CI), 0.43 ng/ml (-0.69, 1.55) ng/ml; p = 0.443) P/O status. Following meal ingestion, however, patients with high P/O levels have a significantly higher PDP S-HT peak (13.99 ng/ml, [mean]) than those with low P/O (8.57 ng/ml: ratio high/low, 1.63 [1.02, 2.62]; p = 0.043). This difference was particularly evident in patients with post-prandial symptoms (patients with high P/O levels [n = 31]: 15.60 ng/ml v patients with low P/O levels [n = 11]: 8.57 ng/ml; ratio high/low, 1.82 [1.12, 2.96]; p = 0.017) and was not related to a difference in symptom severity between the two groups (patients with high P/O levels: 0.70 (mean) v low P/E levels: 0.58; difference high/low, 0.12 (-0.28, 0.53); p = 0.547).

Conclusions: Female sex hormones may play a role in the gastrointestinal tract S-HT response to a meal in female patients with dIBS.

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143 CROHN’S DISEASE AND THE NOD2 GENE: A ROLE FOR PANETH CELLS

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Background and Aims: Mutations in the NOD2 gene predisposing to Crohn’s disease (CD) are predominantly associated with terminal ileal disease. The mechanisms by which these mutations cause ileitis are unknown, as NOD2 is most highly expressed by circulating peripheral monocytes, which are ubiquitously distributed throughout the body. Paneth cells are specialised intestinal epithelial cells situated in the crypts of Lieberkühn in enteric antibacterial defences, which respond to bacterial lipopolysaccharide (LPS) through undefined pathways. They are also most numerous in the terminal ileum, and we therefore determined if Paneth cells as well as tissue macrophages in the terminal ileum expressed the NOD2 gene.

Methods: In situ hybridisation and immunohistochemistry were used to determine RNA and protein expression in tissue sections, and quantitative real time RT-PCR was used to measure gene expression in intestinal epithelial cell lines and peripheral blood mononuclear cells.

Results: Paneth cells and monocytes express NOD2 mRNA and protein in CD affected and normal terminal ileum. In Crohn’s ileitis, monocytes but not macrophages located within the lamina propria and granulomas, express NOD2 protein and RNA. Paneth cells, monocytes, and tissue macrophages also express tumour necrosis factor alpha (TNFα) mRNA in CD. In vitro, a decrease in NOD2 expression is seen in monocytes differentiating into macrophages, which respond to bacterial lipopolysaccharide (LPS) through undefined pathways. They are also most numerous in the terminal ileum, and we therefore determined if Paneth cells as well as tissue macrophages in the terminal ileum expressed the NOD2 gene.

Conclusions: NOD2 expressing Paneth cells could play a critical and hitherto unrecognised role in the pathogenesis of terminal ileal CD, while the role of the NOD2 gene in mononuclear cells probably depends critically on their differentiation state.

144 HIGHER FREQUENCY OF ZERO TPMT DEFICIENCY: A REVIEW OF TPMT REQUESTS TO A NATIONAL REFERENCE LABORATORY

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Background and Aims: Detection of a zero TPMT activity prior to commencing azathioprine (AZA) avoids the risk of severe and potentially fatal myelosuppression. Zero TPMT activity has been estimated by reverse-phase high performance liquid chromatography with fluorometric detection. In addition, symptomatology (0–4: 4 = severe) was assessed throughout the study.

Methods: TPMT data were obtained from the first assay in 1990 to present. Where available, data on AZA treatment and referring centre were recorded.

Results: TPMT demand has risen exponentially since 1990. 500/year were performed in 1998 and 7500 so far in 2002. Requests from gastroenterologists have increased from 34% to 51% in the same period. From an analysis of 5000 consecutive requests, the frequency for zero TPMT activity was 1:210–220 (0.45%). This figure remained important cost implications for those seeking financial justification for checking TPMT prior to commencing AZA. At 1 in 220, it would cost £8800 to prevent each episode of potentially fatal myelotoxicity.

145 ASSOCIATION BETWEEN P47ψ-PSEUDOGENES AND INFLAMMATORY BOWEL DISEASE

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Chronic bowel inflammation is a feature of chronic granulomatous disease, caused by deficiency in components of the neutrophil and monocyte NADPH oxidase. NCF1, an essential component (p47ψ), is found within a region of significant linkage to inflammatory bowel disease (IBD) on chromosome 7. We hypothesised that NCF1 haplo-insufficiency was a susceptibility factor for IBD. We adapted a Genesearch method to identify NCF1 heterozygotes, who were expected to have a high p47ψ pseudogene (νNCF1) to NCF1 ratio (ΔGT:GTGT), in 138 patients with IBD and 37 controls. We were surprised to find an excess of IBD patients with a ΔGT:GTGT ratio of approximately 1:1, which was greater in CD patients (CD 22.4%; control 8.1%; Fisher’s exact test p < 0.05, odds ratio 3.3), than in those with ulcerative colitis (UC) (UC 14.1%; p = 0.28). Co-incidentally1, it has been shown that a 1:1 ratio occurs following DNA exchange by recombination or conceivably gene conversion between NCF1 and νNCF1, to produce a gene hybrid (Type II νNCF1). The presence of Type II νNCF1 means that the ΔGT:GTGT ratio cannot be used to assess NCF1 heterozygosity, so we were unable to confirm our original hypothesis. The functional significance of Type II νNCF1 remained unknown.

Therefore, we assessed the effect of the ΔGT:GTGT ratio on cellular inflammatory responses in an active inflammatory colonic biopsy. In patients with a ratio < 1.2 (n = 10; 5 CD, 3 normal subjects), there was a significant increase in blister cell number compared to those patients with a ratio > 1.2 (n = 62; 28 CD, 26 normal subjects), comprising 5.6+/−1.5 χ104/ml respectively (Mann-Whitney test p = 0.03). This applied to both neutrophils (p = 0.06) and macrophages (p = 0.19), which were quantified in 46 subjects, including 8 with a ratio < 1.2. It is therefore conceivable that the presence of Type II νNCF1 increases the inflammatory response and so predisposes to IBD, particularly CD.


146 CHARACTERISATION OF MUCOSAL ADDRESSIN CELL ADHESION MOLECULE (MADCAM-1) IN INFLAMMATORY BOWEL DISEASE

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Introduction: MADCAM-1 is an endothelial cell adhesion glycoprotein that regulates α4β7 lymphocyte trafficking. It is upregulated in active inflammatory bowel disease (IBD). No satisfactory in vitro models of MADCAM-1 expression have been described. In vitro, brain endothelium (bEnd3) is reported to express MADCAM-1 in response to cytokines. In this study, we used a mouse lymph node endothelial cell line (SVEC4–10), which expresses functional levels of MADCAM-1 in response to TNF-α and is a more realistic model of high endothelial venules.

Methods: Cells were exposed to TNF-α (20 ng/ml) for 0–72 h and incubated with anti-MADCAM-1 antibody, followed by FITC anti-Rat.
IgG. For quantification of fluorescence, 5 fields were selected for each time point and imaged using a Nikon Coolpix 990 digital camera. Using imaging software the total amount of fluorescence was measured for each time point. Mean values were calculated for each time point.

**Results:** Unstimulated SVEC cells exhibited no staining. After TNF-α there was a marked increase in MADCAM-1 immunostaining especially at cell junctions. Surface expression of MADCAM-1 increased to 48 h and remained elevated at 72 h. Quantification of fluorescence revealed that MADCAM-1 expression was increased by 74% (9 h), 187% (23 h), 434% (48 h) and 505% (72 h). The elevation of MADCAM-1 at 24 h was confirmed using microwell plate immunofluorescence of cultured SVEC cells. TNF-α treated cells expressed a 326% increase in MADCAM-1 compared with unstimulated cells. MADCAM-1 expression in normal and inflamed tissues of the gut was also characterised using immunostaining and RT PCR, showing upregulation in active IBD.

**Conclusion:** Our studies demonstrate that MADCAM-1 is upregulated by TNF-α on SVEC 4–10 cells and in inflamed gut tissues. This will provide the basis for investigating the expression and modulation of MADCAM-1 both in vitro and in human disease.

**147** TWO WEEK REFERRALS FOR COLORECTAL CANCER: DOES IT DELAY FINAL DIAGNOSIS?

S. Chaudhri, E. Reay, S. Nair, L. Jones, A. Nath, S. Gonsalves, H. Houg, A.F. Horgan [introduced by N. Thompson]. Department of Colorectal Surgery, Freeman Hospital, Newcastle-upon-Tyne

The two week cancer referral rule was introduced to minimise the delay in diagnosis of cancers and introduce a fast track pathway for management of these patients. It has had significant implications for colorectal surgical practice leading to increased pressure on clinic and endoscopy lists. All patients referred with symptoms suggestive of colorectal cancer over a 6 month period were studied. Patients were seen at the outpatient clinic, flexible sigmoidoscopy clinic, or a direct access rectal bleeding clinic (DARC). In addition all referrals sent via OPD and 97% underwent complete colonic investigation. Colorectal cancer was diagnosed in 6% of these patients, and all but one cancer would have been within range of a flexible sigmoidoscope. The cancer pick up rate was 6% and median time to histological diagnosis of cancer was 63 days (range 34–155). Referrals to the DARC (210) during this 6 month period led to a diagnosis of CRC in 4.8%, with a median time to diagnosis of [x] days. Of 100 patients with colorectal cancer, 90% would have met the eligibility criteria for 14 day referral. Despite compliance with the two week rule, the diagnosis of colorectal cancer in this group of patients is delayed, and the comparison of patients where referral are made directly to flexible sigmoidoscopy clinics. Given that 97% of these patients require complete visualisation of their colon it may be more appropriate to reorganise colorectal services so as to enable a greater number of patients to be assessed directly by means of endoscopic examination.

**148** MUTATIONS OF THE HMSH6 GENE AS A POSSIBLE CAUSE OF HEREDITARY NONPOLYPSIS COLORECTAL CANCER

M. Ponz de Leon, A. Scarselli, P. Benatti, L. Roncucci, G. Ponti, L. Losi, M. Pedroni, F. Barghi, M. Menigatti, C. Di Gregorio. Departments of Internal Medicine and Morphological Sciences, Università di Modena e Reggio Emilia; Pathology Unit, Ospedale di Carpi (MO), Italy

The large majority of mutations causing hereditary nonpolyposis colorectal cancer (HNPPC) occurs in hMLH1 or hMSH2 genes, but recent observations have shown that other genes can be involved. The aim of this study was to evaluate the role of hMSH6 gene in HNPPC, through an immunohistochemical approach. 28 colorectal cancer patients with clinical diagnosis of HNPPC or suspected HNPPC were selected. Immunohistochemical studies of hMSH6, hMLH1, and hMSH2 were carried out in paraffin embedded tumour samples. Immunoperoxidase staining was carried out with the NEX, Automatic System. Monoclonal antibodies to hMLH1 and hMSH2 proteins were used at 1:40 dilution; monoclonal antibody to hMSH6 protein was used at 1:2000 dilution. Each tumour sample was tested for microsatellite instability (MSI). Immunohistochemical expression of hMSH6 locked in 7 of 28 tumours. In 4 cases, absence of hMSH6 expression was associated. The patients (mean age 56.6 years) were all affected by right-sided colon cancer, frequently mucinous and MSI+. Three patients were from HNPPC families fulfilling Amsterdam Criteria I or II. In 2 cases Muir-Torre syndrome (MTS) could be diagnosed, whereas the other 2 were suspected HNPPC. In almost all the pedigrees, an excess of extracolonic tumours was observed: interestingly, in both MTS patients, colorectal cancers and sebaceous dermatologic lesions showed the same immunohistochemical pattern. The complete gene sequencing was carried out in 3 of 7 patients: two hMSH6 and one hMLH1 frameshift mutations leading to stop codon with a truncated protein were detected. In conclusion, hMSH6 mutations could characterise a subset of families with hereditary colorectal cancer. Altered hMSH6 expression (even if often associated with lack of hMSH2 protein), MSH6 proximal localisation, later age at diagnosis, and the association with extracolonic tumours, seem to be features of suspicion for the presence of hMSH6 mutations.

**149** 2300 WEEKS OF HOME PARENTERAL NUTRITION IN A DISTRICT GENERAL HOSPITAL

D.A. Freshwater, A. Saadeddin, B.J.M. Jones. Dudley Group of Hospitals NHS Trust

Background: Home Parenteral Nutrition (HPN) is accepted in the treatment of intestinal failure but is mostly restricted to a few large specialist centres in the UK.

**Methods:** Adult HPN patients at a single district general hospital (Dudley Group of Hospitals NHS Trust) were analysed by indications, complications and outcome.

**Results:** 2310 patient weeks of HPN were provided to 23 patients, aged 18–80 years with intestinal failure (Crohn’s disease 8, small bowel infarction 5, other GI disease 3, radiation enteritis 2, colonic inflammatory bowel disease 2, diverticulitis 1, ulcerative colitis 1, pseudo-obstruction 1, gastric cancer 1, volvulus 1) N.B. some patients had more than one underlying diagnosis. 28% were subsequently able to discontinue HPN. 46% of patients died while on HPN but cause of death was not related to HPN. 82% had a Karnsky Index of 60 (generally self-caring) or greater. HPN complications for 22 of the 23 patients were 14 confirmed line infections with a total of 33 suspected infections being recorded, 10 line occlusions and 6 line breakages. There was a proven catheter sepsis rate of 1 catheter sepsis per 3.17 years with an overall suspected catheter sepsis rate of 1 suspected infection per 1.35 patient years. The overall proven line complication rate was 1 complication per 1.48 patient years. One patient was excluded from complication analysis as he was unable to grasp esophageal techniques.

**Conclusions:** HPN can be practised at DGH level achieving complication rates broadly comparable to large specialist centres, and this lends weight to the argument of using a “hub and spoke” model to widen provision of HPN beyond large specialist centres.

**Oesophagus posters 150–175**

**150** A NEW CONCEPT: FUNCTIONAL OESOPHAGEAL MAPPING

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**Introduction:** Advances in computer software and acquired image quality have meant that new and more sensitive means of interpreting scintigraphic data are possible. Described here is the creation of a three dimensional construction of the function of the oesophagus throughout its length, with time as the fourth variable. This is not an anatomical model. It provides a visual image indicating the site of hold up or delayed transit over the length of the oesophagus and is quantifiable—ie the ratio of the diameter of the cylinder in two scans reflects the change in rate of transit.

**Methods:** The distance travelled by the mode of the scintigraphic count on each acquisition frame is measured by density analysis. This is performed using software. Images from the density analysis programme from the NIH. This series is then plotted against time to produce a curve. An equation for the graph can be generated by computer. The differential of this curve gives its gradient and this, superimposed along the length of a cylinder, gives a functional map of the oesophagus. The model shown is a normal subject with physiological holdup at the striated/smooth muscle junction.
PREVALENCE OF NOVEL MECHANISM OF NITROSATIVE STRESS FROM LENGTH OF BARRETT'S OESOPHAGUS SEGMENT

Aim of work: To evaluate the prevalence of this virulence factor in patients with oesophagitis and Barrett's oesophagus.

Method: 67 patients with reflux oesophagitis, 60 patients with Barrett's oesophagus, and 25 non reflux patients (control group) underwent upper GIT endoscopy. 4 biopsies were taken from each patient, 2 from the oesophagus, 1 from the stomach, and 1 from the antrum. Clo test, ELISA for Hp IgG, Western Blot for Cag, Vac, and HSP 60 of Hp, and histopathological grading of the severity, was performed on each patient.

Results: 22 of the GORD group and 18 of Barrett's patients were Clo positive, of which 87% of GORD patients and 57% of Barrett's patients were positive for Cag, Vac, and HSP 60. HSP 60 was +ve in 23(38%) of the Barrett's patients. The non reflux group (control group) were all Cag, Vac, and HSP 60 negative. When combining the histological grading and serological tests, patients were divided into active, past or never, according to their status of Hp infection. 22 of the GORD group and 18 of Barrett's patients were actively infected, of which 87% of GORD patients and 57% of Barrett's patients were positive for Cag, Vac, and HSP 60.

Conclusion: The risk of both overall and incident cancers is greater for SSB than for segments <3 cm in length, but the greatest risk is for length >6cm (Pearson χ² p=0.02). Whilst demographic factors have previously shown an influence on the risks of developing BO, there is little correlation with the length of segment which develops.

NOVEL MECHANISM OF NITROSATIVE STRESS FROM DIELTARY NITRATE RELEVANT TO GASTROESOPHAGEAL JUNCTION CANCER

Aims: To determine whether nitric oxide generated in the above way will exert nitrosative stress on the adjacent epithelium.

Methods: A benchtop model was constructed reproducing the chemistry occurring at the GO junction and incorporating an epithelial compartment maintained at pH 7.4 separated from the lumen by a thin hydrophobic barrier. The secondary amine morpholine was added to each compartment and Nnitrosomorpholine formation at 15 min measured.

Results: Adding 100µM nitrite to the acidic compartment in the absence of ascorbic acid generated 2.2±0.1µM N-nitrosomorpholine in that compartment and 2.2±0.1µM in the epithelial compartment. When 100µM nitrite was added to the acidic compartment (pH 1.5) containing ascorbic acid, all the nitrite was immediately converted to nitric oxide and no N-nitrosomorpholine was formed within that compartment. However, the nitric oxide rapidly diffused into the adjacent epithelial compartment (pH 7.4) where it generated very high concentrations of eradication treatment. 80% of control patients were Hp negative. In the Hp positive group, the virulent strains, in particular HSP 60, seem to predominate and appear to be associated with dysplasia.

CONCLUSIONS

The risk of both overall and incident cancers is greater for SSB than for segments <3 cm in length, but the greatest risk is for length >6cm (Pearson χ² p=0.02). Whilst demographic factors have previously shown an influence on the risks of developing BO, there is little correlation with the length of segment which develops.

The novel mechanism of nitrosative stress from dietary nitrate relevant to gastroesophageal junction cancer was demonstrated in a benchtop model.
The advantages of high resolution oesophageal manometry (HRM) in clinical practice

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Background: Conventional manometry (CM) with 5–8 oesophageal pressure channels and a lower oesophageal sphincter (LOS) sleeve sensor is limited by poor resolution. HRM techniques with 21–32 pressure channels may increase diagnostic accuracy.

Aim: To analyse quantitatively whether HRM improves the assessment of motility compared to CM, and to determine qualitatively the situations in which HRM provides clinically important information not obtained by conventional investigation including CM.

Method: Control subjects and patients with dysphagia underwent HRM. 93 records were reviewed independently by two blinded physicians using both limited CM (pull-through plus 6 recording sites) and HRM analysis (all 32 sites). Further HRM records from dysphagic patients with non-diagnostic endoscopy and radiology were compared to the limited CM analysis to identify the additional information leading to positive diagnosis provided by HRM.

Findings: Receiver-operating curve (ROC) analysis revealed for HRM at a sensitivity level of 90% a specificity of 100%, whereas for CM a specificity of 89% was associated with a sensitivity of 70%. Qualitative analysis demonstrated that HRM provided positive diagnoses in cases where conventional tests including CM were non-diagnostic. Advantages included: (i) detection of localised disturbances of peristalsis (eg sub-mucosal leiomyoma); (ii) ability to locate and follow LOS movement during oesophageal spasm without loss of detail (eg vigorous achalasia with pseudo-relaxation); and (iii) detailed analyses of LOS pressure topography (eg dysfunction post-fundoplication).

Conclusion: HRM is more accurate than CM and identifies clinically important peristaltic and LOS dysfunction not detected by conventional investigations including CM.

Expression of the CDX2 homeobox protein in Barrett’s metaplasia (BM)

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Background: CDX2 is an intestinal transcription factor that is a key regulator of development and homeostasis of intestinal epithelium. In the adult, CDX2 expression is confined to the small and large intestine. Neo-expression occurs in gastric intestinal metaplasia and ectopic gastric expression of CDX2 leads to an intestinalised mucosa in transgenic mice. Preliminary reports suggest that CDX2 is expressed in BM. We aimed to examine CDX2 expression within various histological sub-types of BM and during malignant progression.

Method: With informed consent, 68 oesophageal surveillance biopsies from 52 patients with BM were studied. Formalin-fixed, paraffin-embedded sections were subject to immunohistochemistry using an anti-CDX2 mAb (BioGenex) and an automated avidin-biotin-based system. Control sections comprised normal colon and duodenum. Both H&E and mucin staining (Gomori’s aldehyde fuschin) were employed in serial sections to identify and type foci of metaplastic epithelium. Nuclear immunostaining was scored semi-quantitatively (0-absent; 1-locally absent or weak; 2-strongly positive). We also screened confluent TET7 cells (oesophageal adenocarcinoma) for CDX2 expression by immunoblotting of cell lysates (CAGCO-2 cells were employed as positive control).

Results: All examples of squamous mucosa, cardiac/fundic-type glands and deep oesophageal glands were negative for CDX2 expression. Staining intensity within intestinal-type mucosa and dysplasia is shown in the table. No CDX2 expression was identified in immunoblots of TET7 adenocarcinoma cells.

Conclusions: Neo-expression of CDX2 is almost invariably in SIM but does not occur in gastric-type variants of Barrett’s oesophagus. Down-regulation of CDX2 may occur during oesophageal malignant progression, consistent with a tumour suppressor function. The molecular mechanisms regulating CDX2 expression during oesophageal carcinogenesis require further study.

Quality of Life Assessment in Patients Undergoing Endoscopic Mucosal Ablation for Dysplastic Barrett’s Oesophagus

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Background: A number of thermal and non-thermal modalities have been applied in an effort to eradicate dysplasia and reverse the Barrett’s epithelium. Quality of life (QOL) assessment is an important outcome measure, since these interventions result in procedure related morbidity.

Aim: To assess QOL measurement in a cohort of patients with dysplastic Barrett’s oesophagus undergoing two different endoscopic mucosal ablation modalities as part of a randomised clinical trial.

Methods: Twenty-nine patients with dysplastic Barrett’s oesophagus underwent mucosal ablation. Photodynamic therapy (PDT) with Photofrin was performed in one session-13 patients and Argon Plasma Coagulation (APC) was performed in 1-6 (mean 3) sessions-16 patients. Treatment and disease specific QOL questionnaire was constructed based on previous validated Gastrointestinal QOL tool. A 10-item questionnaire was constructed with 5 responses in each question. Most desirable option: 5 points, and least desirable option: 1 point (maximum: 50, minimum: 10). Patients were asked to fill the questionnaire immediately before the procedure and 2 weeks after the procedure (in the case of APC after the first session). The scores before and after treatment were compared using the paired t-test and the difference between the two treatment groups was analysed using the unpaired t-test.

Results: All but 3 patients in the APC group completed the study. In the APC group the mean pretreatment QOL score was 4.5 and post-treatment QOL score was 39, p=0.0002 (95% CI 3.54–8.76). In the APC group the mean pre-treatment score was 39 and post-treatment score was 33, p=0.0008 (95% CI 2.80–8.27). There was no significant difference in QOL pre and posttreatment between the two groups.

Conclusion: QOL is significantly affected in patients undergoing endoscopic mucosal ablation therapy for at least 2 weeks following the procedure. Future studies comparing various endoscopic mucosal ablation modalities should assess QOL as well, when comparing the outcomes of the endoscopic intervention.
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<th>Atkinson (n=68)</th>
<th>SEMS (n=52)</th>
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<tr>
<td>M.F. ratio</td>
<td>2.81</td>
<td>1.71</td>
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<td>Mean age (SE) years</td>
<td>76.5 (1.1)</td>
<td>76.2 (1.4)</td>
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<tr>
<td>Mean dysphagia score improvement</td>
<td>1.3</td>
<td>1.5</td>
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<tr>
<td>Immediate complication rate</td>
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<td>Delayed complication rate</td>
<td>33.8%</td>
<td>25%</td>
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<tr>
<td>Recurrent dysphagia</td>
<td>8 (11.8%)</td>
<td>2 (3.8%)</td>
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<tr>
<td>Tumour ingrowth/overgrowth</td>
<td>0%</td>
<td>4 (7.6%)</td>
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<tr>
<td>Replacement rate</td>
<td>17.6%</td>
<td>4.2%</td>
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<tr>
<td>Immediate mortality (%)</td>
<td>1 (0.8%)</td>
<td>0%</td>
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<tr>
<td>Mean survival weeks (SE)</td>
<td>23.3 (3.2)</td>
<td>17.2 (2.8%)</td>
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Efficacy and Safety of Palliative Stenting for Malignant Dysphagia: A Review of 120 Patients

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Background: Oesophageal carcinoma is a largely incurable disease. The main aim of palliation is to restore oesophageal patency. Current oesophageal endoprostheses comprise semirigid plastic stents and self-expandable metal stents (SEMS). In recent years, prospective randomised controlled trials have demonstrated a higher efficacy and a lower complication and mortality rate (0 v 15.8%) for SEMS v plastic stents.

Aims: We reviewed our experience with the efficacy, safety and complications with stents placed for palliation of malignant dysphagia.

Materials and Methods: The case notes of all patients that had a stent inserted between 1985 and 2002 were reviewed. Data including demographics, type of stent, dysphagia score prior to and after implantation of stent, complications and survival were recorded on a database.

Results: A total of 120 stents were implanted during the study period. We used the conventional Atkinson plastic prosthesis and four different types of SEMS: Z-stent (N=22), In-stent (N=21), Uncovered wall stent (N=5) and Choo stent (N=4). Complications were divided into immediate (<1 week) and delayed (>1 week), following stent insertion. Immediate complications for all stents in our series included chest pain – 1 (0.8%), failure to deploy stent – 1 (0.8%), perforation – 8 (6.7%), stent displacement – 4 (3.3%) and death – 1 (0.8%), resulting from the procedure. Delayed complications for all stents included stent displacement – 10 (8.3%), recurrent dysphagia – 10 (8.3%), food impaction – 3 (2.5%), broncho-oesophageal fistula formation – 4 (3.3%), bleeding – 5 (4.2%) and tumour ingrowth/overgrowth – 4 (3.3%).

Conclusions: Both immediate and delayed complication rates were higher in the plastic endoprostheses group. The complication rates are similar to previously reported series. In conclusion, SEMS, are a safer and efficacious mode of palliation for oesophageal carcinoma. However, there is no added survival benefit in this group.

158 Barrett’s Oesophagus—Is Surveillance Required?

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Introduction: Controversy exists about the utility of a screening endoscopy programme and the value of proton pump inhibitors (PPI) in preventing the progression from metaplasia to dysplasia to cancer in Barrett’s oesophagus (BO). Earlier studies to determine the risk of oesophageal adenocarcinoma in BO were conducted largely before the era of widespread usage of PPIs. We present a long term follow up study of subjects with BO, a high proportion of whom were on PPIs.

Aims and Methods: The aim was to determine the efficacy of screening to detect oesophageal cancer in patients with BO in the context of high rates of PPI usage. All cases of BO diagnosed at our hospital from 1990 to 1998 were identified from a histopathology database. Case notes were retrieved and a database prepared. Patients who died during follow up had the cause of death ascertained from the Department of Public Health, Registry of Births and Deaths and Office of National Statistics. PPI usage was recorded at each follow up visit.

Results: A total of 308 patients were identified of whom 35 patients did not have intestinal metaplasia. 19 files could not be traced. Of the 273 subjects with intestinal metaplasia, 179 (65.6%) were male. Total follow up till October 31 2000 was 1145 patient years (1110 years with the untraceable files excluded). Mean age of diagnosis was 66.7±14.1 years (range 21–94 years). 136/156 (87.2%) patients on first follow up endoscopy, 74/79 (93.7%) patients on second follow up endoscopy and 28/32 (87.5%) patients on third follow up endoscopy were on PPIs. 12 (4%) oesophageal/ cardia adenocarcinomas were detected of which 9 were detected on first follow up. 3 cases were suspicious of at initial endoscopy. One of these was confirmed as adenocarcinoma 1 month and the other two 3 months later. Two of the 11 patients had high grade dysplasia. One of these was referred for treatment and is still alive while the other died of an unrelated cancer. 84 patients died during the period of observation. Of these 10 died of oesophageal/gastric cancer.

Conclusion: In the era of PPI therapy, rate of malignant transformation is low and it questions the need for a intensive surveillance endoscopy programme.

159 When Should Antacids Be Ingested After Meals?

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Introduction: Post-prandial reflux (PPR) is a significant component of gastro-oesophageal reflux (GOR) in health and disease. PPR is generally assessed within 2 hours after meals. Various studies have attempted to modify PPR to determine the effectiveness of intervention. However, there is little documentation regarding when maximal PPR occurs. Hence, we attempted to modify PPR to determine the effectiveness of intervention.

Aims: This study examined the PPR profile of pathological GOR patients.

Patients and Methods: A sample of 55 patients (32 males, mean age 50.3 years) was chosen randomly from those with pH-documented GOR disease who had attended the unit in 2002. During 24 hr pH monitoring (Synectics), patients were advised to go about their normal activities and had their usual meals but avoiding food or drink with pH <5. GOR was defined as pH <4. The two-hour PPR periods were divided into 30 min quarters. Kruskal-Wallis and Mann-Whitney statistical tests were used.

Results: There were no significant differences in PPR comparing meals (p=0.92). However, there were significant differences in PPR quarters for each meal (p<0.03). The greatest acid exposure after breakfast was in the 2nd quarter, which was significantly higher than the 1st (p=0.003) and the 4th quarters (p=0.002). After lunch and dinner, the highest GOR occurred in the 3rd quarter, which in both was significantly higher than the 1st quarter (p=0.03) only.

Conclusion: PPR is a major source of GOR and in this group of patients up to 74.4% of the postprandial period demonstrated acid exposure. Maximal PPR occurs in the 2nd or 3rd quarter of the postprandial period. For maximal effect patients with pathological GOR should ingest antacids half an hour after meals.

Abstract 159 PPR per Meals per Quarters (q)

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<tr>
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<th>Breakfast PPR</th>
<th>Lunch PPR</th>
<th>Dinner PPR</th>
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<tr>
<td>Median (range)%</td>
<td>19.9 (0–72.6)</td>
<td>17.3 (1–58.6)</td>
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<tr>
<td>1q 2q 3q 4q</td>
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<td>7.4 21.3 18.5 5.6</td>
<td>4.7 16.5 21.6</td>
<td>12.2 6.9 13.7 23.7 14.9</td>
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COST-EFFECTIVENESS ANALYSIS OF PROTON PUMP INHIBITOR STRATEGIES IN THE MAINTENANCE OF HEALED REFLUX OESOPHAGITIS

J.M. Plumb, S.J. Edwards (introduced by P.D.I. Richardson). AstraZeneca UK Ltd, 600 Capability Green, Luton LU1 3LU, UK

Objective: To assess the cost-effectiveness of combined high and low dose PPI strategies using UK licensed dose for the maintenance of healed reflux oesophagitis over 12 months from the perspective of the UK NHS.

Methods: A decision analysis model was constructed to depict the sequential management of the maintenance of healed reflux oesophagitis, based on a systematic review of remission rate data at 6 and 12 months. Patients relapsing at 6 months followed a healing strategy identified in a survey of UK general practitioners and gastroenterologists. Treatment strategies, in terms of high and low dose PPIs prescribed, were based on UK prescribing patterns. Resource units were multiplied by national published resource unit costs at 2000/01 prices. Sensitivity analyses were conducted to assess the robustness of the model.

Outcome Measure: The measure of clinical effectiveness was, "the proportion of patients relapse-free for 12 months". Relapse was defined as endoscopic evidence of oesophagitis and/or symptomatic relapse.

Results: Esomeprazole dominates all other PPI strategies (ie it is more effective and less costly). In terms of cost alone, the mean cost per patient treated for the esomeprazole strategy is numerically less than the lansoprazole strategy but would be considered cost-neutral (£276.61 v £279.98). However, the additional effectiveness of the esomeprazole strategy compared to the lansoprazole strategy (0.763 v 0.738) results in a lower mean cost per relapse-free patient for 12 months (£362.53 v £379.38). A sensitivity analysis indicated that the results were relatively robust to changes in key model parameters.

Conclusion: Esomeprazole is the most cost-effective strategy for the maintenance of healed reflux oesophagitis over 12 months.

IMPAIRMENT OF TGFβ SIGNALLING IN BARRETT’S ASSOCIATED OESOPHAGEAL ADENOCARCINOMA: ROLE OF SMAD4

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Introduction: The accumulation of somatic mutations during the Barrett’s metaplasia-dysplasia-adenocarcinoma sequence leads to uncontrolled epithelial cell proliferation. Since transforming growth factor β (TGFβ) is a potent anti-proliferative agent, and signalling mutations frequently occur in gastrointestinal malignancies, we hypothesise that alterations in this pathway may be important in oesophageal adenocarcinoma development.

Methods: Western blot, RT-PCR and immunohistochemistry were used to analyse the expression of TGFβ receptors I and II, and Smad2, 3 and 4 in oesophageal samples from normal squamous mucosa (n=20), Barrett’s oesophagus (BE) without dysplasia (n=20), BE with low-grade dysplasia (n=10), BE with high-grade dysplasia (n=10) and BE adenocarcinoma (n=20). TGFβ responsiveness, TGFβ receptor and Smad expression of a panel of oesophageal cell lines were also determined, and mutational analysis was performed by PCR and sequenc-
ing.

Results: There was a significant decrease in the mRNA expression of Smad2 (p<0.001), Smad3 (p<0.001) and Smad4 (p<0.002) in BE samples, and in high-grade dysplasia samples (Smad2 p=0.001; Smad3 p=0.01; Smad4 p=0.001) when compared to squamous epithelium. Smad4 mRNA was also significantly decreased in adenocarcinoma samples compared to squamous epithelium (p<0.05). A shift in protein mobility was seen for Smad4 in 25% of adenocarcinoma samples analysed by Western blot. OE21 cells (squamous carcinomas), OE33 and SEG-1 (BE adenocarcinoma) were responsive to TGFβ. BIC-1 and TE7 (BE adenocarcinoma) were unresponsive to TGFβ, as were KYSE-30 (squamous carcinoma). BIC-1 did not express Smad4 mRNA and protein, due to a base pair substitution in exon 9 of the Smad4 gene. TGFβ receptor and Smad mRNA and protein were expressed in these cells, and no mutations could be identified in exon 3, 5, or 7 of the Tjir1 gene.

Conclusion: The TGFβ signalling pathway is impaired in Barrett’s associated adenocarcinoma and the alteration of Smad4 expression may be an important factor in neoplastic progression.

IMMEDIATE AND EARLY GENE RESPONSE TO IN VITRO ACID EXPOSURE IN A BARRETT’S ADENOCARCINOMA CELL LINE

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Introduction: Acid, a principal component of refluxate, may contribute to the neoplastic progression of Barrett’s oesophagus. Previously published data have demonstrated that brief acid exposure in vivo and in vitro increases cell proliferation. The mechanisms underlying the hyperproliferative response are not well elucidated but may include alterations in Na+/H+ exchanger activity and MAPK signalling pathways.

Aim: To ascertain the effects of acid exposure on gene expression in a Barrett’s adenocarcinoma cell line (SEG-1) using expression micro arrays and RT-PCR.

Methods: SEG-1 cells were grown to 60% confluency and exposed to either acidified DMEM at pH 3.5 (0.1M HCl) or pH 7.4 (control) for 30 min. Changes in gene expression were determined by microarray analysis and real-time RT-PCR.

Conclusions: In response to acid exposure, SEG-1 cells exhibited significant changes in the expression of multiple genes, including those involved in cell cycle regulation, inflammation, and epithelial-mesenchymal transition. These findings suggest that acid exposure may contribute to the dysregulation of gene expression in Barrett’s adenocarcinoma cells, potentially facilitating neoplastic progression.
20 minutes followed by neutralisation of the medium for up to 10 hours. Total RNA was extracted before acid exposure and over a 10 hour time course (0.5, 2, 4, 6, 8, and 10h) and hybridised to an Affymetrix human U133A oligonucleotide array. Data were analysed using the Affymetrix statistical expression algorithms. Only alterations in gene expression >2, <2 were taken as significant and a subset of interest were validated by RTPCR.

Results: An up-regulation of genes associated with proliferation (PCNA, FGF3 and VEGFC) and a down-regulation of genes associated with apoptosis (caspase-9, GADD45A) were shown throughout all time points. DGAT2 and S6, which are involved in the inactivation of the MAPK pathway were down regulated throughout the time course. At specific time points the following cell cycle regulatory genes were significantly altered: E2F (up at 0.5h), Rb binding protein 2 homolog 1 (up at 0.5, 2h), Cyclin E2 (up at 2, 6, 8h) Cyclin E1 (up at 4, 6h) and Cyclins D1 and A1 (up at 8h). Cyclo-oxygenases were unaffected.

Conclusion: Suppression of apoptosis via the p53 pathway, stimulation of proliferation via the MAPK pathway and alterations in cell cycle components may be involved in the proliferative response to an acid pulse. This study provides candidate genes for further studies on cell responses to acid.

164 OPTIMISATION OF AN ENDOSCOPIC BIOPSY PROTOCOL IN LONG SEGMENT BARRET’S OESOPHAGUS: EVIDENCE FROM 125 CONSECUTIVE CASES

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Background: Intestinal Metaplasia within a Columnar Lined Oesophagus (Barrett’s Oesophagus) is believed to be pre-malignant. At present it is not clear how best to diagnose this condition reliably when encountered at endoscopy.

Objectives: We aimed to assess the frequency and distribution of intestinal metaplasia in 125 consecutive patients with endoscopically observed long segment Barrett’s metaplasia to determine the optimal protocol for OGD and biopsy. In addition we assessed whether additional PAS histological staining would improve the diagnostic yield.

Methods: A total of 1646 individual biopsies from 296 endoscopies performed on 125 patients were examined.

Results: Intestinal metaplasia was demonstrated in 80/125 (64%) patients and 150/296 (51%) biopsies, although only 557/1646 (34%) individual biopsies contained foci of intestinal metaplasia. Of 296 endoscopies, 166 contained cardiac mucosa, 158 fundic mucosa, 64 glandular mucosa of no special type and 111 squamous mucosa. The highest rate of intestinal metaplasia detection occurred when 8 biopsies per endoscopy were taken. However, there was a notable increase in the pick-up rate of intestinal metaplasia moving from 4 biopsies per endoscopy to 5 biopsies per endoscopy. Performing multiple biopsies for individual patients resulted in a modest increase in detection of intestinal metaplasia, with no new cases of intestinal metaplasia being diagnosed after the third endoscopy. While PAS staining identified only an extra 5.4% of new biopsies per endoscopy it reliably determined if a patient has intestinal metaplasia.

Conclusions: We recommend taking between 5 and 8 biopsies per endoscopy to reliably determine if a patient has intestinal metaplasia. Conventional H&E staining seems to be the mainstay of diagnosis.

165 ENDOSCOPIC DILATATION OF OESOPHAGEAL STRUCTURES IN EPIDEMIOLYSIS BULLOSA

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Background: Epidermolysis bullosa (EB) is a rare inherited disorder of the stratified squamous epithelium, characterised by blistering and scarring following minor trauma. Patients with the most severe forms, particularly dystrophic EB, develop buccal, inflammation, and scarring of the oesophagus following the ingestion of solid food. This results in dysphagia in the first two decades of life, severely compromising the ability to eat. There is no specific medical treatment for the disease and maintaining an adequate nutritional intake is often a central aim.

Methods: We report the results of 53 adults and children with EB and oesophageal strictures who were treated with endoscopic balloon dilatation. The procedure was performed using propofol anaesthesia and “through the scope” balloons.

Results: The median age at the time of index endoscopy was 16 years (range 3 to 61 years). A median of 2 barium studies (range 0 to 16) were performed per patient, identifying strictures at a median of 20 cm from the incisors (range 15 to 29 cm). 75% of patients had a single stricture (median = 1, range 1 to 6 strictures). Recurrent strictures tended to occur in the same position. The total number of dilatations performed was 182—the median number of dilatations per patient was 2, over a mean follow up period of 3.5 years. The median interval between dilatations was 18 months. The median balloon size used was 45 Fr (range 42–56 Fr). All but three patients had an improvement in the dysphagia score. The median change in weight following the procedure was an increase of 2.6 kg (p<0.0001) over a median 29 days. Apart from self-limiting odynophagia in 3 patients, there were no other post-procedural complications and no oesophageal perforations.

Conclusion: Endoscopic balloon dilatation is a safe and effective treatment for the oesophageal strictures of EB, producing a long-term relief of dysphagia and an improvement in the nutritional status in the majority of patients.

166 HOW BEST TO ASSESS SYMPTOMATIC OUTCOMES OF THERAPY IN GASTRO-OESOPHAGEAL REFLUX DISEASE TRIALS: A SYSTEMATIC REVIEW

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Introduction: Traditionally drug trials have used oesophagitis healing as the main outcome for clinical trial success and the performance of oesophagitis scales have been well characterised. Symptoms are also an important outcome for clinical trials to measure. The optimal symptomatic measures to assess however have not been well characterised. We conducted a systematic review to assess the symptoms that have been evaluated and how well these correlate with oesophagitis healing and relapse.

Methods: The Cochrane Controlled Trials Register, Medline, EMBASE, and CINAHL electronic databases were searched for RCTs evaluating drug therapies in oesophagitis. Experts in the field and pharmaceutical companies were contacted for information on any unpublished RCTs. Articles were included on predefined eligibility and validity criteria. Data were extracted on scales used, method of collecting data, duration of assessment, individual and global symptoms assessed, and whether improvement or absence of symptoms was the main outcome measure, types of symptoms assessed, frequency and severity of symptoms. The proportion of patients with a successful outcome at the selected symptom measures was compared with the proportion of oesophagitis healed/relapsed after therapy. The results are primarily evaluated in the form of L’Abbé plots.

Results: 324 papers were evaluated and data were extractable from 143 eligible trials. L’Abbé plots suggested no or minimal symptomatic improvement correlated well with oesophagitis healing and relapse whereas symptom “improvement” overestimated treatment effects. Trials that measured symptoms over a fixed period of time correlated better with oesophagitis healing and relapse than those that did not state the time period. Heartburn was the most important symptom to measure to predict oesophagitis healing but L’Abbé plots suggested additional information may be obtained from regurgitation and dysphagia.

Conclusions: This systematic review provides a comprehensive summary of the symptom outcome measures that have been used in trials and indicates how these might be improved.

167 RISK OF EXTRA-OESOPHAGEAL MALIGNANCIES IN BARRET’S OESOPHAGUS AND IN GASTRO-OESOPHAGEAL REFLUX

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Introduction: The relationship between Barrett’s oesophagus and extra-oesophageal malignancies (EOM) has been a matter of controversy. Some researchers have pointed out that the incidence of colon cancer is higher in Barrett patients while others have found no such association. The current study explores the relationship between...
Barrett’s oesophagus and EOM in general and colon cancer in particular in 27,813 subjects in General Practice Research Database (GPRD).

**Methods:** The mean follow-up experience was about 6 years and the study subjects constitute four groups: Barrett’s oesophagus group (1677), oesophagitis group (6392), simple reflux group (6328), and normal group (13,416). Respectively the last three groups were 4/1, 4/1, and 8/1 matched to the Barrett group according to their GP practice, date of birth and sex. All malignancies occurring before or in the first year after the diagnosis of Barrett’s, oesophagitis, or reflux were regarded as prevalent and excluded from the analysis. Risk of occurrence of an unrelated condition such as cataract was also explored for comparison. Number of visits to the GP was defined as a date on which there are both medical and drug records available and its confounding effects were controlled. Hazard ratios were calculated using Cox-proportional hazard regression analysis.

**Results:** A total of 2167 EOM, 260 colorectal cancer, and 1918 cataract diagnoses were identified in study subjects of which 1119, 113, and 853 cases were excluded respectively as being prevalent. The hazard ratios have been presented in the table after adjusting for age, sex, and number of visits to the GP.

**Conclusion:** The risk of colorectal cancer was not specifically higher in any of these groups. There were small increases in risk of EOM in the Barrett’s oesophagus, oesophagitis and reflux groups in comparison to the general population. The explanation for these increases is unclear but they may be mediated by smoking if smoking rates are increased in Barrett’s.

**168 GENDER DIFFERENCES IN THE EPIDEMIOLOGY OF GORD**


**Introduction:** GORD affects up to 30% of the population, it is associated with an increased risk of oesophageal adenocarcinoma, a disease that is on the increase. Modern lifestyle has been attributed to the changing epidemiology of oesophageal cancer. We aimed to describe the epidemiology of reflux disease and its complications.

**Methods:** Consecutive consenting patients with symptoms of GORD were recruited from an endoscopy clinic. Demographic data, social habits, and symptom scoring were collected by the administration of a questionnaire, and an upper GI endoscopy was performed. Oesophagitis was graded using the LA grading system.

**Results:** 1165 subjects were recruited, 615 with no endoscopic features of oesophagitis (EN, 52.7%), 318 with evidence of erosive oesophagitis (EO 27.4%) (LA Grades A 43%, B 33%, C 16%, D 8%) and 232 with Barrett’s oesophagus (BO 19.9%). The proportion of male patients was greater in BO subjects (62.5%) than those with EO (52.3%) and EN (35.6%). When stratified for age male subjects with EN, EO, and BO were on average 5 years younger than their female counterparts (P < 0.002), and that subjects with BO were 7 years older than those subjects with EN or EO (P = 0.002), there was no statistically significant difference in age between those with EN and EO. Although males, regardless of diagnosis, on average drink more alcohol (mean 7.7 units/week, female 1.4 units per week, P = 0.001) males and females with BO do not drink more than their counterparts with EN or EO (P > 0.05). There was no difference in pack years smoked between diagnosis and gender. There was no difference in the body mass index between gender and diagnosis.

**Conclusions:** Male subjects are more likely to develop BO, and they are likely to develop the disease at an earlier age. Tobacco consumption and obesity are not associated with increased risk of developing BO. Alternatively women may have some protection against developing BO until later in life. Other factors such as diet or the nature of the refluxate may be important in the gender differences.

**169 MINI-CHROMOSOME MAINTENANCE PROTEINS PROVIDE A NOVEL METHOD FOR DETECTING PATIENTS AT RISK OF DEVELOPING ADENOCARCINOMA IN BARRETT’S OESOPHAGUS**

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**Introduction:** Oesophageal adenocarcinoma incidence is increasing rapidly. Endoscopic screening for the population at risk is not feasible and surveillance of patients with known Barrett’s oesophagus (BE) is prone to sampling bias and the subjective interpretation of dysplasia.

**Aims:** To determine whether a novel marker of cell cycle entry, mini-chromosome maintenance (MCM) protein predicted cancer risk and whether this could be used in combination with a surface sampling method.

**Methods:** Archival specimens (30 squamous oesophagus (SE), 62 BE +/- dysplasia, 16 adenocarcinoma (AC)) were stained for Mcm2. In addition, 9 patients with 3-13 years follow up who developed AC were compared with 18 controls matched for age and length of follow up who did not progress. Endoscopic cytological brushings were taken from a prospective cohort (61 SE, 90 BE +/- dysplasia and 11 AC) and scored blind as Mcm2 positive or negative.

**Results:** Correlation between Mcm2 surface expression and dysplasia (p<0.05 for biopsies and brushings).

**170 PHOTODYNAMIC THERAPY USING MTHPC FOR EARLY BARRETT’S-ASSOCIATED OESOPHAGEAL CANCERS**


**Background:** Oesophageal adenocarcinoma is rising in incidence and it is strongly associated with Barrett’s oesophagus. Oesophagectomy is the standard treatment for early carcinoma but has considerable morbidity and mortality. Photodynamic therapy (PDT) is a non-thermal minimally invasive technique for mucosal ablation. Mesotetrahydroxy-phenylchlorin (mTHPC, Foscan) is a potent photosensitizer which has been used with PDT in small series with squamous-cell oesophageal cancer.
Aims: To assess efficacy and safety of ablating high-grade dysplasia (HGD) or early oesophageal adenocarcinoma by PDT using mTHPC.

Methods: 5 patients with dysplasia (Vienna 4) within nodules and 11 with early adenocarcinoma (Vienna 5) staged by CT and EUS as T2NO or less were included: T1(6), T1/2(3), T2(2). Oesophagectomy was inappropriate because of patient refusal or co-morbid pathology. Patients were photosensitized intravenously with mTHPC (0.15mg/kg). Three days later, at endoscopy, red light (wavelength 652nm) was delivered to the tumour by bare-tipped fibre or diffuser fibre within a windowed silicone bolster. Further PDT was given within 48 hours if needed. Patients were followed up by endoscopy and multiple biopsies (1,3,6,9,12 months) and EUS (3 monthly).

Results: 16 patients have been treated since Sept 1995. One patient died before initial follow-up unrelated to PDT and is excluded from analysis. At a median follow up of 17 months (range 9–73 months) 8/11 (72.7%) cancer patients are clear of carcioma. All 4 patients with HGD are clear of dysplasia (median 15 months). There were 2 serious complications—an aorto-oesophageal fistula from which the patient died (an early case, later recognised as due to excessive light dose), and a tracheo-oesophageal fistula, successfully treated by covered oesophageal stent. Of 3 carcinomas not responding to PDT, there is no evidence of residual carcinoma after subsequent chemoradiotherapy (2) or surgery (1).

Conclusions: PDT with mTHPC offers an effective therapy for early oesophageal adenocarcinoma where surgery is not appropriate.

Bile acids: do they play a role in Barrett’s oesophagus?

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Background/Aims: The incidence of adenocarcinoma of the oesophagus has rapidly increased over the past few decades. Virtually all adenocarcinomas arise in Barrett’s oesophagus (BE), the exact aetiology of which is still unknown. There is increasing evidence that bile acids play a significant role in the pathogenesis of BE. Studies have shown that patients with BE have increased bile reflux compared to patients with uncomplicated gastro-oesophageal reflux. Effects of bile acids on oesophageal cell lines have not been previously demonstrated. Our study aimed at the evaluation of genotoxic potential of physiological concentrations of bile acids on oesophageal cell lines.

Methods: OE33 cells were purchased from ECACC (European Collection of Cell Cultures). Six different bile acids, namely Taurocholic acid (TCA), Glycocholic acid (GCA), Taurodeoxycholic acid (TDC, Glycodeoxycholic acid (GDC, Deoxycholic acid (DCA) and Cholic acid (CA) were used in near physiological concentrations ranging from 50µmol–1mmol. The Cytokinesis Blocked In-vitro (DCA) and Cholic acid (CA) were used in near physiological concentrations of bile acids on oesophageal cell lines. OE33.

Results: All the bile acids induced cytotoxicity in a dose dependent manner. The unconjugated bile acids (DCA & CA) were more cytotoxic than the conjugated bile acids (TCA, GCA, TDC, & GDC). None of the bile acids except DCA showed any significant induction of micronuclei. DCA induced a statistically significant increase in the frequency of micronucleus in comparison with normal control (42 ± 14 micronuclei/2000 cells, p=0.0029, Fisher exact test). DCA was predominantly clastogenic in action as revealed by the kinetochore labelling (66% kinetochore positive and 34% kinetochore negative). DCA also induced significant apoptosis (21 ± 3 ,500 cells, P<0.001). DCA induced apoptosis was maximum at concentrations between 100–200µmol.

Conclusion: Our studies showed that all bile acids were cytotoxic and that DCA in particular can induce DNA damage and apoptosis. Although DCA is found in a very low concentration in patients with BE, the fact that bile acids can become trapped and accumulate within mucosal cells (up to eight times the luminal concentration) makes even small concentrations significant. Our study shows that bile acids could play a major role in the development of oesophageal injury and its subsequent progression to dysplasia and oesophageal adenocarcinoma.

COX-2 expression is an indicator of poor survival in patients undergoing resection for oesophageal adenocarcinoma.

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Introduction: The clinical relevance of cox-2 overexpression in oesophageal adenocarcinoma is uncertain.

Aim: To test the hypothesis that cox-2 overexpression in oesophageal adenocarcinoma is associated with decreased patient survival.

Methods: Oesophageal resection specimens were obtained from a retrospective sample of patients who underwent intentionally curative resection for oesophageal adenocarcinoma (1990–96). Paraffin sections were used for immunohistochemical staining with a monoclonal antibody for cox-2 (Caymen chemicals) at a dilution of 1/100. Cox-2 expression was assessed using a semi-quantitative intensity-proportion scoring system (H-score i.e. intensity (0–3) x proportion of positive cells (%); possible scores from 0–300). Statistical analysis was performed using the Mann–Whitney U test and regression analysis.

Results: Specimens were identified from 79 patients with full pathological and clinical follow up data (minimum five years).

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<table>
<thead>
<tr>
<th>Tumour (n=79)</th>
<th>Mean survival (months)</th>
<th>Mean cox-2 expression (H score) p value</th>
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<tr>
<td>Differentiation</td>
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<td>I</td>
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<td>193</td>
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There was a negative association between cox-2 expression and survival (p=0.03).

Conclusion: Cox-2 overexpression is a marker of poor survival in patients with oesophageal adenocarcinoma. Differences in survival between groups with high and low cox-2 expression were not accounted for by variations in tumour differentiation or nodal stage.

M2-PK expression in the progression of Barrett’s oesophagus to adenocarcinoma

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Background: During tumour formation, the tissue-specific isoenzymes of pyruvate kinase (PK), such as L-PK in liver and M1-PK in muscle and brain are lost and M2-PK is expressed. The dimeric form of M2-PK is accounted for by variations in tumour differentiation or nodal stage.

Material and Methods: Oesophageal biopsies from 113 patients: 17 reflux oesophagitis, 37 intestinal metaplasia of the oesophagus, 21 Barrett’s high grade dysplasia and 38 Barrett’s adenocarcinoma were stained and semiquantified using monoclonal mouse anti-human M2-PK antibody.

Results: All cases of reflux oesophagitis showed positive staining in the superficial layers of the squamous epithelium, where the cells are immature and proliferating. All cases of Barrett’s metaplasia stained positively but staining was very variable from <30% of cells to 100% of the cells. The majority of cases of Barrett’s dysplasia showed widespread positive staining in dysplastic cells, but also some negative areas. All adenocarcinomas cases were strongly positive for M2-PK antibody.
Conclusion: The results of this study have shown inappropriate expression of M2-PK in neoplastic Barrett’s mucosa. There was an increase of M2-PK expression as the Barrett’s metaplasia-dysplasia-adenocarcinoma sequence progressed.

THE USE OF THREE MODALITY SEQUENTIAL STAGING IN OESOPHAGEAL CANCER

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Aim: Following recent government recommendations regarding the management of patients with oesophageal cancer, it was useful to evaluate the process of sequential staging for patients with oesophageal cancer.

Methods: Patients admitted with a diagnosis of oesophageal cancer between 1996 and 2001 were included in the study. Data were collected prospectively. All patients considered for surgery embarked on sequential staging with computerised tomography (CT), followed by endoluminal ultrasound (introduced at the end of 1998), then laparoscopy.

Results: A total of 244 patients were admitted over the six-year period. Seventy-three patients (30%) were turned down for surgery because of high operative risk, while seven (3%) refused the offer of surgery. The remaining 164 patients went on to have staging CT. Thirty-eight patients were refused surgery because of metastatic spread seen on CT. Of 46 patients undergoing endoluminal ultrasound, nine were refused surgery because of signs of widespread disease. Thirty-five of 118 patients (30%) were denied surgery on the grounds of findings at staging laparoscopy. A total of 85 patients underwent resection (35%). Thirty-five patients were given pre-operative chemotherapy. In two patients attempted resection was abandoned because of local spread. Patients who did not undergo surgery were referred for either radical chemoradiotherapy (ten) or palliative treatment.

Conclusions: It is important to select those patients who are most likely to benefit from surgery and to avoid incomplete resection. Three modality, sequential staging is an invaluable tool in this process of patient selection for oesophageal resection.

BARRETT’S OESOPHAGUS IS AN INDEPENDENT RISK FACTOR IN TUMOURS OF THE UPPER GASTROINTESTINAL TRACT

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Background: Epidemiological studies suggest that Barrett’s specialised intestinal metaplasia (SIM) is a pre-malignant precursor for adeno-carcinomas of the oesophagus (OAC) and oesophago-gastric junction (OGJ). Surveillance programmes are currently based on the stringent endoscopic biopsy of all patients with SIM to identify “at risk” individuals.

Aim: To determine whether Barrett’s SIM is an independent prognostic factor in patients with carcinoma of the oesophagus and stomach.

Methods: The Scottish audit of Gastric and Oesophageal Cancer (SAGOC) analysed survival amongst patients with resectable possible contributory factors including Barrett’s oesophagus. Univariate and multivariate analyses were performed to account for compounding factors and hazard ratios (HR) for 1 year survival were derived from this.

Results: A history of pre-existing Barrett’s oesophagus was present in 14% of OACs, 4.3% OGJ tumours, 0.9% squamous cell carcinoma, and 0.9% of gastric tumours. In patients undergoing resectional surgery, Barrett’s SIM was found in 44% of OACs, compared with 17% of OGJ tumours. Pathological data for the presence of SIM were not recorded in up to 44% and 55% respectively. Adjusted hazard ratios were as follows:

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<td>1</td>
<td>1</td>
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<tr>
<td>Barrett’s present</td>
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<td>0.53</td>
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<tr>
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<tr>
<td>p value</td>
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<td>(0.032)</td>
<td>(&lt;0.001)</td>
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SENSITIVITY TO ACID REFLUX IN BARRETT’S OESOPHAGUS IS RELATED TO IMPAIRED OESEPHAGEAL MOTILITY

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Background: Patients with Barrett’s oesophagus have increased acid and duodenogastic reflux compared to non-Barrett’s patients. Impaired sensitivity to acid infusion and distension has also been described, but the relationship between oesophageal motility and symptomatology is poorly documented.

Methods: 74 patients with Barrett’s oesophagus were compared with 216 GORD patients with abnormal acid scores and 50 symptomatic patients who had normal acid exposure. All patients had oesophageal manometry and 24 hour pH monitoring. 36 Barrett’s patients also had 24 hour bile monitoring. Symptoms were assessed by event marker and the Symptom Index (SI) was calculated. Analysis was based on the patient’s motility status.

Results: Barrett’s patients with normal motility had significantly less symptoms than GORD patients for similar acid exposure (p<0.01). Barrett’s patients with abnormal motility had higher acid exposure than those with normal motility (p<0.01), but the SI values for this group were not significantly different from the GORD patients. Bile reflux in Barrett’s oesophagus did not appear to be a significant factor in patient’s symptoms.

Conclusions: Symptoms in Barrett’s oesophagus are less than GORD patients and are related to oesophageal motility. Normal motility in Barrett’s oesophagus is associated with the poorest sensitivity and the presence of increased acid exposure is required in order to achieve sensitivity levels comparable with GORD patients.

IS THERE A RELATIONSHIP BETWEEN PH MEASUREMENTS AND SYMPTOMS? A PROBABILITY BASED ANALYSIS USING NEURAL NETWORKS

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Background and Aims: Ambulatory pH studies are widely accepted as the “Gold Standard” for detecting acid reflux within the oesophagus. However, many difficulties with analyses still exist. Patients frequently have evidence of reflux, on the day of the test, but no correlation with symptoms can be clinically found. This has led some investigators to suggest that more than one pH study would have to be done to identify the reflux pattern for each individual. The aim of this study was to carry out cluster-based analyses on a large database of ambulatory pH investigations and to compare the results of those patients with a clinical correlation of symptoms with acid reflux with those where no such correlation was found.

Methods: A self-organising neural network was used to partition the data from 900 clinical investigations into clusters. First, similar clusters between the two groups were found, e.g investigations with reflux with or without correlating symptoms. Then the numbers of cases within the similar clusters were compared to give an estimate of the probability of correlating reflux with symptoms.

Results: The results show that investigations with reflux can be divided into four classes. Those patients with the highest values of reflux fall in a class indicating that there is up to a 78% probability of reflux correlating with symptoms on the day of the investigation.
While those patients with the lowest levels of reflux have a 49% probability of symptoms correlating with reflux.

**Discussion:** The developed neural network allows the data from any study to be placed into the most appropriate class. This enables the probability of the symptoms being related to the observed reflux to be estimated despite no correlation being found on the day. This study suggests that, by using historical data to form the basis of the network and applying these techniques, a series of repeat tests are not necessary to assess the individual patient.

**ATTITUDES OF BSG MEMBERS TO THE DIAGNOSIS AND MANAGEMENT OF BILIARY DYSPKINESIA**


**Introduction:** Sphincter of Oddi dysfunction (SOD) and acalculous cholecystitis (AC) are contentious causes of biliary pain that require specialised investigative techniques. While data exist to support their diagnosis and treatment, many gastroenterologists doubt their existence.

**Aim:** to survey the attitudes of British gastroenterologists towards these functional diagnoses.

**Methods:** We contacted all BSG full members listed in the 2002 handbook.

**Results:** 1225 questionnaires were sent, of which 535 (43.7%) were returned. Of these, 355 (66.4%) were medical gastroenterologists, 118 (22.1%) were surgeons, and 62 (11.6%) were “other”. Respondents were asked what diagnoses they would consider in “unexplained” abdominal pain.

**Conclusions:** Of those BSG members who returned questionnaires, the majority would consider a diagnosis of SOD in previously unexplained abdominal pain. Standard diagnostic criteria for SOD are accepted although a significant minority would not accept pain alone as a reason to consider SOD. Cholecystectomy is largely accepted for AC, particularly amongst those surgeons performing the procedure.

<table>
<thead>
<tr>
<th>Abstract 178, Table 1</th>
<th>Numbers of respondents that would consider a diagnosis of SOD, AC, or both AC and SOD</th>
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<tbody>
<tr>
<td>SOD (%)</td>
<td>AC (%)</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Total</td>
<td>141 (26.4)</td>
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<thead>
<tr>
<th>Abstract 178, Table 2</th>
<th>SOD diagnostic criteria accepted by respondents</th>
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<tr>
<th>SOD1-3+IP</th>
<th>SOD1-3</th>
<th>SOD2-3</th>
<th>SOD2-3+IP</th>
<th>None</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>83 (15.5)</td>
<td>22 (4.1)</td>
<td>31 (5.8)</td>
<td>80 (20.0)</td>
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</tbody>
</table>

SOD1, pain plus two abnormal test results; SOD2, pain plus one abnormal test result; SOD3, pain only; IP, idiopathic pancreatitis; none, would not consider SOD.

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<thead>
<tr>
<th>Abstract 178, Table 3</th>
<th>Numbers who would recommend cholecystectomy for AC</th>
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<table>
<thead>
<tr>
<th>All respondents</th>
<th>Yes</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>327 (61.1)</td>
<td>112 (20.9)</td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy surgeons</td>
<td>62 (73.8)</td>
<td>11 (13.1)</td>
</tr>
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</table>

**THE ASSOCIATION BETWEEN ELECTROGASTROGRAPHY AND GASTRIC EMPTYING IN NON-ULCER DYSPPEPSIA**

P. Wang, M. Harbord, M. Jacovic, O. Epstein. Centre for Gastroenterology, Royal Free Hospital, London NW3 2QG, UK

**Background:** In non ulcer dyspepsia (NUD), radionuclide imaging and electrogastrography (EGG) are used to assess gastric emptying (GE) and gastric pacemaker (slow wave) activity respectively.

**Hypothesis:** In NUD, gastric dysrhythmia predispose to gastric dysmotility.

**AIM:** (1) To correlate GE and EGG findings in patients with NUD.

**Methods:** A GE study and pre- and post-prandial EGG were performed in 51 patients (34 female; mean age 40 years) with NUD (chronic epigastric symptoms, normal endoscopy, negative Helicobacter pylori and no other cause for symptoms). GE was reported as normal, rapid, or delayed and EGGs as normal (70% slow waves, with mean frequency of 3 cycles/minute), tachygastria or bradygastria. The symptoms were epigastric pain (n=27); nausea with or without vomiting (N&V) (n=15); epigastric bloating (n=3); nausea and bloating (n=3); and reflux and belching (n=3). Linear regression was used to assess any association between age, gender, and symptoms.

**Results:** (1) Both GE and EGG were normal in 12 patients (24%). GE was abnormal in 33 patients (65%) of whom 21 had delayed emptying. The EGG was abnormal in 18 patients (36%), with tachygastria reported in 13. In these 18 patients, the pre-prandial EGG was normal in 15, the post-prandial EGG abnormal in 5, whereas GE was normal in 6 (all tachygastrias). (2) GE was abnormal in 16 patients (59%) with pain (delayed in 10), in 11 (73%) with N&V (delayed in 6), in the 3 patients with nausea and bloating (delayed in 2), and delayed in the 3 patients with bloating. GE was normal in the patients with reflux. (3) EGG was abnormal in 12 patients (44%) with pain (tachygastria in 9), in 5 patients (33%) with N&V (bradygastria in 4), and in 1 patient with bloating. There was no correlation between gender, age, GE, and symptoms.

**Conclusions:** Abnormality of GE or gastric slow wave activity occurs in up to 76% of NUD patients. There appears to be no association between abnormal GE and EGG. Abnormal GE or EGG does not correlate with the dominant symptom complex although 73% of patients with N&V had abnormal GE. Abnormal EGG usually normalises after a meal. A further study is required to determine whether delayed GE (but normal EGG) predisposes to bloating.

<table>
<thead>
<tr>
<th>179</th>
<th>SMALL BOWEL MANOMETRY ON CHILDREN WITH SUSPECTED SMALL INTESTINAL MOTILITY DISORDER</th>
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<tr>
<td>E. Yazaki, N. Meadows, F. Smith, K. Wiles, M. Hirata, S.K. Arthur, D.F. Evans. Adult and Paediatric Gastroenterology, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, UK</td>
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</tbody>
</table>

**Background:** Small bowel manometry (SBM) has widely been used to investigate adult patients with gastrointestinal motility disorder. However, the use of this technique to paediatrics is uncommon. The aim of this study was to evaluate feasibility of SBM on paediatric patients with suspected small intestinal motility disorder.

**Methods:** We have performed SBM on 14 paediatric patients (age range 2–10 years) who had symptom(s) including recurrent abdominal pain (n = 10), nausea (n = 5), vomiting (n = 7), abdominal distension (n = 2) and constipation (n = 2). A 3-channel manometry catheter was introduced nasally and placed in the proximal small bowel under fluoroscopic control. Ambulatory recordings were made for 24 hours using a portable recorder. Recorded data were analysed using dedicated software.

**Results:** Four had normal motility when applied to the normal ranges in adults. At least one of the following abnormalities was found in eight patients; possible neuropathy findings including excess of motor activity (n = 3), prolonged Phase III (n = 2), Phase III like prolonged bursts (n = 3), non-propagated Phase III (n = 2), retrograde propagation of Phase III (n = 2), and low-amplitude Phase III (n = 1) suggesting possible myopathy. Intubation failed in two patients due to no migrations of the catheter into the small intestine.

**Summary:** In this study a high proportion of the patients had abnormal small intestinal motility and this suggests that SBM can be used to evaluate those conditions. Normal values during infant and childhood development need establishing before adopting the technique for clinical diagnosis.
**Cell/molecular biology posters 181–213**

### 181 SODIUM BUTYRATE MEDIATED SP3 ACETYLATION REPPRESSES HIGFBP-3 EXPRESSION IN INTESTINAL EPITHELIAL CELLS


**Introduction:** Butyrate induces histone acetylation, but this does not easily explain the down-regulation of HIGFBP-3 by butyrate, as histone acetylation is associated with expansion of the nucleosome. Furthermore, the down regulation occurs in the absence of de novo protein synthesis, excluding the induction of a repressor as a possible mechanism, and previous studies revealed the butyrate responsive element that included binding sites for p300 and Sp1/Sp3.

**Methods:** We examined the acetylation and activity of Sp3 in hIGFBP-3 expression.

**Results:** Transfection of Caco-2 cells with E1A, an inhibitor of p300 acetyltransferase activity, reversed the butyrate induced repression of hIGFBP-3. Sp3 is a known repressor of gene activation. Its potential for acetylation has recently been reported. We hypothesized that butyrate might increase the acetylation of Sp3. We, therefore, performed EMSA and supershift studies on nuclear extracts from butyrate treated and non-treated Caco-2 cells with the hIGFBP-3 promoter. We also studied nuclear extracts by Western blotting analysis and immunoprecipitation. 5mM butyrate retarded the acetylation of an isoform of Sp3 in the presence of NaB, whereas the total amount of Sp3 protein was unchanged. Western blot analysis revealed the acetylation of an isoform of Sp3 in the presence of NaB as evidenced by semi-quantitative PCR and Western blot analysis.

**Conclusions:** Our evidence supports the hypothesis that butyrate down-regulates hIGFBP-3 by butyrate by the acetylation of the repressor Sp3 and involves p300. We have shown for the first time that butyrate affects the acetylation status of a non-histone DNA-binding protein.

### 182 CHARACTERISATION OF BINDING OF CLOSTRIDIUM DIFFICILE TOXIN A TO MEMBRANE PREPARATIONS OF HUMAN COLONIC EPITHELIAL CELLS

N.A. Ali, Y.R. Mahida. Division of Gastroenterology, University Hospital, Queen’s Medical Centre, Nottingham, UK

**Introduction:** Clinical presentation after C difficile infection can range from asymptomatic carriage to pseudomembranous colitis. C difficile induces diarrhoea and colonic inflammation via secreted toxins A and B. To induce disease, the toxins have to first interact with colonic epithelial cells. We have investigated the binding of C difficile toxin A to membrane preparations of primary human colonic epithelial cells.

**Methods:** Primary colonic epithelial cells from different individuals (n=10) were cultured by treatment with EDTA and used for membrane preparations (confirmed by electron microscopy). Caco2 cell membrane preparations were also obtained (and shown to be enriched for sucrase-isomaltase and alkaline phosphatase). Purified C difficile toxin A was labelled with tritium [3H] using the Bolton-Hunter reagent N-succinimidyl [2,3-3H] propionate. Binding studies were carried out using purified epithelial membrane preparations and [3H]toxin A. Specific binding was calculated by subtracting non-specific binding in the presence of 1000-fold excess unlabelled toxin A.

**Results:** Biological activity of [3H]Toxin A was confirmed using Vero cells. In studies using membrane preparations from different individuals, binding of [3H]Toxin A varied markedly (binding per mcg protein, expressed as % of binding to Caco2 membrane preps: A - 25.7%, B-32.8%, C-184.9% and D-0.8%). Using pooled samples of membrane preparations, specific binding of [3H]Toxin A occurred at 4°C, 19°C, and 37°C. The binding achieved saturation in the presence of increasing concentrations of [3H] toxin A, and reached equilibrium within 60 min at 4°C.

**Conclusions:** The specificity of [3H]toxin A binding to membrane preparations of colonic epithelial cells and the ability to saturate this binding suggests involvement of receptor-ligand interaction. Variation in the binding of [3H]toxin A to membrane preparations from different individuals may explain the different types of clinical presentation in patients infected with toxigenic C difficile.

### 183 BONE MARROW DERIVED CELLS CONTRIBUTE TO A POPULATION OF FIBROBLASTS AND MYOFIBROBLASTS WHICH ENGRAFT TO MULTIPLE SITES, INCLUDING THE GASTROINTESTINAL TRACT


**Background:** Our previous work has shown that bone marrow can make important contributions to the myofibroblast population in the lamina propria after bone marrow transplantation (Gut 2001;49578-7-9). Here we show that the bone marrow can also contribute to fibroblast populations in sites of injury, and in fact, the engraftment of cells destined to be myofibroblasts from the bone marrow appears to be a systemic phenomenon not confined to gastrointestinal tissues.

**Methods:** C57/black female mice were irradiated with a total of 12 Gray to ablate the bone marrow followed immediately by I.V. injection of male wild type whole bone marrow. The mice received 2 doses of paracetamol at 5 and 8 weeks post transplantation at a dose of 400mg/kg I.P. Tissue sections were examined using in situ hybridisation to detect the Y-chromosome and immunohistochemistry for intermediate filaments and cytokeratins.

**Results:** Examination of the intestine and stomach showed numerous myofibroblasts of bone marrow origin distributed throughout the gut wall. In addition, areas of fibrosis contained numerous Y chromosome positive cells with a fibroblastic phenotype. Myofibroblast engraftment was also demonstrated in the skin, adrenal capsule, lung, and kidney.

**Conclusions:** We conclude that bone marrow provides a circulating population of cells which can contribute to myofibroblasts in healing tissues. Our data also suggest that these cells can adopt a fibroblastic phenotype and contribute to fibrosis. We therefore hypothesise that circulating bone marrow-derived precursors are available which are able to colonise injured tissues and give rise to myofibroblasts and then fibroblasts. These conclusions have important connotations for tissue repair in gastrointestinal and other tissues.

### 184 INTERPHASE FLUORESCENCE IN SITU HYBRIDISATION (FISH) TO DETECT CHROMOSOMAL ABNORMALITIES IN GASTRIC CANCER PROGRESSION

L. Williams1, J.G. Williams1, A.P. Griffiths1, T. Brown1, S.H. Dook1, G.J.S. Jenkins1, E.M. Parry1, J.M. Parry1. Neath General Hospital, Neath, UK; 2Morrison Hospital, Swansea, UK; 3School of Biological Sciences, University of Wales Swansea, UK

**Introduction:** Gastric cancer is the second commonest fatal cancer worldwide and Helicobacter pylori has been causally linked with cancer progression. Gastric cancer presentation is at the advanced stage, and survival rates are poor. As such, interest in the causative agents and genetic changes responsible for gastric carcinogenesis has increased. Advanced gastric cancer shows widespread chromosomal rearrangement of chromosomes 20, 8, and 17(p53). In addition, chromosome 4 has previously been implicated in Barrett’s oesophagus.

**Aim:** To develop FISH to look at chromosomal abnormalities (using 4, 8, 17, 20) in gastric tissue and to correlate the chromosomal abnormalities with histological diagnosis, patient characteristics, H pylori presence and subtype.

**Methods:** Patients were enrolled, gastric biopsies were taken for histology and for PCR to detect H pylori (and Cag A status). Gastric/oesophageal cytology brushes were taken and FISH performed with centromeric probes 20, 8, and 4, and a locus specific probe for p53. In addition, surgical resections of dysplastic/cancer patients were obtained for FISH analysis.

**Results:** Oesophageal cells show little chromosomal instability, whilst histologically normal gastric cells do show genetic instability,
possibly due to the adverse environment of the stomach. Histologically normal gastric cells show significantly more chromosome abnormalities than with probes (p<0.0001), when compared to oesophageal cells or normal gastric cells. This demonstrates the increasing genetic instability in the histological progression of gastric cancer. Specifically, p53 gene deletion, chromosome 8, and 4 amplifications and chromosome 20 instability is detected.

In the surgically resected specimens, a range of histological subtypes were noted (normal, intestinal metaplasia, dysplasia, adenocarcinoma). The same chromosomal abnormalities seen in the premalignant cells (above), were seen in these cancer cells, but the incidence of these abnormalities was greater.

Conclusion: Cytogenetic analysis allows accurate numbers of gastric cancer cells to be collected and analysed. This approach allows cytogenetic screening of gastric cancer progression to be performed. Importantly, the chromosomal instability detected in premalignant gastric tissues increased during the histological progression to cancer. This suggests that these specific chromosomal alterations are important in cancer progression.

Work in progress: PCR for H pylori in the gastric biopsies collected from enrolled patients to correlate the chromosome data with H pylori presence and subtype (cag A).

185 PROSTAGLANDIN E2 RECEPTOR (EP RECEPTOR) EXPRESSION IN PRE-MALIGNANT AND MALIGNANT GASTRIC MUCOSA
A. Wood, A.B. Ballinger, G.V. Smith. St Barts and the London, Queen Mary’s School of Medicine, London, UK

Prostaglandin E2 (PGE2) is significantly over-expressed in gastric adenocarcinoma and as a result of H pylori (Hp) infection. This is associated with over expression of cyclooxygenase 2. The effects of PGE2, are mediated by both nuclear and cell surface receptors. The PGE2 cell surface (EP) receptors activate several intracellular homeostatic mechanisms and have been implicated in cell cycling. The expression of these receptors in gastric carcinogenesis is poorly understood.

Methods: Paraffin embedded sections of normal gastric mucosa, Hp gastritis, mucosal atrophy, intestinal metaplasia (IM), dysplasia and cancer were analysed immunohistochemically for the expression of the four subtypes of EP receptor. Polyclonal antibodies raised against these receptors were utilised. Controls comprised oesophageal and duodenal biopsies. Negative controls were analysed by substitution of the primary antibody with diluent or its pre-incubation with a specific control peptide for each receptor. Two observers scored each slide. Median scores were compared with a Mann–Whitney analysis.

Results: See table.

Discussion: Significant variations in EP receptor expression are seen in gastric pathology. EP4 receptors appear to be up-regulated in inflammatory conditions associated with H pylori infection, whereas EP2 and EP3 are over-expressed in premalignant and malignant tissue. These patterns of expression, at the time of increased PGE synthesis, may provide a mechanism for increased cell cycling and proliferation and play a significant role in inflammation and neoplasia.

186 THE ROLE OF PPARγ IN THE ANTI-COLORECTAL CANCER ACTIVITY OFINDOMETHACIN
G. Hawcroft, S.H. Gardner, M.A. Hull. Molecular Medicine Unit, University of Leeds, St James’s University Hospital, Leeds LS9 7TF, UK

We have previously shown that indomethacin inhibits proliferation and induces apoptosis of several human colorectal cancer (CRC) cell lines in vitro. The anti-proliferative effects of indomethacin (100–600 µM) were associated with a decrease in expression of β-catenin and the β-catenin/TCF target gene cyclin D1 (CD1), in a COX2-independent manner. However, mutation of the TCF-binding site in the CD1 promoter did not abolish down-regulation of CD1 by indomethacin, implying that other cis and/or transacting elements must also mediate the effects of indomethacin on CD1 expression. It has previously been demonstrated that indomethacin can activate peroxisome proliferator-activated receptor γ (PPARγ) in adipocytes and that growth arrest by PPARγ ligands can occur via PPAR-dependent repression of CD1. Therefore, the aim of this study was to investigate whether growth arrest and down-regulation of CD1 expression by indomethacin occurs via a mechanism involving PPAR activation in human CRC cells.

SW480 and HCT116 human CRC cells expressed PPARγ mRNA and protein. PPARγ function was tested using the transactivated (TZD) PPARγ ligand troglitazone (10–50 µM) and a PPAR response element-luciferase (PRE-luc) reporter gene. Both SW480 and HCT116 cells contained functional PPARγ that was also activated by indomethacin (HCT116 > SW480). The functional relevance of PPAR activation for the anti-proliferative effects of indomethacin was tested by transient transfection of dominant-negative PPARγ (dnPPARγ) into HCT116 cells. dnPPARγ inhibited TZD-induced PRE-luc activity. However, dnPPARγ expression did not inhibit indomethacin-induced down-regulation of CD1.

Despite the fact that indomethacin directly activates PPARγ in human CRC cells, PPARγ activation does not explain the anti-proliferative activity of indomethacin (including down-regulation of CD1) in human CRC cells and does not represent a COX-independent mechanism of the anti-CRC activity of the NSAID indomethacin.

187 INDOMETHACIN ALTERS HELICOBACTER PYLORI INDUCED EFFECTS ON GASTRIC EPITHELIAL CELLS IN VITRO
M.W. James, R.H. Argent, R.J. Thomas, C.J. Hawkey, J.C. Atherton. Division of Gastroenterology, University Hospital, Nottingham, UK

Introduction: Helicobacter pylori infection is a major risk factor for distal gastric adenocarcinoma. Pathogenicity determinants include production of an active form of vacuolating cytotoxin (VacA) and possession of the cag pathogenicity island (cag PaI). Toxigenic strains cause marked epithelial cell vacuolation in vitro whilst cag negative strains include rearrangement of the actin cytoskeleton to form a “hummingbird” phenotype. NSAID ingestion is associated with a reduced incidence of gastric adenocarcinoma, although mechanisms are unclear. We tested the hypothesis that NSAIDs modulate H pylori-induced effects on epithelial cells, in particular effects induced by VacA and the cag PaI.

Methods: AGS cells (1–2 × 10⁵ cells/ml) were co-cultured with H pylori strain 60190 (cag+, vacA s1/m1) or its VacA or CagE isogenic mutants at a bacteria:cell ratio of 0.02–70:1. Indomethacin (non-selective NSAID) or vehicle control was added at a concentration of 0.01–100µM. After overnight incubation with 5% CO2 at 37°C, vacuolated and hummingbird cells were counted directly using field contrast microscopy. Statistical analysis was by ANOVA and Student’s paired t-test.

Results: Co-culture with H pylori strain 60190, but not its VacA mutant, increased AGS cell vacuolation from 0.8 ± 0.8 to 25.4 ± 6.5%. Indomethacin had no significant effect in the absence of H pylori, but inhibited H pylori-induced vacuolation in a dose-dependent manner (100µM: by 56 ± 14%, p=0.02; 1µM: by 42 ± 15%, p=0.05; 0.1µM: by 26 ± 13%, p=0.26). Co-culture with H pylori strain 60190, but not its CagE mutant increased AGS hummingbird cells from 0 to 6.2 ± 1.7%. Indomethacin had no effect in the absence of H pylori. In the presence of H pylori, indomethacin at 100µM significantly increased hummingbirds by 240 ± 98%, p=0.05.

Conclusion: Indomethacin reduces H pylori-induced vacuolation, but in contrast, at high concentrations, increases H pylori-induced cytoskeletal changes. We speculate that these actions contribute to NSAID-induced reduction in H pylori-associated gastric cancer risk.

188 EFFECTS OF SULINDAC SULPHIDE ON MITOCHONDRIAL OXYGEN CONSUMPTION AND MEMBRANE POTENTIAL
M.J. Garle, B. Middleton, C.J. Hawkey. Division of Gastroenterology and School of Biomedical Sciences, Queens Medical Centre, Medical School, University of Nottingham, NG7 2UH, UK

Introduction: Sulindac (active metabolite: sulindac sulphide [SS]), is useful for the chemoprevention of colorectal cancer. Sulindac derivatives are active against COX-negative cancers by promoting apoptosis indicating that mechanisms unrelated to prostaglandin synthesis
are involved. We have shown that SS inhibits β-oxidation of long chain fatty acids. To explore precise mechanisms, we measured ADP-stimulated oxygen consumption, proton transport (mitochondrial membrane potential (MMP)), and peroxide generation with different metabolic fuels: octanoate (OCT, C8 fatty acid), palmitoyl carnitine (PC, C16 fatty acid), pyruvate (PYR, glycolytic intermediate) and succinate (SUC, TCA cycle intermediate).

Methods: Rat liver mitochondria were prepared by differential centrifugation and ADP-stimulated oxygen uptake was measured using a Clark oxygen electrode. MMP and peroxide generation was determined in HCT116 cells using JC-1 accumulation and dichlorofluorescin oxidation respectively.

Results: SS (100µM) inhibited octanoate and succinate, but stimulated pyruvate, oxidation (see table). It enhanced MMP by 86% but suppressed peroxide generation.

Conclusions: SS selectively inhibits fatty acid and succinate oxidation. Our data imply flavoproteins, eg succinate dehydrogenase, and medium chain acyl CoA dehydrogenase as possible targets. Suppression of peroxide formation may indicate an additional antioxidant action of SS.

**189** EXPRESSION OF THE CYTOPROTECTIVE TREFOIL PROTEIN TFF2 IN HUMAN GASTRIC AND DUODENAL BIOPSIES

C.E. Johns, J.L. Newton, B.R. Westley, F.E.B. May. University of Newcastle, UK

Introduction: TFF2 is the second member of the trefoil family of peptides. These small proteins are found in epithelial surfaces and contribute to mucosal repair and protection. It has been suggested that the glycosylated form of TFF2 is more active in promoting ulcer healing in rats. Immunohistochemical studies have demonstrated TFF2 in the antral glands of the stomach and the Brunner’s glands of the duodenum. The relative amounts in these areas have not been quantified previously in man.

Methodology: Seven patients attending for routine oesophagogastrroduodenoscopy gave written informed consent. In each subject gastric antral and first part of the duodenum biopsies from each of the first, second and third parts of the duodenum. Separate parallel biopsies were taken for immunohistochemistry. The amount of TFF2 in the biopsies was measured by quantitative Western transfer analysis.

Results: High glycosylated TFF2 levels were found in the gastric antrum and first part of the duodenum. There was no difference between these areas; means both 3.4 ng per µg total protein; p=0.99 95% CI -4.2,4.1). TFF2 was present in D2 in all subjects, and 4 had detectable TFF2 in D3 (mean 0.2 ng per µg protein). The proportion of total TFF2 that is non-glycosylated was greater in the duodenum than in the stomach, (means 7.5% and 3.1% respectively, p=0.03, CI -7.9, -0.44). The profile of TFF2 glycosylation in the duodenum was different from that in the stomach.

Discussion: The presence of TFF2 in D3, beyond the pancreatic duct, where Brunner’s glands are thought to be absent, indicates that Brunner’s glands may not be the only source of TFF2 in the human duodenum, and that TFF2 is active in D3. The higher proportion of non-glycosylated TFF2 in the duodenum suggests this peptide may have a different function here.

**190** THE EXPRESSION OF MUCIN GLYCOPROTEINS AND TREFOIL PEPTIDES IN THE HUMAN FETUS

D. Carroll, P. Soothill, C. Sergi, R.D. Spicer, A. Corfield. Departments of Paediatric Surgery and Paediatric Pathology, Bristol Children’s Hospital, Department of Biochemistry, University of Bristol, Professor, Department of Fetal Medicine, Bristol University.

Introduction: Mucin glycoproteins are important constituents of the supramucosal barrier. Trefoil peptides are fundamental to the maintenance of epithelial integrity. Immaturity of the gastrointestinal tract is associated with a number of pathological conditions. We sought to examine the timing of expression of the gene products of these proteins within the developing gastrointestinal tract.

Methods: fetal gastrointestinal tract was collected with maternal consent and prior approval of the regional ethics committee from 9 fetuses from 8-13 weeks gestation. Tissue was immediately fixed in formalin for 24h and embedded in paraffin. Sections were subjected to in situ hybridisation and immunohistochemistry. Sections were then examined by two independent observers under light microscopy to determine the cellular and subcellular pattern of gene and protein expression in the developing gastrointestinal tract. Data analysis was performed using independent t test in SPSS for Windows v.10.

Results: Mucin gene expression was not detected before 9+3 weeks gestation in the fetal gastrointestinal tract by either in situ hybridisation or immunohistochemistry. From 10 weeks gestation mucin gene expression adopted a pattern similar to that seen in normal neonatal tissue. Trefoil factor 3 product was detected in primitive secretory cells of the small and large intestine from 10 weeks gestation onwards.

Conclusions: Mucin glycoproteins and trefoil peptides are present in detectable levels in the gastrointestinal tract from late in the first trimester. Deficiencies in post-translational modification or quantitative changes in expression may account for presumed deficiencies in the integrity of the supramucosal barrier.

**191** PEPTIDE TARGETING OF CCK-2 RECEPTOR IN TUMOUR CELL LINES

M. Stubbs, K. Khan, S.A. Watson, S. Grimes, D. Michaeli, K. Savage, M. McCay, A.P. Dhillon, M.E. Caplin. Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK

Background: Gastrin binds preferentially to the CCK2 receptor. We have previously demonstrated expression of the CCK2 receptor in a number of hepatopancreatobiliary cancers and uptake of gastrin analogue peptides by CCK2 expressing tumour cell lines. The study also demonstrated dimerization of the peptides in solution.

Aim: To compare the uptake of dimer and monomer forms of gastrin analogue peptides in hepatic and pancreatic cancer cell lines.

Methods: 4 derivatives of GRTL-1 were labelled using Alexa Fluor 488 dye (Molecular Probes, USA); untreated GRTL-1, GRTL-1 with the cysteine sulfhydryl group protected with N-ethylmaleimide (GRTL-1-NEM), a GRTL-1 dimer with a bismaleimidodihexane linker (GRTL-1-BMH), and a GRTL-1 dimer with a bismaleimidotetraethyleneglycol spacer linker (GRTL-1-BM(PEO)). The labelled peptides were exposed to HepG2 (human hepatocyte carcinoma), AR42J (rat pancreatic adenocarcinoma) and PLC/PRF/5 (human liver hepatoma) cells at a concentration of 20 µg/ml for 1 hour at 37°C. Cells were fixed with buffered formaldehyde and examined under a fluorescence microscope.

Results: [GRTL-1], BMH [AR42J] and PLC/PRF/5 and GRTL-1 (HepG2) gave the highest proportion of cells with visible uptake of labelled analogue. High uptake was also seen with [GRTL-1], BM(PEO), but the fluorescence intensity was slightly less intense than [GRTL-1] or [GRTL-1]-BMH. The level of GRTL-1-NEM uptake was much lower.

Conclusion: Dimeric forms of GRTL-1 show more endocytosis than the monomeric form. GRTL-1 with unsubstituted cysteine undergoes significant dimerization in aqueous solution, so the high uptake seen with this form is probably due to the dimer. Dimeric GRTL-1 therefore shows greater potential for intracellular delivery of potential therapeutic agents to CCK2 positive tumours.

**192** HELICOBACTER PYLORI INFECTION IN MONGOLIAN GERBILS INDUCES A TH1 GASTRIC MUCOSAL RESPONSE

M.A. Abashkiwa, A.H.T. Jeremy, M. Court, M.F. Dixon, P.A. Robinson, J.E. Crabtree. 1Department of Paediatric Surgery and 2Department of Pathology, The General Infirmary, Leeds, UK

Introduction: Chronic H pylori infection in Mongolian gerbils has been demonstrated to result in gastric cancer. The gastric mucosal inflammatory and immune response to infection has not been characterised. The aims of this study were to identify transcripts for gerbil cytokines and to examine the gastric cytokine responses to chronic H pylori infection.

Methods: Female Mongolian gerbils were orally challenged three times with H pylori SS1 strain. Infected animals (n = 15) plus controls...
SPECIFIC SERUM ANTIBODIES ARE INVOLVED IN H PYLORI-INDUCED PLATELET AGGREGATION

P.A. Carcoran, S.W. Kerrigan, D. Cox, J.C. Atherton, D.J. Fitzgerald, F.E. Murray, M.F. Byrne. Clinical Pharmacology/Gastroenterology, RCS/ Beaumont Hospital, Dublin, Ireland and Duke University Medical Center, NC, USA

Background: Clinical studies have suggested an association between cardiovascular disease and infection with H. pylori. We have described strain specific H pylori-induced platelet aggregation that involves platelet glycoprotein Ib and von Willebrand factor (vWF). We examined the role of H pylori antibodies in this aggregation.

Methods and Results: Addition of pooled immunoglobulin (Ig) and fibrinogen along with H pylori strain 60190 (coated in vWf) to washed platelets led to platelet aggregation (60±4%, n=3). Antibodies involved were specific to H pylori as bacteria incubated in pooled Ig and subsequently washed could support platelet aggregation (49±7%, n=3). To confirm this, pooled Ig was incubated with H pylori or Streptococcus sanguis. Bacteria were removed by centrifugation and the depleted Ig used in aggregation assays. H pylori-depleted Ig showed greatly reduced platelet aggregation to H pylori (13±9%, n=3, p<0.01) while the S sanguis-depleted Ig was not affected (54±3%, n=3, p=NS). All 20 plasma donors were tested for H pylori seropositivity using a H pylori EUSA. All 4/4 of the positive volunteers consistently aggregated in response to H pylori while only 2/15 of the H pylori negative donors aggregated consistently (p=0.039, Fisher’s Exact Test). The relative risk of H pylori positivity for aggregation was 7.5 (CI 2.0-27.3).

Conclusions: H pylori-induced platelet aggregation requires binding of H pylori-specific IgG. This pro-aggregatory phenotype is not unique to H pylori and has been described with S sanguis and P gingivalis. Exposure to oral bacteria such as S sanguis can lead to infective endocarditis and, in the case of P gingivalis, to enhancement of atherosclerosis in animal models. Reported exposure to pro-aggregatory bacteria such as certain strains of H pylori may not cause coronary artery disease but could accelerate the progression of the disease. Local platelet effects may also contribute to the pathogenesis of H pylori-associated atherosclerotic ulcer disease.

STIMULATION OF MATRIX METALLOPROTEINASE-7 (MMP-7) BY HELICOBACTER PYLORI IN GASTRIC EPITHELIAL CELLS: ROLE IN EPITHELIAL CELL MIGRATION

A. Varro, L.E. Wroblewski, A. Pagliocca, D.M. Pritchard, P.J.M. Noble, C.A. Hart. Physiological Laboratory, Cambridge and Medical Microbiology, University of Liverpool, Liverpool, UK

Background and Aims: Epithelial cell responses to bacterial infection include induction of MMP-7. We have examined the cellular mechanisms of H pylori stimulation of MMP-7 in gastric cells, and the consequences for gastric epithelial cell migration.

Methods: Gastric biopsies of H pylori positive and negative subjects were probed for MMP-7 by Western blot. Biopsies were cultured for up to 72hr and MMP-7 localised by immunocytochemistry; cell migration in these cultures was examined by time lapse videomicroscopy. Cellular signalling mechanisms were examined using a MMP-7-promoter/luciferase (luc) reporter vector transfected into AGS cells.

Results: Gastric IFNγ transcripts in H pylori infected gerbils were significantly increased at 12 (p<0.05) and 36 weeks (p<0.01) p.i. compared to uninfected controls. IFNγ:β-actin ratio 12 weeks 0.85 ± 0.07, 36 weeks 1.51 ± 0.16. IL-12p40 transcripts in H pylori infected gerbils were significantly increased (p<0.05) at 25 weeks p.i. compared to controls (1.512 ± 0.512). In contrast, no differences in IL-10 or TGFβ transcripts were observed with H pylori infection, although an age-related increase in TGFβ transcripts was evident in both infected and control gerbils.

Conclusions: Long term chronic infection with H pylori in the Mongolian gerbil is associated with upregulation of the Th1 cytokines IFNγ and IL-12p40 in the gastric mucosa. The lack of upregulation of key inflammatory cytokines IL-6 and TGFβ in H pylori infection may contribute to the severe pathology associated with infection in the Mongolian gerbil.

INTERACTION BETWEEN THE HELICOBACTER PYLORI VULNERANCE FACTORS CAGA AND VACA


Introduction: H pylori strains possessing the cag Pathogenicity Island (cag Pol) or expressing active vacuolating cytotoxin (vacA) are associated with increased risk of peptic ulceration and gastric adenocarcinoma. Most strains have both or neither of these virulence factors. This is unlikely to be due to genetic linkage as H pylori recombine freely and the loci are distant on the chromosome. We hypothesised that the association was due to a gain of function from possessing both factors.

Methods: In two toxigenic cag+ strain backgrounds, 60190 and 84-183, we constructed separate isogenic mutants null for vacA, and for each of two genes encoded on the cag Pol, cagA and cagE. These data were compared with those of isogenic mutants lacking vacA and, for each of these genes, of wild type strains. All isolates were examined for the Pathogenicity Island (cagA or cagE) and vacA alleles.

Results: In H pylori positive patients there was increased MMP-7 in both corpus and antrum. MMP-7 was localised to mucus and chief (but not parietal or dendritic) cells in cultured gastric epithelial cells, and was identified in lamellipodia at the advancing edge of migrating cells. The spreading of gastric glands was significantly increased in H pylori positive cultures compared with control and migration was inhibited by MMP-7 antisense oligonucleotide. In addition, H pylori stimulated AGS cell migration and invasion and this was inhibited by an MMP-7 antibody. In AGS cells, H pylori induced expression of MMP-7-luc and this was significantly inhibited by co-transfection with dominant negative (DN) forms of Rac and, and by inhibitors of NFκB (BAY11-7082) and MEK (PD98059). A constitutively active (CA) form of Rac also stimulated MMP-7-luc, and this was inhibited by BAY 11-7082, PD98059 and DN-Jun; in contrast, stimulation of MMP-7-luc by CA-Rac was inhibited by BAY but not DN-Jun.

Conclusion: MMP-7 increased in both corpus and antrum in response to H pylori. 2. MMP-7 plays a role in H pylori stimulated cell migration. 3. H pylori acts via Rac, AP-1 and NFκB to stimulate MMP-7 expression.

THE IMPORTANCE AND GENETIC DETERMINANTS OF DIFFERENCES IN VACA TRANSCRIPTION BETWEEN HELICOBACTER PYLORI STRAINS

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Introduction: Levels of vacuolating cytotoxin gene (vacA) transcription vary among laboratory and clinical isolates, and may be an important determinant of the success of different H pylori strains in vivo. We therefore examined the transcriptional activity of vacA in a selection of clinical isolates from patients with peptic ulcer disease and compared these with the transcriptional activity of vacA in laboratory isolates. We also examined the transcriptional activity of vacA in different H pylori strains and explore whether specific genetic determinants within vacA explained these differences.

Methods: H pylori single colonies were isolated from gastric biopsy specimens from 8 patients and their vacA type determined by allele-specific PCR. Total RNA was prepared for each isolate and for

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the control strains 60190 (Tox+; vacA s1/m1) and Tx30a (Tox−; s2/m2). Level of vacA transcription was determined by densitometric analysis of RNA dot blots. Level of VacA protein production was determined by densitometric analysis of immunoblots of 24 hour brood culture supernatants. For each isolate, nucleotide sequences were determined for the region between vacA and its 5′ gene, cysS (the cysS-vacA intergenic region) and for 122 nucleotides of the 5′ end of vacA. Finally, the vacuolating activity of each strain was determined by cell culture assay.

Results: vacA transcription varied 6 fold among the clinical isolates. VacA RNA levels correlated closely with protein levels suggesting that variation in vacA production resulted mainly from variation in transcription. Level of vacA transcription was not related to vacA genotype (genotypes of wild type isolates were: 2 s1/m1; 4 s1/m2; 1 s2/m2; 1 s2/m1) nor was it associated with disease state or specific gastric histological features. Analysis of the cis−vacA intergenic region revealed 70% identity across all 10 strains (including control strains 60190 and Tx30a). The −10 and −35 promoter regions were well conserved. Identity within the vacA S′ untranslated region was 77%. Despite high variation within the cis−vacA intergenic region, none of the genetic differences were associated with vacA transcription level. A potential stem-loop structure at the +4 site was conserved between all strains.

Conclusion: Level of vacA transcription appears to be the main determinant of vacA production. This is independent of vacA genotype and has no consistent association with nucleotide sequence differences in the vacA promoter region. Interestingly, a conserved, potential stem-loop region was identified which may regulate vacA expression through mRNA stability, and we are investigating this.

197 GLUCOCORTICOID (GC) ACCESS AND ACTION IN THE RAT COLON: EXPRESSION AND REGULATION OF MULTIDRUG RESISTANT GENE 1A (MDR1A), GLUCOCORTICOID RECEPTOR (GR), MINERALOCORTICOID RECEPTOR (MR) AND 11-BETA-HYDROXYSTEROID DEHYDROGENASE TYPE 2 (11βHSD2)

F.M. Moodie, J. Noble, J. Satangi, J. Seckl. GI and Mol. Endocrinology Units, Western General Hospital, Edinburgh, University, UK

Background: Recent studies suggest that altered tissue sensitivity to glucocorticoids may underlie steroid insensitivity in patients with Ulcerative Colitis (UC). The expression of mdr1a, GR, MR and 11βHSD2 (a key enzyme in the inactivation of circulating glucocorticosteroids-GCs) along a healthy colon and the effect of altered levels of GCs on these key targets has not been studied in detail.

Methods: Wistar rats were either adrenalectomised (ADX), sham operated or had no surgery, and injected daily for one week with either dexamethasone (dex) [200μg/kg] or vehicle [2.5% et/OH]. Rats were sacrificed, colons removed, sectioned and snap-frozen. Radioactive in situ hybridisation was used to analyse mRNA distribution of the above genes in colonic epithelial cells (ECs).

Results: The expression of mdr1a mRNA was increased in the proximal colon compared to the distal colon (p<0.001), especially within the upper crypts. Dex treatment decreased mdr1a mRNA in all ECs. After ADX, mdr1a expression was increased in the upper crypt ECs (p<0.001). Both GR and MR increased after ADX (p<0.001), although dex treatment only reduced GR mRNA levels (p<0.05). 11βHSD2 mRNA was highest in ECs in the upper crypts compared to the base of the crypts (p<0.01), however in the distal colon all ECs expressed high levels. After ADX 11βHSD2 mRNA increased both within cells in the crypt axis and along the colon.

Conclusion: Expression of mdr1a and 11βHSD2 varies within the crypt axis and along the colon, in contrast to GR and MR. In particular GC excess down-regulation of GR may reduce steroid sensitivity, but this is set against dex-induced reduction in MDR and 11βHSD2 which favours GC. GCs influence colonic expression of these genes, and may directly influence the efficacy of steroids in the treatment of UC.

198 FATTY ACIDS ACT DIRECTLY ON INTRACELLULAR CALCIUM STORES TO RELEASE CALCIUM IN THE ENTEROENDOCRINE CELL LINE, STC-1

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Background and Aims: Nutrient-sensing mechanisms in the gut epithelium are poorly characterized. Fatty acids with chain length =12 carbon atoms increase intracellular Ca++ levels to stimulate cholecystokinin (CCK) release from enterodocrine cells. Using the CCK-producing enterodocrine cell line, STC-1, and monitoring intracellular Ca++, we investigated (a) whether classical intracellular pathways transduce the fatty acid signal, or (b) whether fatty acids act directly on intracellular stores to release Ca++.

Methods: STC-1 cells were loaded with Ca++ sensitive fluorescent dyes, and the intracellular Ca++ level was measured ratiometrically using a fluorescence-microscope imaging system. (a) Intact cells (Fura-2-loaded cytoplasm) were exposed to fatty acid solutions (C8, C10, C12, C18:1) under several conditions, e.g. removal of extracellular Ca++, or pretreatment with drugs that block candidate signal transduction pathways. (b) To examine direct effects of fatty acids on the intracellular Ca++ store, Ca++ release was measured in cells permeabilised using Streptolysin O. In permeabilised cells, the calcium store compartment was loaded with the lower affinity dye, Mag-fura-2.

Results: (a) Fatty acids (C12 and C18:1), but not C8 or C10 induced a dose-dependent increase in the cytosolic Ca++ level, occurring in the presence or absence of extracellular Ca++. Various G protein blockers, phospholipase inhibitors, protein kinase inhibitors, IP3 receptor antagonists and ryanodine receptor antagonists all failed to abolish fatty acid-induced Ca++ responses. (b) In permeabilised cells, C12 induced release of stored Ca++ in a dose-dependent manner, as did the physiological Ca++ releaser IP3. The fatty acid chain length specificity in permeabilised cells was unchanged from intact cells.

Conclusions: Fatty acids (= C12) induce Ca++ release from intracellular Ca++ stores, independently of the presence of extracellular Ca++. The data strongly suggest that fatty acids can act directly on the intracellular Ca++ store to release Ca++, by a novel nutrient sensing mechanism, operating independently of the major transcellular signal pathways.

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199 C DIFFICILE TOXIN A INDUCES RAPID AND SELECTIVE MONOCYTE CELL DEATH

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Introduction: C difficile causes an intense inflammatory colitis through the actions of secreted toxins A and B. Responses of immune cells to C difficile toxins appear to be pivotal in the progression of the

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<td>0.12 (± 0.008)*</td>
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*p < 0.05, †p < 0.01, ‡p < 0.001
Here we investigate whether a 32bp deletion of this gene (CCR5 32), implicated in susceptibility to, and progression of, HIV disease, is associated with BD.

Methods: We studied 350 BD patients and 559 healthy ethnically matched controls recruited from 3 ethnic groups (Turkish: 109 BD, 96 controls; Palestinian: 100 BD, 98 controls; UK white Caucasian: 131 BD, 365 controls). Genotyping for the CCR5 32 deletion was performed using PCR-SSP. Data were stratified by the presence of HLA-B*51, an allele previously shown to be associated with BD in the 3 ethnic groups.

Results: The CCR5 32 allele was significantly more common in UK white Caucasians than in either the Turkish or Palestinian cohorts (control allele frequency 14.2%, 4.2% and 0.5% respectively; P<1x10^-6). No association was found with the CCR5 32 allele and BD in any of the three cohorts, even when stratified by the BD-associ- ated HLA-B*51 allele.

Conclusions: The CCR5 32 allele is common in UK white Cauca- sians but rare in both Turkish and Palestinian populations. The CCR5 32 allele is not associated with Behcet’s disease in white UK Cauca- sians, Turkish, or Palestinian populations.

202 FUNCTIONAL CANNABINOID RECEPTOR EXPRESSION IN NORMAL HUMAN COLONIC EPI THELIUM

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Background and Aims: We investigated the presence of functional cannabinoid receptors in normal human colonic epithelial cells and purified normal human colonic epithelial cell lines, HT29 and CaCo.

Methods: The location of both the CB1 and CB2 receptors in normal human colonic biopsies was determined by immunohistochemistry. Purified normal human colonic epithelial cells from resected tissue and human colonic epithelial cell lines were treated with both synthetic and endogenous cannabinoids in vitro. Phosphorylation of the p42/44 mitogen-activated protein kinases (MAPKs) and glycogen synthase kinase (GSK3α/β) was tested by Western immunoblotting.

Results: CB1 receptor expression was evident in colonic epithelium as well as smooth muscle and the submucosal myenteric plexus. The signal was particularly strong on the apical membrane of the epithelial cells. CB2 receptor expression was expressed on plasma cells and macrophages in the lamina propria. Both purified primary colonic epithelial cell lines and related cell lines responded to cannabinoids by activation of the p42/44 MAPK pathway and phosphorylation of GSK3α/β.

Conclusions: Given the accepted role of colonic epithelium in immune host responses and the inflammatory bowel diseases, the presence of functional cannabinoid receptors in normal human colon implies a role for the endocannabinoid system in normal gastrointestinal physiology, which may impact on mucosal immunity and modulate inflammation.

203 IMMUNITY TO CRYPTOSPORIDIUM PARVUM: A ROLE FOR IL-4 IN THE EARLY ADAPTIVE IMMUNE RESPONSE

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Introduction: Immunological control of Cryptosporidium parvum infection is dependent on a Th1 response with interferon-γ production. However, in a neonatal murine infection model we have shown that the Th2 cytokine IL-4 is also involved as BALB/c IL-4 knockout (KO) mice develop more intense oocyst shedding at the peak of infection (Day 7) than wild-type mice. Paradoxically, at this time, no increase in IL-4 mRNA could be detected in the intestines of wild-type mice.

Methods: The CCR5 32 allele is common in UK white Cauca- sians but rare in both Turkish and Palestinian populations. The CCR5 32 allele is not associated with Behcet’s disease in white UK Cauca- sians, Turkish, or Palestinian populations.

204 ANALYSIS OF THE CC CHEMOKINE RECEPTOR CCR5 32 MUTATION IN BEHCETS’ DISEASE

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Background: Behcet’s disease (BD) is a chronic multi-system inflammatory disorder characterized by recurrent oral and genital inflammation, uveitis and pathergy. Reports of an association between HIV-1 infection and BD suggest that retroviruses may play a role in the pathogenesis of this disease. Chemokine receptors, CCR5 acts as a co-receptor permitting entry of the HIV-1 virus into CD4-positive T cells.
**TUMOUR NECROSIS FACTOR ALPHA MEDIATES HEPATOCYTES BEARING THE PHILADELPHIA CHROMOSOME TRANSLOCATION IN HUMAN LIVER**

I.S. Lean, S.A.C. McDonald, V. McDonald (introduced by A.B. Ballinger). Barts and the London Queen Mary’s School of Medicine and Dentistry, UK

**Introduction:** It has been suggested that TNF-α may play a role in immunity to infection by the intracellular parasite C parvum. Increased mucosal expression of this pro-inflammatory cytokine has been noted in the intestine of infected mice and humans whilst exogenous TNFα has been shown to reduce oocyst shedding in susceptible mouse models. However, its exact mechanisms of action and its importance in human infection have yet to be established.

**Methods:** The human enterocyte cell lines HT 29, Caco2 and the mouse enterocyte cell line CMT 93 were pre-incubated for 24 h with TNFα prior to infection with C parvum. Cells were incubated for a further 24 h then fixed and stained in Giemsa and the number of parasites estimated per 50 high power fields. Using previously established in vitro models of infection, the possible mechanisms of action involved were also studied. Finally, C57BL/6 TNFα deficient neonatal mice were infected with C parvum and the outcome of disease measured.

**Results:** TNFα inhibited the development of C parvum in all 3 enterocyte cell lines. In HT 29 cells TNFα led to a 29 (+/-10)% decrease in parasite numbers in concentrations as low as 0.04 ng/ml. One mechanism identified was the inhibition of invasion. Tryptophan depletion and alteration of intracellular iron did not appear to be involved. In the murine model of infection however, no significant difference was noted in either the course of infection or parasite burden between controls and mice lacking the functional gene for TNFα.

**Conclusion:** We have demonstrated that TNFα inhibits C parvum development in enterocytes. We have also identified, for the first time, a possible mechanism of its action. Although TNFα appears to have an inhibitory effect in vitro, it does not appear to be essential for recovery against infection in an in vivo mouse model.

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**HEPATOCYTES BEARING THE PHILADELPHIA CHROMOSOME REVEAL TRANSDIFFERENTIATION OF BONE MARROW TO LIVER WITHOUT TRANPLANTATION**

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**Introduction:** Bone marrow cells can cross lineage boundaries and transdifferentiate into a wide variety of cell types. Such plasticity is indicative of the possibility of a new combination therapy for the treatment of colon cancer.

**Methods:** Immunoprecipitations using anti-human topoisomerase II rabbit polyclonal antibodies were performed on proteins extracted from a pair of human colon cancer cell lines, HCT116 (WT, p53 KO, isogenic), following treatment with etoposide (VP16), a topoisomerase II inhibitor. Samples were subjected to 1 and 2 dimensional electrophoresis and associated proteins identified by MALDITOF mass spectrometry and confirmed by counter-immunoprecipitations. Newly identified interactions were then disrupted using chemical inhibitors in growth inhibition assays. The effect of the drugs, when used in combination with topoisomerase II inhibitors was also tested.

**Results:** Mass spectrometry and subsequent counter-immunoprecipitations identified heat shock protein 90 (HSP90) to be specifically associated with topoisomerase II. The use of VP16, a topoisomerase II poison, and geldanamycin (GA), an HSP90 inhibitor, when used in combination produced synergistic growth inhibition at concentrations where there is little or no effect when they are used individually.

**Conclusions:** (1) There is a direct physical interaction between topoisomerase II and HSP90. (2) Upon treatment with VP16 and GA it is stimulated a synergistic effect upon growth inhibition. (3) This is independent of p53 status. (4) These data demonstrate the possibility of a new combination therapy for the treatment of colon cancer.

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**THE MATURATION AND CYTOKINE EXPRESSION OF HUMAN DENDRITIC CELLS ARE DIFFERENTIALLY MODULATED BY PROBIOTIC BACTERIA**

A.L. Hart1,2, M.A. Kamm3, S.C. Knight1, A.J. Stagg1. 1APRG, Imperial College; 2St Mark’s Hospital, Harrow, UK

**Introduction:** Dendritic cells (DC) are antigen-presenting cells present throughout the gastrointestinal tract that interact with bacteria and determine the subsequent T cell response. Probiotic bacteria are effective in the treatment of some inflammatory bowel diseases. Probiotic bacteria modulate immune function, but the effect of these bacteria on DC is uncertain. This study aimed to determine whether probiotic bacteria influence DC phenotype and cytokine production.

**Methods:** DC were identified by multi-colour flow cytometry as an HLA-DR+ lineage (CD3, CD14, CD16, CD19, CD34, CD56) population in blood. Cell wall fractions of the 8 probiotic bacteria present in the probiotic combination VSL#3 in addition to Streptococcus faecalis, Escherichia coli Nissle strain and Lactobacillus casei (LPS) were prepared by sonication and centrifugation and cultured with whole blood. Changes in maturation and co-stimulatory markers (CD80, CD86, CD83 and CD40) and cytokine production (IL-12 and IL-10) were analysed by flow cytometry.

**Results:** The combination of organisms in VSL#3 downregulated IL-12 and upregulated IL-10 production by DC in a dose-dependent manner. All the individual components downregulated IL-12 production, but only the bifidobacteria strains enhanced IL-10 production. All the bacteria upregulated all the co-stimulatory and maturation markers...
with the exception of the bifidobacteria strains which downregulated CD80 expression. An anti-IL-10 antibody did not prevent this effect. LPS had opposing effects to VSL#3, enhancing IL-12 and decreasing IL-10 production. Co-culturing VSL#3 with LPS indicated cross-regulation of the DC cytokine response. The enhanced IL-12 seen with LPS alone was reduced in the presence of VSL#3 but IL-10 production seen with VSL#3 alone was maintained in the presence of IL-10. 

**Conclusions:** Probiotic bacteria differentially activate DC in vitro in a manner that may favour an anti-inflammatory T cell response.

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**EFFECT OF COX-2 INHIBITION ON SPECIFIC IMMUNE RESPONSES TO COLON CARCINOMA CELLS**

A.J. Walmsley1, S.E. Christmas2, A.J.M. Watson11 1Department of Medicine and 1Department of Immunology, University of Liverpool, UK

**Background:** We have previously demonstrated effective suicide gene therapy of MC26 colorectal cancer cells in vivo using the HSV-TK/GCV model system in mice. This therapy achieves successful tumour regression, possibly involving the immune response. This may be enhanced by inhibition of the cyclooxygenase-2 (COX-2) enzyme, which produces potentially immunosuppressive prostaglandins in vivo (e.g. PGE). COX-2 is also overexpressed in colon tumours, suggesting it has a role in colon carcinogenesis.

**Hypothesis:** Selective COX-2 inhibition will augment the specific host immune response to colon carcinoma cells.

**Methods:** The effect of a COX-2 inhibitor was studied on murine T-cell proliferation in response to mitogen and tumour cells. Splenocytes were isolated from control mice and mice that had undergone tumour induction with MC26 cells and regression following HSV-TK suicide gene therapy without tumour recurrence. The erythrocytes were lysed and the splenocytes were treated with either Con-A (2µg/ml) or irradiated MC26 cells (1:100 ratio of irradiated MC26: splenocytes), and the COX-2 inhibitor Rofecoxib. Proliferation was measured by 3H-thymidine incorporation after 3 or 7 days.

**Results:** Rofecoxib increased splenocyte proliferation in a mitogenic response over 3 days by 50% at concentrations above 1µM, which is known to inhibit PGE, production by >90% in vivo. Irradiated MC26 cells induced a 60% increase in control splenocyte proliferation over 7 days, enhanced to 100% by 1µM Rofecoxib. Splenocytes from treated mice showed a 300% increase in proliferation in response to irradiated MC26 cells also over 7 days, amplified to 450% by 1µM Rofecoxib.

**Conclusions:** A specific immune response is generated to tumour cells in mice that have undergone HSV-TK suicide gene therapy. COX-2 inhibition enhances this effect, possibly by inhibition of PGE production.

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**THE IDENTIFICATION OF P53 MUTATIONS IN METAPLASTIC BARTHET’S TISSUES: A PROGNOSTIC MARKER?**


We have analysed multiple biopsies from over 40 Barrett’s patients with a range of pre-malignant conditions, for the presence of p53 mutations. We have employed a molecular technique, the Restriction Site Mutation (RSM) assay to detect the presence of low-frequency p53 mutations. We have analysed multiple biopsies from over 40 Barrett’s patients with a range of pre-malignant conditions, for the presence of p53 mutations. We have employed a molecular technique, the Restriction Site Mutation (RSM) assay to detect the presence of low-frequency p53 mutations. The advantage of employing the RSM methodology in this study is that microdissection or flow cytometry of the tissue is not required to enrich the mutant cell population. Instead, the RSM methodology selects mutated sequences at the DNA level. Hence p53 mutations. We have analysed multiple biopsies from over 40 Barrett’s patients with a range of pre-malignant conditions, for the presence of p53 mutations. We have employed a molecular technique, the Restriction Site Mutation (RSM) assay to detect the presence of low-frequency p53 mutations. We have analysed multiple biopsies from over 40 Barrett’s patients with a range of pre-malignant conditions, for the presence of p53 mutations. We have employed a molecular technique, the Restriction Site Mutation (RSM) assay to detect the presence of low-frequency p53 mutations.

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**208 EFFECT OF COX-2 INHIBITION ON SPECIFIC IMMUNE RESPONSES TO COLON CARCINOMA CELLS**

A.J. Walmsley1, S.E. Christmas2, A.J.M. Watson11 1Department of Medicine and 1Department of Immunology, University of Liverpool, UK

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**Methods:** The effect of a COX-2 inhibitor was studied on murine T-cell proliferation in response to mitogen and tumour cells. Splenocytes were isolated from control mice and mice that had undergone tumour induction with MC26 cells and regression following HSV-TK suicide gene therapy without tumour recurrence. The erythrocytes were lysed and the splenocytes were treated with either Con-A (2µg/ml) or irradiated MC26 cells (1:100 ratio of irradiated MC26: splenocytes), and the COX-2 inhibitor Rofecoxib. Proliferation was measured by 3H-thymidine incorporation after 3 or 7 days.

**Results:** Rofecoxib increased splenocyte proliferation in a mitogenic response over 3 days by 50% at concentrations above 1µM, which is known to inhibit PGE, production by >90% in vivo. Irradiated MC26 cells induced a 60% increase in control splenocyte proliferation over 7 days, enhanced to 100% by 1µM Rofecoxib. Splenocytes from treated mice showed a 300% increase in proliferation in response to irradiated MC26 cells also over 7 days, amplified to 450% by 1µM Rofecoxib.

**Conclusions:** A specific immune response is generated to tumour cells in mice that have undergone HSV-TK suicide gene therapy. COX-2 inhibition enhances this effect, possibly by inhibition of PGE production.
expression of the mutant forms of both human and mouse p53. However, highest degrees of apoptosis were obtained in these cell lines with expression of the Scottin gene. No apoptosis was seen following expression of any of the constructs in OE19 cells.

**Conclusion:** We have succeeded in inducing apoptosis in three different oesophageal cancer cell lines following introduction of wild type p53. This effect was enhanced using mutant forms of p53 and was greatest following expression of the Scottin gene. Having established a successful gene transfer model for induction of apoptosis in cell lines, it would be of great interest to test this on human oesophageal biopsies to explore its potential as a future gene therapy.

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**212 BREAST MILK LACTOFERRIN REGULATES GENE EXPRESSION BY BINDING TO EXTRACELLULAR PRO-INFLAMMATORY CPG DNA SEQUENCES, BUT NOT NUCLEAR DNA**

P. Mulligan, N.R.J. White, G. Monteleone, P. Wang, J.W. Wilson, Y. Ohhtsuka, I.R. Sanderson. 1Department of Adult and Paediatric Gastroenterology, St. Bartholomew’s and the Royal London School of Medicine and Dentistry, London, UK; 2Unita di Gastroenterologia, Dipartimento di Medicina Interna, Universita di Roma Tor, Vergata, Roma, Italy; 3Department of Pediatrics, Juntendo University, Tokyo, Japan

We hypothesised that lactoferrin (LF) alters the expression of immune genes in the infant intestine by binding to DNA. We examined both the direct and indirect effects on immune gene regulation of its binding to DNA. Two biologically relevant compartments were studied: binding to pro-inflammatory, bacterial DNA sequences (CpG motifs) in the extracellular environment, and binding to gene promoters in the cell nucleus. LF inhibited CpG motif-induced NF-κB activation and IL-8 and IL-12 gene transcription in B-cells at LF concentrations greater than 0.5 μM. However, the interesting finding was that cell lines, Caco-2 and HT-29, were unresponsive to CpG motifs under a variety of conditions. Using three independent techniques, we demonstrated that LF does not regulate reporter gene transcription, nor does it bind specifically to putative response elements. We concluded that no LF localisation into enterocyte and lymphocyte nuclei by tagging the LF with green fluorescent protein. Purification of intact, DNA-binding LF from the urine of preterm infants has been previously described, indicating significant survival and transcytosis or leakage of LF across the infant intestine. This suggests that lymphocytes in the lamina propria and Peyer’s patches of the infant intestine are exposed to high concentrations of LF. We conclude that DNA binding by LF extracellularly, but not in the nucleus, is an important mechanism of immune gene regulation. Such a mechanism is likely to function in B-cells exposed to bacterial DNA in the lamina propria and Peyer’s patches of the breast-fed infant.

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**213 THE EFFECT OF SIROLIMUS ON THE NEUTROPHIL OXIDATIVE BURST**

I. Gee, A. Trull, S. Charman, G.J. Alexander. Departments of Medicine & Biochemistry, University of Cambridge School of Clinical Medicine, Addenbrooke’s Hospital, Hills Road, Cambridge, CB2 2QQ, MRC biostatistics unit, Cambridge

**Introduction:** Sirolimus is an immunosuppressive drug that is being used increasingly in transplant recipients. It has been observed that some patients develop bacterial sepsis during treatment.

**Methods:** We have developed a physiological in vitro model to investigate the effects of therapeutic concentrations of sirolimus on the neutrophil oxidative burst (NOB), a mechanism by which immunity to bacterial and viral infection may be impaired. Whole blood from 24 healthy subjects was equilibrated with 0, 1, 5, 10 and 50g/L sirolimus or 60ng/L propofol (a known inhibitor of neutrophil function) for 2 hours at 37°C. The cells were washed and the neutrophils stimulated with phorbol myristate acetate (PMA). NOB was measured by flow cytometry using the fluorescent marker dichlorofluorescin.

**Results:** A significant mean inhibition of NOB (95% C.I. of mean % inhibition did not overlap zero) was found with 50ng/L sirolimus (mean 6.3; C.I. 1.5, 11.1 %) and 60ng/L propofol (mean 5.1; C.I. –1.3, 10.6; NS) but inhibition was <1.5% at lower concentrations. Repeated measures ANOVA confirmed a linear relationship between sirolimus concentrations and inhibition of NOB (P<0.01). The two hour incubation period had no effect on red blood cell integrity or white cell viability in vitro.

**Conclusion:** Sirolimus had a dose-dependent inhibitory effect on NOB but this was not significant at low therapeutic concentrations. This may partly explain the predisposition to sepsis in patients receiving sirolimus. The 2 hour exposure of blood cells to sirolimus in these studies probably underestimates the in vivo effects of sirolimus and we are currently investigating the effect of chronic oral dosing with sirolimus on NOB.

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**214 INFLAMMATORY BOWEL DISEASE POSTERS: 214–258**

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**215 FAECAL CALPROTECTIN AS AN AID TO DIAGNOSIS IN INTESTINAL INFLAMMATION**

S. Dolwani, J. Wassell, M. Metzner, H. Lasty, A. Yong, B.W. Lawrie, A.B. Hawthorne. 1Departments of Gastroenterology, 2Clinical Biochemistry & Radiology, University Hospital of Wales, Cardiff, UK

**Background/aims:** The neutrophil derived protein Calprotectin has previously been found to be raised in intestinal inflammatory conditions. We aimed to evaluate the discriminant value of a stool calprotectin assay in predicting the likelihood of an abnormal result on a Barium follow through examination (BaFT) in patients being investigated for abdominal pain and diarrhea.

**Patients and Methods:** Patients being investigated for abdominal pain and diarrhea undergoing a BaFT as part of their workup (n=65) provided a one off stool sample for estimation of calprotectin level. This was compared with patients with known active Crohn’s disease (positive controls), normal healthy volunteers & patients with irritable bowel syndrome (IBS) as negative controls. The biochemist
INNATE IMMUNOGENETICS AND INFLAMMATORY NOD2/CARD15 MUTATIONS IN THE DISTINCT SUBSET OF CHEMOKINES, INDUCED IN Type.

Two novel MAL (TIRAP) SNPs, 4 novel Triggering receptor expressed hypo-responsiveness) HC 4.4, CD 3.1 (0.34) and UC (4.9 (0.71).

The University of Oxford, Oxford, UK

Patient’s being investigated in a gastroenterology clinic for diarrhoea and or abdominal pain do not need small bowel radiology to rule out Crohn’s disease if their stool calprotectin level is <60 µg/g.

**216 INNATE IMMUNOGENETICS AND INFLAMMATORY BOWEL DISEASE (IBD)**


**Background:** The identification of NOD2(CARD15) as a susceptibility gene for Crohn’s disease (CD) confirms the role of innate immunity in IBD. More recently a haplotype at IBD5 (Ch 5) has shown association with CD.

**Aims:** To identify and test innate immunity single nucleotide polymorphisms (SNPs) for association with IBD.

**Methods:** Interesting (positional and functional) SNPs were identified from databases or by direct sequencing. A two-stage approach was adopted to overcome problems of multiple testing. Stage 1: Case-control analysis (191 CD, 247 ulcerative colitis (UC) and 240 controls (HC)). Stage 2: Positive results from stage 1 to be confirmed by the transmission-disequilibrium test (TDT) (556 IDB (294 CD and 252 UC) trios). All results were stratified by phenotype and NOD2/IBD5 genotype.

**Results:** Case-control analysis (all % allele frequency (p value)): Toll-like receptor (TLR) 2, 3 intrinsic SNPs and 1 microsatellite marker, no IBD association. TLR2 ‘bacterial hypeersponsive’ SNP (R753Q), HC 4.0, IBD 2.5 (0.13), UC 2.4 (0.12) and CD 2.6 (0.25). Fulminant UC requiring surgery (135 cases) 0.4%

**Conclusion:** Patients being investigated in a gastroenterology clinic for diarrhoea and or abdominal pain do not need small bowel radiology to rule out Crohn’s disease if their stool calprotectin level is <60 µg/g.

**217 A DISTINCT SUBSET OF CHEMOKINES, INDUCED IN COLONIC EPITHELIUM BY IL-1β, DOMINATES THE MUCOSAL CHEMOKINE RESPONSE IN ULCERATIVE COLITIS**

J. Puleston1, M. Cooper2, S. Murch1, S. Makki1, P. Ashwood1, F. Torrente1, A. Bingham1, H. Green1, P. Moss1, A. Dhillon1, R. Gelinas1, R. Pounder1, A. Platt1, Royal Free Hospital, London, NW3 2QG, UK; 2Celltech R&D Ltd, Cambridge, CB1 6DS, UK

**Purpose:** Inflammatory bowel disease (IBD) is characterised by intense mucosal recruitment of activated leukocytes. As chemokines determine inflammatory leucocyte recruitment and retention, we compared expression of the entire chemokine family within colonic mucosa from IBD patients and uninflamed controls.

**Methods:** A microarray, representing every member of this superfamily and their cognate receptors, was hybridised with probes derived from colonoscopic biopsies. The array levels were correlated with histopathological inflammatory scores and expression of their cognate receptors by quantitative PCR and immunohistochemistry. Flow cytometry was performed on mucosally-derived colonic cells, Caco-2 and keratinocyte cell lines were stimulated with IL-1β and TNF-α, and analysed using the same microarray.

**Results:** A distinct subset of chemokines, consisting of CXCLs 1–3 and 8 and CCL20, was upregulated in active colonic IBD compared to uninflamed areas or tissue from controls. This corresponded to histopathological scores. Increased expression of their cognate receptors, CXCR1, CXCR2, and CCR6, was confirmed by quantitative PCR and immunohistochemistry. Flow cytometry revealed an increase of CCL20 expression on epithelial cells in IBD specimens, particularly in severe disease. An identical chemokine response was induced in Caco-2 cells by stimulation with IL-1β, but not TNF-α. By contrast, IL-1β and TNF-α were synergistic in keratinocytes.

**Conclusion:** IL-1β appears to be the pivotal mediator of an epithelial response that dominates the mucosal chemokine environment in ulcerative colitis. These data suggest several new therapeutic targets for IBD, as well as identifying a previously unrecognised co-ordinated epithelial chemokine response.

**218 NOD2/CARD15 MUTATIONS IN THE EXTRAGUTTENAL MANIFESTATIONS (EIMS) OF INFLAMMATORY BOWEL DISEASE**

T.R. Orchard2, T. Ahmad2, D.P. Jewell1, 1St Mary’s Hospital, London, UK; 2Gastroenterology Unit, University of Oxford, UK

**Introduction:** There has been much interest in the role of the innate immune system in inflammatory rheumatological conditions. CARD15 plays an important role in triggering an immune response to bacterial LPS, and polymorphisms in this gene are associated with Crohn’s disease (CD). We have previously shown a genetic predisposition to EIMs, and have demonstrated abnormalities in the humoral immune response to enterobacteria in patients with arthritis associated with IBD. This study was performed to investigate whether polymorphism in the CARD15 gene are associated with the presence of EIMs in IBD.

**Methods:** DNA was obtained from 104 patients who had suffered Type 1 or Type 2 peripheral arthritis, erythema nodosum (EN) or uveitis (60 Crohn’s disease and 44 ulcerative colitis). Genotyping for the 3 common polymorphisms of CARD15 (Arg702Trp, Gly908Arg and Leu1007fsinsC) was undertaken by SSP PCR, and allele frequencies were compared with 354 healthy controls and 244 CD patients.

**Results:** Allele frequencies (%) are shown in the table below: EIMs were significantly associated with CARD15 polymorphisms, when compared to controls, particularly type 1 arthritis and EN. Further analysis was undertaken by IBD diagnosis, and the association between CARD15 polymorphisms and EIMs was seen in both UC and Crohn’s patients.

**Discussion:** CARD15 polymorphisms may be important in determining the EIMs of IBD, suggesting that bacteria may trigger

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**Abstract 215**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Normal BoFT</th>
<th>Abnormal BoFT</th>
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</thead>
<tbody>
<tr>
<td>Calprotectin &lt;60 µg/g</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Calprotectin &gt;60 µg/g</td>
<td>15 (6 IBD, 4 IBS, 4 others)</td>
<td>16 (1 awaiting colonoscopy)</td>
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</table>

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**Abstract 218**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Controls n=354</th>
<th>CD pts n=244</th>
<th>EIMs n=104</th>
<th>Type 1 PeA n=40</th>
<th>Type 2 PeA n=30</th>
<th>EN n=27</th>
<th>Uveitis n=21</th>
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</thead>
<tbody>
<tr>
<td>Arg702Trp</td>
<td>5.2</td>
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<td>12.5*</td>
<td>11.3*</td>
<td>11.7*</td>
<td>12.9*</td>
<td>14.3*</td>
</tr>
<tr>
<td>Gly908Arg</td>
<td>1.4</td>
<td>3.3*</td>
<td>1.4</td>
<td>3.8</td>
<td>0</td>
<td>5.6</td>
<td>2.4</td>
</tr>
<tr>
<td>1007fsinsC</td>
<td>1.6</td>
<td>9.4*</td>
<td>8.7*</td>
<td>12.5*</td>
<td>6.7</td>
<td>14.8*</td>
<td>9.5*</td>
</tr>
</tbody>
</table>

* vs controls p<0.001.
Abstract 219, Table 1 Allelic frequencies for CD, UC, and HC. Results are expressed as percentages and comparisons are between CD and HC.

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
<th>HC</th>
<th>χ²</th>
<th>p value</th>
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<tr>
<td>A299G</td>
<td>10.3</td>
<td>6.8</td>
<td>8.8</td>
<td>0.53</td>
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<tr>
<td>T159C</td>
<td>49.0</td>
<td>52.5</td>
<td>50.5</td>
<td>1.2</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Abstract 219, Table 2 Genotype frequencies for CD, UC and HC (%). Genotypic status did not correlate with any phenotypic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>WW</th>
<th>WM</th>
<th>MM</th>
<th>WW</th>
<th>WM</th>
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<th>WW</th>
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<tbody>
<tr>
<td>CD</td>
<td>79.5</td>
<td>19.7</td>
<td>0.8</td>
<td>25.6</td>
<td>50.8</td>
<td>23.6</td>
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<tr>
<td>UC</td>
<td>86.3</td>
<td>12.9</td>
<td>0.8</td>
<td>21.9</td>
<td>50.6</td>
<td>27.5</td>
<td></td>
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<tr>
<td>HC</td>
<td>83.0</td>
<td>16.5</td>
<td>0.5</td>
<td>20.9</td>
<td>54.8</td>
<td>23.3</td>
<td></td>
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</tr>
</tbody>
</table>

In order to investigate the contribution of rare variants to CD we have selected 100 Crohn’s patients who are heterozygous for one of the three associated DSAs (R702W, Q891X, or 1007fs) for comprehensive mutation screening. The coding sequence of CARD15 was screened by denaturing HPLC for mutations to identify both common polymorphisms and rare variants. 21 patients had one or more additional rare CARD15 mutations, 10 of which were non-synonymous. One of these was a novel nonsense mutation that would produce a truncated protein (R996X), and four (R235C, S431L, A612T, R1019G) were amino acid substitutions that were predicted to alter the function of the protein. The finding that only a minority of patients who are heterozygous for common disease susceptibility alleles in CARD15 have a second mutation is consistent with the gene dosage model for CARD15 in Crohn’s disease.

221 GENETIC EVIDENCE FOR INTERACTION OF THE 5Q31 CYTOKINE LOCUS AND THE CARD15 GENE IN CROHN’S DISEASE

M.M. Mirza1, S.A. Fisher2, K. King1, A.P. Cuthbert1, J. Hampe3, J. Sander1son1, J. Mansfield1, P. Donaldson1, A. Macpherson1, A. Forbes1, S. Schreiber1, C.M. Lewis1, C.G. Mathew1. 1Dept of Medical & Molecular Genetics, OKT School of Medicine, Guy’s Hospital, London, UK; 2Dept of Gastroenterology, St Mark’s Hospital, Harrow, UK; 3Inst. of Experimental Immunology, Christian-Albrechts-Universität, Kiel, Germany.

Introduction: Three sequence variants in the CARD15 gene have recently been reported to be strongly associated with Crohn’s disease (CD) in Canadian families. We analysed 2 SNPs from this haplotype (C2063G and C2198G) in 267 individuals, and found them to be in strong linkage disequilibrium (D* = 0.91). The C2063G SNP was then genotyped in Northern European IBD families which contained a total of 511 offspring affected with CD and 320 with ulcerative colitis (UC). Excess transmission of the 2063G allele was observed in CD (p = 0.011) but not in UC. Genotyping of C2063G in an independent set of unrelated British cases with CD (n = 684) and UC (n = 388) and in 701 British controls showed that the 2063G allele was present at a significantly higher frequency in CD cases than in controls (p = 0.008), but was not increased in UC. However, the increase in disease risk was small (odds ratio 1.49 for homozygotes, 95% CI: 1.11–2.0). The disease risk haplotype frequency was significantly elevated in 943 CD patients who also carried mutations in the CD susceptibility gene CARD15 (p = 0.0018).

Conclusion: These results suggest that genetic variants at the 5q31 (IBD3) locus may hasten the onset of Crohn disease, and cooperate with CARD15 in disease causation.

222 PHOSPHOINOSITIDE SIGNALLING IN INFLAMMATION AND COLORECTAL CANCER

C.L.E. Osborne, O. Ogungbiyi, S. Keshav. Departments of Medicine and Surgery, Royal Free and University College Medical School, London, UK.

Background and Aims: Phosphoinositide 3-kinase gamma (PI3-Kγ) is a lipid kinase activated by G-protein coupled receptors (GPCR) to regulate such cellular functions as chemotaxis, cell proliferation and apoptosis. Transgenic mice that lack PI3-Kγ are immune suppressed and develop colorectal cancer (CRC), and mice lacking the G-protein subunit Ga11 that interact with PI3-Kγ develop ulcerative colitis (UC) and CRC. Patients with UC have a 30% lifetime risk of CRC and UC associated CRC (UC-CRC) develops by a distinct pattern of genetic changes to sporadic CRC. We investigated the expression of PI3-Kγ in colonic tissue from patients with UC, UC-CRC and CRC.

Methods: PI3-Kγ expression was investigated in normal colon, UC, CRC and UC-CRC by immunohistochemistry and in situ hybridisation. Using RT-PCR and western blotting, PI3-Kγ expression was determined in normal colonic mucosa, colonic epithelial cells, and the colon cancer cell line (Caco2). Methylation specific PCR was performed on Caco2 cell, sporadic CRC and UC-CRC DNA to determine if silencing of PI3-Kγ was associated with hypermethylation.

Results: The PI3-Kγ expression was demonstrated in leukocytes, colonic epithelial cells and Caco2 cells. All UC specimens expressed PI3-Kγ protein at higher levels than normal tissue, and expression was lost in the majority of UC-CRC. PI3-Kγ mRNA was detected in normal...
tissue, CRC and UC, but was absent in UC-CRC. In Caco2 cells treated with stimulated lymphocyte conditioned medium, expression of PI3-Kγ was increased, and as the gene is unmethylated in these cells, it is probably upregulated by inflammation, and subsequent loss of expression may be mediated by hypermethylation.

**Conclusion:** Loss of expression of PI3-Kγ is seen more frequently in UC-CRC than sporadic CRC and our data suggest that it plays a critical role in intestinal epithelial cell function in the context of inflammation, where its expression is increased. We hypothesise that subsequent loss of PI3-Kγ expression, possibly through hypermethylation, promotes neoplastic transformation in the inflamed colonic epithelium.

### 223 ANTI-INFLAMMATORY EFFECT OF N-ACETYLCYSTEINE (NAC) IN A MODEL OF COLITIS

O.G. Azzoq, A. De Silva, D.S. Rampton, A.B. Ballinger. Dept of Adult & Paediatric Gastroenterology, Barts & The London, Queen Mary’s School of Medicine & Dentistry, London, UK

**Introduction:** Oxidative stress is a potential mechanism in the pathogenesis of inflammatory bowel disease (IBD) where reactive oxygen species (ROS) are produced in excess by the intestinal mucosa. N-acetylcysteine (NAC) is a synthetic thiol compound which has antioxidant properties and suppresses production of NKx8, and proinflammatory cytokines including TNF-α.

**Aims:** The aim of this study was to assess the effect of NAC on the severity of colonic inflammation in a rat model of colitis.

**Methods:** Colitis was induced in Wistar rats by intrarectal administration of 2,4,6-trinitrobenzenesulfonic acid (TNBS) and rats treated with i.p. NAC (50 or 200 mg/kg/day) or saline control (B/group). 16 healthy controls were treated with either NAC (50 mg/kg/day) or saline. Animals were sacrificed 5 days after induction of colitis. Severity of intestinal inflammation was assessed macroscopically, and by measurement of colonic tissue myeloperoxidase (MPO) and water content. ROS were measured by chemiluminescence (CLS).

**Results:** TNBS induced distal colitis with ulceration, increased tissue MPO concentration and water content, and CLS (table). NAC reduced all these measures of intestinal inflammation except water content. There was no significant difference between 200 and 50 mg/kg of NAC.

**Conclusion:** NAC has anti-inflammatory effects in the acute phase of TNBS-induced colitis. This treatment may be worth further assessment in the treatment of human IBD.

### 224 SENESCENCE RATES AND TELOMERE SHORTENING IN CULTURED RECTAL FIBROBLASTS IN ULCERATIVE COLITIS

K.M. Getliffe, D.M. aldulaimi, C.U. Nwokolo. University Hospitals Coventry and Warwickshire NHS Trust and Dept of Biological Sciences, University of Warwick, UK

**Introduction:** Human somatic cells have a finite lifespan and cease to divide after a certain number of cell divisions, a phenomenon known as replicative senescence. One mechanism believed to trigger this process is continuous shortening of chromatosomal ends (telomeres), with each cell division until a critical length is reached at which cell replication ceases. In cancerous and normal proliferating cells (including the epithelial cells of the bowel) this mechanism can be bypassed by telomerase, which adds telomeric repeats to the ends of chromosomes to maintain their length and thereby prevent senescence. A telomerase knockout mouse suffers ulceration and atrophy of the bowel. In ulcerative colitis (UC), the colonic mucosa is deficient in telomerase and epithelial cells in inflamed areas have short telomeres. Furthermore, in UC patients we have observed a decrease in lymphocyte telomerase activity and others have found lymphocyte chromosomal abnormalities.

**Aim:** To determine whether these observations are caused simply by the increased cell turnover inherent in the inflammatory process or whether UC patients have a global telomere maintenance defect which contributes to the disease.

**Methods:** Rectal fibroblast cultures were generated from 9 UC patients and 9 age-matched non-UC controls; their rates of senescence and telomere lengths were assessed throughout their life span in culture. Senescence rates were measured by counting the percentage of cells staining for the proliferation marker Ki67 at each passage and telomere lengths were measured using a standard TRF measurement southern blotting assay.

**Results:** Preliminary results have identified little difference between the rates of senescence in UC and non-UC fibroblasts, suggesting that telomere/telomerase dysfunction is not global but may be a downstream effect of inflammation in this disease. However, this study is ongoing and further cultures are in the process of being analysed.

### 225 CIRCULATING TUMOUR NECROSIS FACTOR ALPHA CONCENTRATIONS AND PERIPHERAL CD4+ T CELL CHEMOKINE RECEPTOR EXPRESSION IN PATIENTS WITH PYODERMA GANGRENSUM

T.N. Brooklyn, A.M. Williams, C.S. Prabert. Bristol Royal Infirmary, Bristol, UK

**Background:** Pyoderma gangrenosum (PG) is recognised as an extraintestinal manifestation of inflammatory bowel disease (IBD). Recent reports of PG responding to infliximab suggest that tumour necrosis factor alpha (TNFα) may be important, although in our hands the response of PG to infliximab has been variable. Subsets of CD4+ T cells are functionally polarised according to their cytokine profile and one of the ways of identifying these groups of cells is to examine the chemokine receptors they express. Little is known of the cytokines involved in the development of PG and it is not known whether the disease fits a T-helper type 1 (Th1) or Th2 pattern.

**Aims:** To investigate the hypothesis that, if PG responds to infliximab, TNFα must be important in the pathogenesis of the disease and it is also likely that PG would display a Th1 phenotype.

**Patients:** Ten patients with PG, half of whom also had underlying IBD, were compared with seven healthy controls.

**Methods:** The concentration of circulating TNFα was determined using enzyme linked immunosorbent assay (ELISA). The expression of the chemokine receptors CCR4 and CXCR3 on CD4+ T cells was determined by flow cytometry. The results were compared using the Mann-Whitney U test.

**Results:** The plasma concentrations of TNFα in the PG patients were found to be significantly higher than in the healthy individuals (p=0.002). The expression of CCR4 on CD4+ T cells was significantly higher in the PG patients (p=0.048), but there was no difference in the expression of CXCR3.

**Conclusions:** Plasma concentrations of TNFα in patients with PG are significantly greater than those found in normal individuals, but not as high as those found in active IBD. Patients with PG preferentially express CCR4 not CXCR3 on peripheral CD4+ T cells, suggesting that PG may be a Th2 disease. These findings may explain the variable clinical response to infliximab.
**EFFECTS OF NICOTINE ON SPONTANEOUS AND LPS-INDUCED NF-κB ACTIVATION AND APOPTOSIS IN COLONRECTAL CELLS: RELEVANCE TO INFLAMMATORY BOWEL DISEASE?**

M.C. Aldhous, L.A. Stark, M.G. Dunlop, J. Satsangi. Gastrointestinal Research Laboratory, University of Edinburgh Department of Medical Sciences, and MRC Human Genetics Unit, Western General Hospital, Edinburgh, Scotland UK

**Background:** Complex genetic, environmental, and immunological interactions are involved in the pathogenesis of Crohn’s disease (CD). Mutations within the NOD-2 gene are present on up to 50% of patients with CD and clearly influence disease susceptibility and behaviour. Early functional data implicate NOD-2 as an intracellular sensor of bacterial lipopolysaccharide (LPS) which directly induces NF-κB activation. Cigarette smoking is the best defined environmental behaviour. Early functional data implicate NOD-2 as an intracellular marker of UC associated CRC, where it may play a role in B activation. Cigarette smoking is the best defined environmental behaviour. Early functional data implicate NOD-2 as an intracellular

**Methods and Results:** We have examined the effect of nicotine on NF-κB activation in SW480 colon cancer cells. Immunohistochemistry for NF-κB (p65) expression showed a dose-dependent increase in NF-κB activation after 30 minutes with nicotine alone, which was reversed by addition of LPS. Cells stimulated overnight with nicotine and/or LPS, showed a dose-dependent decrease in apoptosis with nicotine alone, which was modified by LPS. In kinetic studies using western blot analysis, nicotine induced degradation of the NF-κB inhibitor protein, IκB, within 1 hour and levels returned to baseline by 5 hours. Pre-incubation with nicotine for 1–5 hours inhibited IκB degradation in response to LPS.

**Conclusion:** These data indicate that nicotine directly influences NF-κB activity and suggest that nicotine may modify cellular responses to LPS. The consequent effects on cytokine production and apoptosis may help explain the effects of smoking in CD and have implications for the use of nicotine in smoking cessation therapy.

**DEVELOPMENT OF HUMAN ANTI-MURINE ANTAGONISTICS IN PATIENTS FOLLOWING TREATMENT WITH INFliximab**

L.P. Maiden, J.G. Lawson, A.W. Harris. Kent and Sussex Hospital Tunbridge Wells, Kent TN4 6AT, UK

**Introduction:** Infliximab is a 75% human and 25% murine antibody directed against tumour necrosis factor-alpha. Human anti-mouse antibody (HAMA) directed against the murine component of this antibody could develop in patients given infliximab. The estimated prevalence of HAMAs varies widely. Some studies report HAMAs in 1–80%. Most immuno-assays involve the use of mouse antibodies, e.g. thyroid function tests (TFTs). If present, HAMAs could interfere with these assays giving rise to misleading results with clinical consequences. The aim of this pilot study was to assess whether patients receiving infliximab for Crohn’s disease or Rheumatoid arthritis subsequently developed abnormal TFTs. If so, this could be due to the development of HAMAs as a result of exposure to infliximab.

**Method:** Patients who had received infliximab at the Kent and Sussex or Homeopathic Hospitals as treatment for Crohn’s disease or Rheumatoid arthritis between March 2000 and August 2001 subsequently had their TFTs assessed using the standard hospital assay. If any results were abnormal, the assay could be confirmed using “blocking agents” which filter out the HAMAs by binding to them.

**Results:** 19 patients (15 female; mean age=50 years, range 21–70), with either Crohn’s disease (n=3) or Rheumatoid arthritis (n=16), received infliximab (mean dose=3 infusions at 5mg/kg, range 1–7 infusions). TFTs were assessed between 3 and 15 months (mean=7 months) after the last infusion. One patient had abnormal TFTs. This patient was already known to be hypothyroid and was regularly taking thyroxine. No patients required repeat assays with blocking agents.

**Conclusion:** This pilot study has failed to show that HAMAs develop following, at least, a single infusion of infliximab. HAMAs may persist for up to 30 months after exposure. HAMAs may have developed but subsequently disappeared prior to the TFT assay, given that 3 patients had assays up to 15 months after their last infusions. Larger studies are needed to confirm these findings as the prevalence of HAMAs may be less than 1%.

**METASTATIC PANETH CELLS IN ULCERATIVE COLITIS AND COLORECTAL CANCER**

C.L.E. Osborne, A. Khan, O. Ogunbiyi, S. Keshav. Royal Free & University College Medical School, London, UK

**Background and Aims:** Paneth cell metaplasia (PCM) in the colon of patients with inflammatory bowel disease (IBD) represents a distinct form of host inflammatory response. Paneth cells secrete an array of antimicrobial proteins including lysozyme, defensins, and type IIa protease. Paneth cell granules can be used as an indicator of disease activity in UC and is also identified by the presence PLA2-IIa protein in Paneth cell granules. In the mouse model of familial adenomatous polyposis. We therefore investigated PLA2-IIa expression in UC, CRC, and UC-associated CRC by indirect immunohistochemistry. We compared ded sections of colon from UC, sporadically occurring CRC and UC-associated CRC.

**Results:** PLA2-IIa expression with positive (anti-CD45 antibody) and negative (anti-CD45 antibody) controls. Duration of one GMA session was 60 minutes, flow rate 30mL/minute. At week 12, CIA was 28.8% (n=46). The first two patients were in remission, 2 had improved, and 2 had relapsed. The treatment was well tolerated and no serious side effects were observed. In conclusion, GMA appeared to be an effective adjunct to standard drug therapy of active UC by promoting remission and suppressing relapse during steroid tapering. It seems that reduction of circulating level of activated granulocytes alleviates inflammation and improves the outcome of UC therapy.

**A REPORT ON THE CLINICAL EFFICACY AND STEROID SPARING EFFECT OF GRANULOCYTE AND MONOCYTE ADSORPTIVE APERESISIS IN PATIENTS WITH CORTICOSTEROID DEPENDENT ULCERATIVE COLITIS**


Frequent relapse during steroid tapering is common in many patients with ulcerative colitis (UC) who initially respond to intensive medication including a corticosteroid. Such cases are said to have steroid-dependent (SD) UC. Further, increased granulocyte and monocyte counts, activation and prolonged survival time is a feature of mucosal inflammation in active UC. Likewise, faecal calprotectin (a neutrophil protein) level parallels intestinal inflammation and predicts mucosal inflammation in active UC. Likewise, faecal calprotectin (a neutrophil protein) level parallels intestinal inflammation and predicts mucosal inflammation in active UC. Likewise, faecal calprotectin (a neutrophil protein) level parallels intestinal inflammation and predicts mucosal inflammation in active UC.
contributes to remission. However, the full efficacy of GMA is unlikely to be due to reduction of granulocytes per se. Results from other studies together with basic research indicate a marked decline in inflammatory cytokine generation and reduced CXCR3 expression by peripheral blood leucocytes post Adacolumn apheresis.

**References**


**230 A DOUBLE BLIND, PLACEBO CONTROLLED RANDOMISED TRIAL OF CURCUMIN EXTRACT IN THE TREATMENT OF STEROID DEPENDENT INFLAMMATORY BOWEL DISEASE**

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**Introduction:** Nuclear factor kappa B (NFκB) is a pro-inflammatory transcription factor which plays an integral part in the pathogenesis of inflammatory bowel disease (IBD). Curcumin has anti-inflammatory properties through prevention of NFκB activation and is effective in the TNBS model of colitis. We present the results of a trial of Curcuma extract (PYM 50014) as a steroid sparing agent in patients with IBD.

**Methods:** 27 patients with steroid dependent colitis were entered into the 16 week study. All patients were in remission on 5–30mg prednisolone per day, were 6 weeks from their last clinical relapse and were not being continued on another steroid sparing agent (e.g. azathioprine). Disease activity was assessed by either Ulcerative Colitis Index (UCI) or Crohn’s disease activity Index (CDAI), standard laboratory parameters (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count, albumin) and flexible sigmoidoscopy. Randomisation to PYM 50014 (3×220mg b.i.d) or placebo was at 2 weeks and steroid reduction began 2 weeks later. Patients were assessed every two weeks and their prednisolone reduced as long as they remained in remission. Primary end points were remission at 16 weeks, or relapse, and were not on any other steroid sparing agent (e.g. azathioprine). 13 patients received PYM 50014 (8 UC, 5 CD) and 14 placebo (8 UC, 6 CD). The groups were matched for sex, duration of disease and disease activity, although the PYM 50014 group tended to be younger (36.9 ± 10.3, 52.3 ± 12.7 years). 5 (38%) patients in the PYM 50014 group tended to be younger (36.9 ± 10.3, 52.3 ± 12.7 years). 5 (38%) patients in the PYM 50014 group tended to be younger (36.9 ± 10.3, 52.3 ± 12.7 years). 5 (38%) patients in the PYM 50014 group tended to be younger (36.9 ± 10.3, 52.3 ± 12.7 years). 5 (38%) patients in the PYM 50014 group tended to be younger (36.9 ± 10.3, 52.3 ± 12.7 years). 5 (38%) patients in the PYM 50014 group tended to be younger (36.9 ± 10.3, 52.3 ± 12.7 years).

**Discussion:** Whilst apparently safe, PYM 50014 does not appear to enable steroid dependent patients to reduce their steroid requirements. There may be a role for PYM 50014 in milder disease and further evaluation may be warranted.
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION OF DA-6034, A NEW INFLAMMATORY BOWEL DISEASE TREATMENT IN RATS


The absorption, distribution, metabolism, and excretion of DA-6034, which is being developed for the treatment of inflammatory bowel disease as an oral dosage form, were investigated using fluorescence-HPLC and LC/MS/MS method. The detection limit was 0.3 mg/ml in plasma. After intravenous administration of DA-6034, 10 mg/kg to rats, the plasma concentrations of DA-6034 declined polyexponentially with the mean terminal half-life of 3.4 hr. Total body clearance and renal clearance were 26.3 and 9.48 ml/min/kg, respectively and fraction of dose excreted in urine for 24 hr was 35.7%. The tissue to plasma ratios in S.I., L.I. and kidney were large, indicating high affinity of DA-6034 to rat GI tract tissues. After oral administration of DA-6034, 10 mg/kg to the rats, the absolute bioavailabilities were only 1.34%. Percents of dose remaining in the gastrointestinal tract were 55.2% of dose at 24 hr after oral administration of DA-6034. It was considered that the superior effect in experimental animal models of inflammatory bowel disease after oral administration of the drug was due to the local action of DA-6034. No metabolites of DA-6034 were produced in the rat liver microsome without and with NADPH generating system. Glucuronide- and sulfate- conjugation were not involved in DA-6034 metabolism. And DA-6034 was not a substrate for OATP or OATP transporter, involved in DA-6034 metabolism. And DA-6034 was not a substrate of human CYP3A4, therefore, clinically significant drug interactions are not expected.

THIOPURINES, BUT NOT CORTICOSTEROIDS OR 5-ASA, REDUCE THE NUMBER OF PLATELET-LEUCOCYTE AGGREGATES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background: We have previously shown that formation of platelet-leucocyte aggregates (PLAs) is increased in patients with IBD (UEGW 2000) and correlates with platelet activation (BSG 2001). To see if drugs commonly used to treat IBD affect PLA formation, platelet and neutrophil activation.

Methods: Of 66 patients with IBD (31 Crohn’s, 35 ulcerative colitis), 17 patients were on thiopurines (11 azathioprine, 2 6-mercaptopurine), 17 prednisolone or hydrocortisone and 35 5-ASAs. Venous blood was drawn into EDTA/CTAD anticoagulants. Samples were immediately mixed and then analysed by flow cytometry for P-selectin (CD62P for platelet activation), L-selectin (CD62L for neutrophil activation) and CD42a/CD45 (platelet-leucocyte aggregates). The detection limit was 0.5 ng/ml in 10 UL.

Results: Patients taking thiopurines had fewer PLAs (median (IQR)) (0.28 (0.20–0.38) × 10^10/L, n=17) than those that were not (0.37 (0.25–0.60), n=49, P<0.05). The number of platelets expressing P-selectin was similar in both groups (thiopurines 3.1 (1.1–6.0) × 10^10/L, no thiopurines 3.7 (1.9–8.7) × 10^10/L) as was expression of L-selectin on neutrophils (thiopurines 802 (793–814), no thiopurines 792 (780–808)). There was no difference in any of these variables between patients taking and not taking corticosteroids or 5-ASAs.

Conclusions: Thiopurines, but not corticosteroids or 5-ASAs, decrease the number of platelet-leucocyte aggregates in patients with IBD. None of these agents appeared to affect platelet and neutrophil activation. It is conceivable that inhibition of platelet-leucocyte aggregate formation could contribute to the therapeutic efficacy of thiopurines in IBD.

TREATMENT OF ZERO AND INTERMEDIATE TPMT PATIENTS WITH A TAILORED DOSE OF AZATHIOPRINE

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Background: Deficiency of thiopurine methyl transferase (TPMT) is associated with a high risk of adverse effects on azathioprine (AZA) therapy. Conventionally, AZA is avoided in patients with zero TPMT (1 in 300) and those with heterozygous TPMT deficiency (1 in 10).

Aims: To study the outcome of TPMT deficient patients receiving a tailored low dose of AZA.

Methods: According to a department protocol, patients with zero TPMT were offered treatment with 5% usual dose, heterozygotes with 1mg/kg AZA. Thioguanine nucleotide (TGN) levels were assayed in a proportion of cases. In addition, a questionnaire was sent to physicians regarding the outcome of patients referred for TPMT assay from outside the author’s institution.

Results: Two patients with zero TPMT (one CD, one UC) responded to 5% dosing with a prompt and full clinical remission (HBI / Truelove and Witts score). Both had remained in steroid-free remission for two years. TGN levels were very high yet both remained free of myelotoxicity. 26 heterozygotes 12 CD, 7 UC, 2 autoimmune hepatitis, and 5 with oral ulceration were treated. 20 (77%) patients responded to treatment, 1 did not respond and 5 withdrew treatment as a consequence of side effects (19%). TGN levels were variable and did not correlate with response or side effects. Of 92 questionnaires sent, 51 replies were obtained. Of these, only 15 patients started azathioprine at 1mg/kg. 11/15 (73%) responded to treatment, 2 failed, and 2 withdrew due to side effects. In 36/51 (71%) the requesting physician decided not to use azathioprine due to the low TPMT level.

Conclusions: Physicians generally avoid AZA in patients with TPMT deficiency. However, the results of this study show that heterozygous patients respond well to low dose AZA. Furthermore, zero TPMT patients can be successfully treated with a very low dose of AZA.
GENETIC DETERMINANTS OF THE THIOPURINE METHYLTRANSFERASE INTERMEDIATE ACTIVITY PHENOTYPE

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Background and aims: Polymorphism in the TPMT gene open reading frame (ORF) is associated with reduced TPMT activity. Variable number tandem repeats (VNTR*3 to VNTR*9) in the promoter region of the TPMT gene have been previously reported to modulate the TPMT activity phenotype. The aim of this study was to investigate the relationship between TPMT activity and ORF and VNTR genotypes.

Methods: Groups of patients were selected with non-overlapping TPMT activities from the intermediate activity range (4–8 U, 108 patients) and normal range (12–15 U, 53 patients) and were genotyped for VNTR type, and TPMT*3A, TPMT*3C, and TPMT*2 ORF mutations. To investigate the influence of the number of VNTR repeat units on TPMT activity, the number of Type A, B, or total repeat units summed for both alleles of the ORF heterozygous, wild type intermediate and normal activity groups and were compared in an analysis of variance.

Results: 41% of patients from the intermediate TPMT activity group were heterozygous for a TPMT ORF mutation. Marked linkage disequilibrium was noted between VNTR*6b - TPMT*3A (D = 1), VNTR*7b - TPMT*3C (D = 0.67) and VNTR*8b - TPMT*1 (D = 1) alleles. For Type A and total repeats, significant differences (p<0.05) in the median number of repeats were found between the heterozygous intermediate activity group and the wild type intermediate and normal activity groups. There was no significant difference in the median Type A, B, or total repeat number between the two wild type groups.

Conclusions: These results suggest that TPMT gene VNTRs do not significantly modulate TPMT enzyme activity.

THIOPURINE POLYMORPHISM IN THE MTHFR GENE AFFECTS TPMT ACTIVITY

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Background: Polymorphisms in the thiopurine methyl transferase (TPMT) gene only explain a proportion of side effects on azathioprine (AZA). S-adenosylmethionine (SAM) is the methyl donor for methylation by TPMT and is converted to S-adenosyl-homocysteine (SAH). The adenosyl moiety of SAM is cleaved and homocysteine can be remethylated to methionine in a folate dependent pathway. A common polymorphism in the methylene tetrahydrofolate reductase (MTHFR) gene, the 677C>T variant is associated with decreased MTHFR enzyme activity and thus may indirectly affect TPMT activity.

Methods: MTHFR TI genotype frequency was assessed in 52 patients with wild type TPMT genotype but intermediate TPMT activity (4–8U) and compared to 53 patients with normal TPMT activity and genotype (in the range 12–15U). MTHFR genotype frequencies were then compared between 57 IBD patients with adverse drug reactions to AZA therapy and 71 patients tolerant to AZA.

Results: MTHFR TI genotype was significantly underrepresented in the normal compared to the intermediate activity group (7.3% vs. 23% (p=0.0296)). Despite this, MTHFR genotype was not significantly associated with an increase in overall side effects to AZA. The MTHFR 677C>T allele was less frequent amongst those with hepatitis and pancreatitis on AZA (4/16(25%) vs 35/71(49%) but this association did not reach statistical significance (p=0.6).

Conclusions: MTHFR genotype influences TPMT activity such that wildtype MTHFR genotype is associated with high methylation capacity. High TPMT activity has been suggested as a cause of pancreatic and hepatic side effects but could not be confirmed in this study. Larger studies are needed to explore this relationship further.

ADENOMATOUS POLYPS ARE RARE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Objective: The prevalence of adenomatous colorectal polyps in inflammatory bowel disease (IBD) is unknown, although recent reports suggest they might be rare in patients with ulcerative colitis (UC). Previous work has suggested 5-ASA compounds may protect against colorectal cancer. The aim of this study was to compare the prevalence of left sided adenomas in patients with IBD with a local age matched control population.

Method: We reviewed the medical notes of 106 patients with histologically proven IBD, aged 55–64 years at the time of endoscopy for the presence of left sided colonic adenomas. Patients were identified through our endoscopy/histology databases. The prevalence of adenomas was compared with a healthy control population in Leicestershire aged 55–64 years who participated in a screening programme for colorectal cancer with flexible sigmoidoscopy.

Results: Of 106 patients (61 male, 45 female, mean age 59 years), 80 suffered from UC, 20 from Crohn’s disease and 6 from indeterminate colitis. All patients had undergone at least a flexible sigmoidoscopy and 75% had a colonoscopy. Adenomas were found in 3 patients with ulcerative colitis compared to 67 of 749 controls (2.8% v 8.9%, chi² =4.6, p=0.03). Of the 3 patients that had polyps, one patient with a 15 year history of UC had a 8mm rectal tubular adenoma, a second patient had a 4 year history of proctitis had a 2mm rectal adenoma and the third patient had, at diagnosis, a 2 cm tubulovillous adenoma. Dysplasia associated with colitis was seen in a further 4 (3.2%) patients. Pseudopolyps were found in 6 (5.6%) patients and metaplastic polyps in 2 (1.8%) patients. 75 (71%) of the IBD patients were maintained on a 5-ASA compound.

Conclusions: The results suggest that adenomatous polyps are rare in patients aged 55–64 years with IBD compared to a control population. This supports the hypothesis that lesions other than polyps are important for the development of colorectal cancer in patients with IBD and it also supports evidence that the 5-ASA compounds could protect against adenoma formation.
WHAT DO PATIENTS THINK OF COLONOSCOPIC SURVEILLANCE IN ULCERATIVE COLITIS?

M.D. Rutter, B.P. Saunders. St Mark’s Hospital, Harrow, UK

Background: Colonoscopic surveillance for cancer in ulcerative colitis (UC) has been performed for 30 years, yet there are few data on patients’ quality of life (QOL) or views of cancer surveillance.

Method: At our hospital, patients with over 8 years of extensive UC are counselled about their increased risk of colorectal cancer (CRC) & offered surveillance. A 98 question survey was sent to all patients on surveillance. Information was gathered on demographics, general health (EQ-5D), & views on surveillance, cancer risk, & surgery.

Results: 332 questionnaires were sent. 1 patient had died, & 2 had moved. Of the remaining 329, 276 responded (84%). Median responder age was 55 (range 26–84; 112 female, 164 male). QOL on surveillance was high, but lower than the general population (EQ-5D visual analog scale mean 77.5, c.f. population mean 82.5; p<0.0001). There was no significant reduction in QOL with age. 84% stated they would choose surgery after 10 years of colitis. 65% on dysplasia detection, 24% on CRC detection, & 4% said they would not have surgery even on CRC diagnosis.

Conclusion: Responders maintain a good quality of life on surveillance. 98% feel surveillance is important to them, although 11% hypothesically opted for a management strategy other than colonoscopic surveillance (surgery at 10 years, or no surgery even on CRC diagnosis). Most patients believe surveillance greatly reduces their chance of dying of CRC. Although most patients are content with the current information provided, 1/3 sought other information, and no patient felt they had received too much. Ongoing discussion with patients is necessary to reiterate the surveillance rationale & to clarify their wishes.

HOW EFFECTIVE IS CANCER SURVEILLANCE IN ULCERATIVE COLITIS?

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Background & Aim: Patients with longstanding extensive ulcerative colitis (UC) are at increased risk of colorectal cancer (CRC). We assessed the value of a long-running colonoscopic surveillance programme.

Methods: Patients on biennial colonoscopic surveillance (from 1975 onwards) with histologically proven UC of at least 8 years duration, macroscopically extending proximal to the splenic flexure were included. All patients were followed up to 1/1/01. Data were obtained from our prospective UC surveillance database, medical records & reports, GP’s, other hospitals & the Office of National Statistics.

Results: 600 patients underwent 2627 colonoscopies & 5080 years of surveillance. 68 patients (11%) had dysplasia or cancer detected during surveillance. Initial dysplasia was low-grade (46), high-grade (10), & CRC (12). 89 patients underwent surgery (86 colectomies, 3 partial resections). Fourteen operations were for a pre-operative diagnosis of CRC, 16 for HGD (6 cancers in specimens), 14 for LGD (3 cancers in specimens), & one for an adenoma. 44 operations were for symptoms (5 cancers in specimens). In addition, 2 patients died of CRC without surgery. In total, 30 patients developed CRC within the surveillance programme. Of the 25 surveillance-detected CRCs, 15 (60%) were Dukes’ A or B. A further 16 patients had colectomies for dysplasia, & had dysplasia confirmed in the colectomy specimen. Thus 31 patients benefited from surveillance. This equates to one benefit per 19 patients, or one benefit per 164 surveillance years. 13 patients presented with Dukes’ C or disseminated malignancy within the surveillance programme.

Conclusion: The current colonoscopic surveillance programme benefits approximately 3/4 of patients who are likely to develop life-threatening cancers. However, it requires considerable effort and expense over a prolonged period of time. A significant minority of patients still present with advanced cancer despite surveillance. Improved criteria for surveillance are required.


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Background and aims: There is good evidence to suggest that the incidence of Crohn’s disease has increased in western nations including the UK since the mid 20th century. Whether this rise is ongoing however is less clear and has been the subject of debate and disagreement for some years now. We have examined changes in Crohn’s disease incidence over 30 years in Derby.

Methods: All diagnoses of Crohn’s disease made at Derby’s two DGHs were collected via the use of hospital activity reports, histopathology records and the personal records of gastroenterologists. Diagnoses were validated via hospital notes. Subjects resident outside the city of Derby were excluded. Diagnoses were counted by quinquennia. Official estimates of Derby’s population were obtained for the same time periods and used to calculate incidence rates.

Results: In total 326 persons living in Derby were diagnosed with Crohn’s disease between 1970 and 2000. Of these 131 were male 195 were female. The table shows incidence rates for each quinquennium overall and by site.

Conclusions: This study supports the findings of other recent work suggesting that the incidence of Crohn’s disease has ceased to rise[2]. An apparent peak in incidence occurred between 1976 and 1990 which predominately consists of disease involving the colon. The small numbers of cases prevent firm conclusions as to any change in distribution but it is interesting to speculate upon the role of changing diagnostic tests.


EVIDENCE OF NORTH-SOUTH GRADIENT IN INCIDENCE OF JUVENILE-ONSET IBD IN SCOTLAND

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Introduction: The north-south gradient of IBD incidence was first described in Europe but the recent EC-IBD study suggests that the difference is narrowing. We and others have shown a high and rising...
Scottish incidence of IBD in the <16 age range, and using our unique dataset now aim to assess its variation with latitude.

**Methods:** The Scottish hospital-discharges-linked database was used to identify 933 patients less than 19 years old who were ICD coded as having had IBD between 1981 and 1995. All case records were reviewed, diagnoses confirmed and postcode at symptom onset noted. Incident cases (580) were those with symptom onset up to 16 years of age within the period 1 January 1981 to 31 December 1995. Incidence rates were calculated per 100,000 population per year for each of the 15 Scottish postcode districts and were standardised to the 1991 census population. The latitude of the principal town in each postcode district was used.

**Results:** The highest sex-standardised incidence was found in the Shetland isles (7.62, latitude 60°N, 9°W), this was followed by Orkney/NE Scotland (6.64, latitude 58°, 59°) The lowest incidence occurred in the Motherwell district (2.36, latitude 55.48°N). The r² value for the correlation between latitude and incidence is 0.71.

**Conclusion:** The high incidence of IBD in NE Scotland is consistent with Kyles' previous data, in addition we have shown a marked north south gradient in the incidence of juvenile-onset IBD in Scotland. The mechanism underlying this geographical pattern remains uncertain.

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**Abstract 245**

**NEUROLOGY OF INFLAMMATORY BOWEL DISEASE**

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**Background:** The literature on the extra-intestinal complications of inflammatory bowel disease (IBD) has always included reference to the neurological problems that occur in patients with these conditions. These patients tend to be more prone to stroke and sensorineural deafness but there is only a small literature on associations with other neurological diseases occurring concurrently with IBD.

**Aim:** To find if there is any association between inflammatory bowel disease (IBD) and other neurological conditions.

**Patients and Methods:** We studied prospectively 888 patients attending a single IBD clinic and as hospital controls used 700 patients who attended for open access endoscopy at 2 hospital units. Patients were asked to complete a questionnaire. Subjects for whom there was a high suspicion of neurological disease from the questionnaire were then contacted by telephone by the neurological team to determine more accurately the nature of the problem or the reason for any of the neurological investigations, as were a similar number of negative responders.

**Results:** Of the IBD patients, 7 (0.8%) had clinically definite multiple sclerosis (MS) compared to none in the control group (p<0.025). One further IBD patient has clinically probable MS. Peripheral neuropathy and epilepsy were also more common in our IBD group, 12 (1.4%) v 4 (0.6%) and 14 (1.6%) v 5 (0.7%) respectively, but this was not statistically significant (p<0.2). Stroke (1.6% v 2.4%), myasthenia gravis (0.1% v 0.2%), deafness (8.4% v 11.1%) and migraine (18.4% v 17%) were equally represented in the IBD group and hospital controls respectively.

**Discussion:** We conclude that there is a true association between multiple sclerosis and IBD. We also found an increased prevalence of peripheral neuropathy and epilepsy. Further work is ongoing to look at possible immunological and genetic similarities between MS and IBD.

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**Abstract 247**

**PATIENTS WITH INFLAMMATORY BOWEL DISEASE TAKE AS MUCH COMPLEMENTARY/ALTERNATIVE MEDICINE AS PATIENTS WITH FUNCTIONAL BOWEL DISEASE**


**Introduction:** In recent years, the public awareness and usage of complementary/alternative medicine (CAM) has increased. The use of CAM (for example, aloe vera) has previously been described in adult patients with functional bowel disease.

**Aim:** To assess the incidence of CAM usage by gastroenterology patients at a single university centre.

**Method:** Patients attending luminal gastroenterology clinics (from June 2002) completed a 30-point, structured questionnaire assessing their use of CAM. A gastroenterologist verified the patient diagnosis.

**Results:** There were 790 patients recruited. The main diagnostic categories were inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other gastrointestinal diseases (GID; for example colonic polyps). Demographics and CAM usage in each group are shown in the table below.

<table>
<thead>
<tr>
<th>Category</th>
<th>IBD</th>
<th>IBS</th>
<th>Other GID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n) of patients</td>
<td>383</td>
<td>153</td>
<td>254</td>
</tr>
<tr>
<td>Number of females</td>
<td>200</td>
<td>110</td>
<td>133</td>
</tr>
<tr>
<td>Age range (years) (mean)</td>
<td>17.9 (49)</td>
<td>17.98 (48)</td>
<td>19.97 (61)</td>
</tr>
<tr>
<td>Number using CAM</td>
<td>157</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>% using CAM</td>
<td>41</td>
<td>48</td>
<td>24</td>
</tr>
</tbody>
</table>

Chi-squared analysis demonstrated significant differences between the IBS versus other GI group (p<0.0001) and IBD versus other GI group (p<0.0001). Multivariate logistical analysis of the entire cohort showed significant demographic differences for sex: female versus male (p<0.05). 64% of all CAM users were women. For every 1-year increase in age there was a 1% reduction in the use of CAM (p<0.03). 87% of all CAM users (253/291) felt they derived some symptomatic benefit.

**Conclusion:** The percentage of CAM users amongst patients with IBD is similar to those with a functional diagnosis. Patients with IBD are using CAM in addition to conventional treatment. Awareness of this will prevent adverse CAM and conventional drug interactions.

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**Abstract 248**

**CAUSES OF MORTALITY IN CROHN’S DISEASE**

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**Introduction:** It is recognised that life expectancy in Crohn’s disease is slightly reduced (Jess et al, Gastroenterology 2002;122:1808) but few studies have addressed causes of mortality.

**Abstract 248**

<table>
<thead>
<tr>
<th>Group</th>
<th>Post operative &lt;30 days</th>
<th>Crohn’s related malignancy</th>
<th>Others</th>
<th>Cardiovascular</th>
<th>Cancer</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>IBS</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Other GID</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>
Methods: All patients attending our centre have been logged onto a central database since 1996. This includes 676 patients with Crohn’s disease with a median age of 43 years, range 17–93 years. During the study period (Jan 1996–June 2002) 32 of these patients died with a median age of 57, range 18–89. Case notes were available for 30 of these patients but contained incomplete data in 4; the remaining 26 were analysed with regards to cause of death.

Results: Eleven (42%) of the deaths were attributable to Crohn’s disease. Apart from post-operative deaths and Crohn’s related malignancy (small intestinal cancer 1, rectal cancer 1, rectal lymphoma 1) these included amyloidosis and renal failure (1), right atrial thrombus complicating TPN (1) and malnutrition in an elderly patient (1). The median age for those whose death was related to Crohn’s disease was 48 years (range 36–83) and for those that died of other causes was 72.5 years (range 32–89). All 8 non-malignant Crohn’s related deaths in patients receiving systemic corticosteroids compared to 39% of those who died of other causes. Seven (64%) patients who died of Crohn’s disease were smokers at the time of death compared to 40% of those who died due to unrelated causes.

Conclusion: Crohn’s disease is still associated with considerable mortality. Further study is justified to assess whether use of systemic corticosteroids may contribute to this mortality.

249 ANTIBODIES TO ASCA IN CROHN’S DISEASE ARE ASSOCIATED WITH ILEAL DISEASE BUT NOT NOD2 MUTATIONS IN A SCOTTISH COHORT

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Background: Crohn’s disease (CD) and ulcerative colitis (UC) can be difficult to differentiate clinically. Anti-Saccharomyces cerevisiae antibodies (ASCA) have been proposed as diagnostic tools for CD. Mutations in the NOD2 gene engender susceptibility to CD but not UC. We investigated the possible relationship between NOD2 mutations, disease phenotype and ASCAs in CD, and whether ASCAs were related to antibodies to other fungal proteins.

Methods: Serum from 308 patients (150 CD, 73 UC, 7 with indefinite colitis (IC)) and 78 healthy controls (HC) were assayed for ASCA antibodies (IgA+IgG) using the Medizym ELISA kit. Antibodies (IgA, IgG) to other fungal proteins (Fusarium species ATCC20334, MP) were measured in the same samples using an in-house ELISA assay. NOD2 mutations in these patients had been identified previously using PCR. The antibody responses were compared with the known NOD2 genotype and disease phenotype of these patients.

Results: ASCA was present in 56% of CD, 16% of UC, 43% of IC, and 8% of HC. ASCA-ve status was a predictor for CD (OR 10.6 (95% CI 1.13–3.75)) and could discriminate CD from all IBD patients (OR 5.5 (95% CI 0.86–4.66)). Sensitivity of ASCA for CD was 56%, specificity was 89% and positive predictive value was 83%. ASCA was associated with ileal ileocolonic rather than colonic disease (p<0.001), but not with NOD2 mutations. There was no association between ASCA and antibodies to MP (IgA or IgG). MP IgA titres were higher in CD than HC (p<0.01), while MP IgG titres were associated with ileal, but not ileocolonic nor colonic disease.

Conclusions: ASCA was found to be a specific marker for CD and associated with disease involving the ileum, but not NOD2 mutations. MP antibody titres were higher in CD patients and independently associated with ileal disease alone. These results help to further the understanding of CD pathogenesis.

250 INCIDENCE AND PHENOTYPIC ASSOCIATIONS OF NOVEL ANTIBODY MARKERS IN CROHN’S DISEASE

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Introduction: The diagnostic value and pathogenic importance of serological markers in patients with inflammatory bowel disease remain under evaluation. Antibodies directed against Saccharomyces cerevisiae (ASCA), and the perinuclear component of neutrophils (pANCA) have been the most widely studied and may be of diagnostic importance. OmpC and I2, antibodies directed against luminal bacterial components (E coli and pseudomonas respectively), have recently been described in Crohn’s disease (CD). The data reported in the Los Angeles population suggest a selective loss of tolerance to microbial antigens in CD. Phenotypic associations of these antibodies are unknown. We aimed to assess the frequency of ASCA, pANCA, OmpC, and I2 in an independent CD cohort and establish phenotypic associations.

Methods: 141 well-characterised CD patients (76 females, median age 39 years (17–88)) and 78 healthy controls (HC) were studied. OmpC had ileal disease, 58 had colonic disease and 57 had both ileal and colonic disease. 42 had associated perianal disease. 73 had undergone previous surgery. ELISA assayed ASCA, ANCA, OmpC, and I2. The pattern of ANCA positivity was assessed by immunofluorescence.

Results: All antibodies were more prevalent in CD than HC (ASCA 34% vs 4%, ANCA 1% vs 1%, OmpC 1% vs 1%, p<0.001). A positive serum ASCA was associated with ileal disease (76% vs 42%, p<0.001) and previous surgical resection (73% vs 37%, p<0.001) whereas pANCA was a marker for colonic disease (63% vs 30%, p<0.05). OmpC and I2 were associated with increasing age, increasing disease duration and the need for intestinal resection (p<0.001). OmpC is also associated with ileal disease (p<0.01).

Conclusion: We have confirmed the previous association of ASCA and ileal disease and ANCA and colonic disease. OmpC is also associated with ileal disease and OmpC and I2 are associated with increasing disease duration.

251 PREVALENCE AND MANAGEMENT OF INFLAMMATORY BOWEL DISEASE: DATA FROM PRIMARY CARE RECORDS, INCLUDING 5-ASA PRESCRIBING AND COMPLIANCE

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Background: Data from general practice (GP) records in North Tees (Rubin et al, 2000) suggested a higher prevalence of inflammatory bowel disease (IBD) to previous estimates from hospital data. Regular prescribing of 5-aminosalicylic acid (5-ASA) therapy can reduce the risk of colorectal cancer in patients with ulcerative colitis (UC).

Aims: To estimate IBD prevalence from GP records in the Trent region of central England and describe the management of patients with this condition, including data regarding 5-ASA prescribing and compliance in UC.

Methods: 15 general practices recruited through the Trent Focus Collaborative Research Network provided data on confirmed cases of IBD using a standardised data collection form.

Results: 344 patients with IBD were identified from a combined GP list size of 86 801, suggesting a prevalence of 396 per 100 000 (95% confidence interval 356 to 440), much higher than previous estimates from secondary care and similar to results from North Tees. Approximately one third of patients with IBD were considered by GPs to be solely under their care and only 59% of IBD patients had actually been seen as hospital inpatients or outpatients during the previous year. Only 57% of patients with UC (including proctitis) had been prescribed a 5-ASA during the previous 6 months and good compliance in prescribing and taking 5-ASA medication was suggested from the prescribing records of only 42% of these patients (23% of all UC patients).

Conclusions: Data collection from hospital records may miss some IBD patients. GPs may play an important role in caring for patients with IBD; they should therefore receive good education regarding IBD management, including the importance of 5-ASA therapy in UC.


252 COMPARISON OF IN VITRO CHARACTERISTICS OF TWO UK MESALAZINE 400MG PRODUCTS

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Background: The release profile of mesalazine from different aminosalicylates preparations is matched to the site and extent of an individual patient’s inflammatory bowel disease. A new enteric coated mesalazine 400mg tablet [Ipecol] has been launched in the UK. Analytical assessment of Asacol and Ipecol was undertaken for comparative purposes.

Methodology: Three methods were used: scanning electron microscopy for coating thickness; near infrared absorption for coating thickness and tablet composition (evaluated by principal component
THREE YEARS OF PATIENT-LED THERAPY IN ULCERATIVE COLITIS WITH A SINGLE AMINOSALICYLATE, BALSALAZIDE: A LONG TERM OBSERVATIONAL STUDY

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Patient-led therapy in ulcerative colitis (UC) may have significant advantages for patients but this has never been formally observed in long term practice. Use of a single therapy effective in acute relapse and maintenance of remission [in different doses] could simplify long term management by enabling patients to choose an appropriate dose.

Balsalazide, an aminosalicylate prodrug, is effective and well tolerated at all doses for both these indications in UC. To assess its practicability, safety and efficacy of patient-led dosing, two groups of patients in remission from UC (52 in long-term stable remission (SR) and 76 in recent remission (RR)) were prospectively followed in a 3 year open, non-comparative study receiving balsalazide in a variable dose.

Conclusions: The two formulations exhibit significantly different coating characteristics and in vitro dissolution profiles. Since they are not pharmaceutically equivalent this raises concerns about their substitutability.

PREDICTING OUTCOME AND RISK ASSESSMENT IN SEVERE ULCERATIVE COLITIS

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Backgrounds/Aims: The rate of failure of medical therapy in severe ulcerative colitis (UC) remains high (30–40%). We have identified predictive factors associated with poor outcome in patients presenting with severe attacks of UC and devised a numerical scoring system that categorises patients by risk.

Methods: All patients admitted with severe UC [defined by the modified Truelove and Witts criteria] in three gastroenterology units in the Lothian region between January 1995 and March 2002. Fifty-six clinical and demographic parameters were analysed. Predictive factors were identified using multiple logistic regression and risk score was formulated using statistical modelling. Outcomes were categorised to non-responders (colectomy during hospitalisation) and responders.

Conclusions: Disease severity is the main determinant of overall QoL in IBD with greatest impact being on systemic wellbeing. QoL scores were lower in CD than UC overall and CD sufferers had greater loss of “social” days. Younger age is associated with lower ratings for emotional functioning.

Abstract 254 Risk score for categories according to coefficients from logistic regression modelling

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
</table>
| Categories | t<4 | 25% <4 and t<6 | t>6 but <9 | t>9 | 100%
| Albumin | >30 g/l | >20 but <30 g/l | >10 but <20 g/l | <10 g/l | <5 g/l |
| Colonic dilatation | >30 g/l | >20 but <30 g/l | >10 but <20 g/l | <10 g/l | <5 g/l |

(1Mean stool frequency of first 3 days of medical therapy).

Results: Of 167 patients admitted, 68(40%) failed to respond to medical therapy. Mean stool frequency, albumin, and colonic dilatation were significantly different across the 3 groups. A numerical score was formulated using these variables (table 1). Patients with scores of 0–1, 2–3 and >4 had a 53%, 86% and 100% chance of non-response respectively.

Conclusion: Using this novel scoring system, we can clearly stratify patients to low, intermediate and high risk groups of non-response.

HEALTH-RELATED QUALITY-OF-LIFE (HR-QOL) IN INFLAMMATORY BOWEL DISEASE (IBD): SURVEY OF A PREVALENCE COHORT

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Introduction: Studies of HR-Qol aim to assess the influence of disease on patients’ lives by seeking patient-perceived valuations of health across discrete domains including physical and psychosocial function. The aim of the present study was to measure HR-Qol in an unselected cohort of IBD patients and to correlate with demographics, disease type, extent and severity.

Methods Subjects: We identified a 6-month prevalence cohort of 479 IBD patients receiving any form of care for IBD at our centre by cross referencing multiple hospital databases (outpatient letters, in-patient coding, diagnostic reports). Disease type, extent and severity (using a published grading system) were abstracted from casenotes.

Postal survey: Self-administered questionnaire, the UK-IBDQ (modified to include an item about interference with household or recreational activities). The IBDQ has 5 domains (Social; Emotional; Bowel 1; Bowel 2 & Systemic). Data analysed by linear regression.

Results: 233 (48.6%) responded (CD n=87, UC n=122, indeterminate colitis n=24). Data incomplete in 12. Mean age (sex): CD 48.5 yrs (28 male); UC 48 yrs (61 male). Table summarises total IBDQ scores (% optimal function). Total scores for UC were higher than CD (76% vs 70%, p<0.001) and lowest domain scores were in the Systemic domain (CD 55%; UC 64%). Emotional (p=0.011) and Bowel (p=0.03) scores were significantly lower in younger patients. Mean last days from household / recreational activities in 6 months: CD 21 d; UC 12 d.

Abstract 255

<table>
<thead>
<tr>
<th>Category</th>
<th>CD Median (IQR)</th>
<th>UC Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-consulting</td>
<td>3 (38–93)</td>
<td>4 (48–92)</td>
</tr>
<tr>
<td>Remission</td>
<td>7 (39–97)</td>
<td>15 (58–96)</td>
</tr>
<tr>
<td>Postsurgical remission</td>
<td>7 (59–79)</td>
<td>1 (N/A)</td>
</tr>
<tr>
<td>Mild disease</td>
<td>33 (42–98)</td>
<td>67 (43–100)</td>
</tr>
<tr>
<td>Severe, drug responsive</td>
<td>7 (68–50)</td>
<td>5 (49–92)</td>
</tr>
<tr>
<td>Severe, drug dependent</td>
<td>12 (77–44)</td>
<td>13 (68–41)</td>
</tr>
<tr>
<td>Severe, drug refractory</td>
<td>11 (50–97)</td>
<td>5 (25–72)</td>
</tr>
</tbody>
</table>

Conclusions: Disease severity is the main determinant of overall QoL in IBD with greatest impact being on systemic wellbeing. QoL scores were lower in CD than UC overall and CD sufferers had greater loss of “social” days. Younger age is associated with lower ratings for emotional functioning.
SOFT STOOLS, SOFT BONES AND SOFT EVIDENCE: WHAT INFLAMMATORY BOWEL DISEASE PATIENTS THINK OF OSTEOPOROSIS MEDICATION

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Background: The British Society of Gastroenterology guidelines for osteoporosis in inflammatory bowel disease imply the screening of a large proportion of inflammatory bowel disease patients and treatment with antiresorptive medication if necessary. Despite this, only a small percentage of patients will benefit from fracture prevention as a direct result of taking this medication.

Aims: To explore inflammatory bowel disease patients’ attitudes towards taking medication for osteoporosis in the light of present best evidence for fracture reduction with such medication.

Methods: Questionnaires were sent to all patients on an inflammatory bowel disease database at a district general hospital in North East England. The main outcome measure was the lower limit of absolute risk reduction of fracture below which subjects were not prepared to take a hypothetical osteoporosis drug for three years. All respondents were followed up with a telephone interview.

Results: 121 (45%) patients responded. The median value for the lower limit of absolute risk reduction of fracture acceptable to the study population was 50%. There was no significant correlation between the value expressed by the patient and their age, number of previous fractures or current or previous steroid use. Patients who had suffered a fracture within the previous two years showed a significantly lower threshold to taking osteoporosis medication than those with no previous fracture. Patients exhibited wide variations in their attitudes towards taking the preventive treatment with 20% being concerned about possible side effects. 85% wished to have a discussion about the expected benefits of any new preventive drug prior to starting treatment.

Conclusions: Inflammatory bowel disease patients may not be prepared to take osteoporosis medication if they were aware of its true likelihood of benefit. Gastroenterologists should consider their patients’ attitudes as well as the medical criteria before deciding to treat for osteoporosis.

OSTEOPOROSIS IN CROHN’S DISEASE IS NOT DETERMINED BY VITAMIN D RECEPTOR AND INTERLEUKIN-6 GENOTYPE

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Background: Osteoporosis is a common and very important complication of Crohn’s disease. The risk of osteoporosis is known to be related to body mass index, use of corticosteroid therapy and disease activity. These factors do not fully account for the variation between patients, genetic factors may also be important.

Aim: To determine whether bone density in Crohn’s disease is related to polymorphisms which influence bone density in other conditions: the vitamin D receptor (VDR TaqI) (Exon 9), the VDR Start codon (VDR FokI) (Exon 1), the VDR promoter (VDR BaqI) (Exon 9), the IL-6 gene (IL-6 SNP-174) (Exon 3) and the IL-1β gene (IL-1β SNP-889) (Exon 2).

Methods: 255 patients had their bone density assessed by DEXA scanning at the lumbar spine and hip. Osteoporosis was defined by WHO criteria as a T(30) score worse than –2.5 at any site, osteopenia as a T(30) score between –1 and –2.5. DNA was genotyped for VDR SNPs, TaqI and FokI, and the IL-6 G/C SNP.

Results: There were no significant differences in genotype, or allele frequency between the groups or compared to healthy controls.

Conclusion: VDR TaqI and FokI SNPs, and IL-6 G/C SNP do not appear to contribute to the incidence of osteoporosis in Crohn’s disease.

DIFFERENTIATION OF EUROPEAN “ASACOLS”

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Background: The original developers of “Asacol” in Europe were Tillots Laboratories. The subsequent out-licensing of the product across Europe has given rise to potential of variations in tablets. If the company changes excipients &/or manufacturing processes, this can affect the release profile. This in turn influences availability of the product locally in the intestinal mucosa & the amount of product absorbed systemically & hence the products’ overall profile. Analytical assessment of different European “Asacols” (400mg tabs) was undertaken to evaluate tablet characteristics. Tablets were sourced from France (Fivasa), Germany (Asacolitin), Italy (Asacol It), the Netherlands (Asacol NL) & the UK (Asacol UK).

Methodology: Three assessment tools were used in the analysis; scanning electron microscopy (SEM) for coating thickness; near infrared (NIR) absorption for coating thickness & tablet composition, (which was evaluated by principal component analysis (PCA)); & in vitro disintegration and dissolution testing to characterise 5-ASA release. Batches of each product were purchased commercially & assessed under good laboratory practice.

Results: PCA of NIR absorption demonstrated clear differences in individual spectra. These spectra are influenced by coating thickness, formulation & tablet shape. SEM results further showed a range of coating thicknesses. Asacol (Il) had the thinnest (39–62μm) & Asacol (NL) the thickest (64–129μm) coating. Since the coating is critical to the release mechanism of “Asacol”, all the variations shown both in NIR & SEM analysis would be expected to impact the in vitro dissolution profile of 5-ASA release. Differences between the products were identified in terms of the initial release pH & overall profile.

Conclusion: The currently available “Asacol” 400mg tablets across Europe differ from each other in vitro with respect to the pH at which 5-ASA release started and their overall release profile at pH 7.2. Their interchangeability should therefore be viewed with caution until in vivo results are available to demonstrate their equivalence.

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APPROPRIATENESS OF UPPER GASTROINTESTINAL ENDOSCOPY: A HOSPITAL BASED RETROSPECTIVE STUDY

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Aim: To evaluate whether upper gastrointestinal endoscopy (UGE) is used appropriately according to the British (BSG) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines in a hospital setting and whether there is any relationship between appropriateness of UGE and the presence of lesions detectable by endoscopy.

Materials and Methods: Indications and endoscopic findings for 525 consecutive UGE performed in 500 patients, between Jan 1995 and Dec 2000 in Downe Hospital, retrospectively evaluated using BSG and ASGE guidelines to determine appropriateness of referrals. The endoscopic findings that had direct therapeutic or prognostic consequences were classified as positive; the other were classified as negative.

Results: There were 237 male and 263 female patients with mean age 57.3 years (range: 17–94). In all, 62.9% of UGEs were positive, 37.1% were negative, and 22.7% and 26.7% were inappropriate according to BSG and ASGE guidelines, respectively (p = 0.024). The probability of finding a positive endoscopy was significantly higher in UGE rated as appropriate on the basis of both BSG (p < 0.0001) and ASGE guidelines (p = 0.002). Endoscopies rated as inappropriate according to BSG and ASGE guidelines showed a positive finding in 46.2% and 52.1% of cases, respectively. On multivariate analysis,
Objectives: To investigate the relationship between clinical experience and performance with regard to colonoscopic procedures performed on the HT Immersion Medical Colonoscopy Simulator. The hypothesis is that the performance of the novice, intermediate, and experienced operator is different on simulators just as on real patients. This validating HT Immersion Medical Colonoscopy Simulator.

Methods: Postgraduate doctors were divided into three groups according to their level of colonoscopic experience. Candidates at random performed colonoscopy on module 3 or 4 of the HT Immersion Medical Colonoscopy Simulator. Candidates in the first group called “novice”, had each performed less than 10 colonoscopies and included 4 PGY5s, 5 SpRs, and 2 Consultants. This group completed 80 episodes. The second group, called “intermediate”, had each performed 11–100 colonoscopies and included 5 SpRs and 2 Research fellows. This group completed 65 episodes. Members of the third group, called “experienced”, had each performed more than 100 colonoscopies, who in turn performed 100–400 episodes and included 1 SpR and 6 Consultants. This group completed 45 episodes. A result of 3600 seconds (1 h) was used to denote perforation.

Results: The experienced were shown to perform better than the intermediate or the novice on episode one. The efficiency ratio was better than the novice and the intermediate. The assessment was made on multiple factors, including time taken to complete the test, percentage of the mucosa visualised, incidence of colonic perforations, and path length used. The results were statistically highly significant for all these factors, p < 0.0001 except mean number of loops.

Conclusions: Operators who differ in terms of their clinical experience and technical ability also differ in their performance of simulated colonoscopy. Thus the simulator technology has been shown to be a powerful discriminator of manipulative skills in colonoscopy. The experienced perform better than the intermediate that is the novice on the simulator, thus validating HT Immersion Colonoscopy Simulator.

Objectives: To investigate the learning curve for colonoscopic procedures performed on the HT Immersion Medical Colonoscopy Simulator without any feedback. The hypothesis is that no learning curve exists without a feedback. In other words, the student does not learn the simulation machine itself, instead of the colonoscopy technique that it is primarily meant to teach.

Methods: Twenty-two postgraduate doctors were recruited, including 5 research fellows, 4 PRHOs, 6 SpRs and 7 Consultants. Candidates were asked to perform colonoscopy on the HT Immersion Medical Colonoscopy Simulator. Modules 3 and 4 were used at random. In total, each candidate was asked to perform five consecutive virtual colonoscopies on the same module. These five episodes were collectively referred to as one trial. A time result of 3600 seconds (1 h) was used to denote perforation. No guidance or feedback was given to candidates before, during or after each procedure.

Results: Twenty-two candidates had five attempts or episodes each, meaning on trial each, on only one module of the colonoscopy simulator. (Total 115 episodes over 23 trials). Another 15 people recorded five attempts, meaning one trial each, on two modules of the colonoscopy simulator. (Total 150 episodes over 30 trials). Therefore the total episodes recorded were 265, over 53 trials. There was no improvement in performance on the simulator from first attempt to the fifth in absence of feedback. The outcomes measured included time taken to complete the test, percentage of the mucosa visualised, depth of the instrument inserted, and the path length used. The results were statistically very significant p < 0.0001 for all outcomes.

Conclusions: This study has demonstrated that in absence of feedback, it is not possible to improve performance on the HT Immersion Medical Colonoscopy Simulator. There is no learning curve for the machine itself. The information from this study is vital for using the simulators in training and assessment because any learning curve would be of procedure only and not the machine.
other 9%. Formal training was undertaken by 19% of respondents on average of 7 years ago. Training in sedation reversal identified 67% of respondents had undergone informal training of which junior colleagues trained 64%. Basic life support training had been attended by 69% of which 31% of these attended within the previous 12 months. Advanced life support training had been attended by 41% of which 79% of these had attended within the previous 3 years. 89% of respondents ensure oxygen is administered to sedated patients. 74% monitor paediatric and elderly patients differently. 63% of respondents would like to undertake a recognised qualification. 47% of respondents would be prepared to attend yearly simulated sedation incident workshops.

Conclusion: This study identifies the continued lack of formal sedation training that was highlighted by The Royal College of Surgeons Report in 1993. There is a need to implement training to comply with current recommendations and best practice.

### Abstract 265

**DIAGNOSIS OF HELICOBACTER PYLORI IN A DISTRICT GENERAL HOSPITAL (DGH): ACCURACY, COST AND PATIENT PREFERENCE FOR SIX WIDELY AVAILABLE TESTS**


Introduction: The detection of *H pylori* forms part of the care pathway for dyspepsia. However, there are many tests to choose from, and no clear guidance as to which one to use.

**Aims:** To determine the positive and negative predictive value (PPV and NPV), sensitivity (Sens) and specificity (Spec) and cost of the urea breath test (UBT), in-house prepared rapid urease test (RUT), histology (histo), culture (cult), serology (sero), and faecal antigen (HpSA) in *H pylori* diagnosis, and to examine the patient’s preference.

**Methods:** 109 patients were recruited from an open access endoscopy unit between March 1999 and October 2002 was performed. In addition, the referring consultant and GP were contacted to obtain follow up information.

**Results:** 29 patients (17 male, 12 female) with a mean (range) age of 66 (43–93) underwent insertion of an enteral stent for malignant gastric or duodenal obstruction. The primary tumour was in the stomach in 14 (48%), the pancreas in 10 (34%) patients, and metastatic in 5 (17%) patients. A stent was successfully placed in all patients; the sites of placement included the stomach (n = 5), across the pylorus (n = 6), through a previous surgical anastomosis (n = 3), or the duodenum (n = 15). Two stents blocked after insertion, one required dilatation, and the other patient had a second stent inserted. No patients required surgery. 26 patients have subsequently died, the median (range) survival being 2.8 months (2 weeks to 10 months), 22 patients survived at least one month. 25 (86%) patients were discharged from hospital: 19 home, 6 to a hospice. During follow up 8 (27%) patients returned to a solid diet, 17 (59%) required a soft diet, and 3 (10%) patients tolerated liquids only.

**Conclusion:** The use of enteral stents achieves good palliation in the majority of patients with malignant gastric or duodenal obstruction, allowing discharge from hospital and re-introduction of an enteral diet.

### Abstract 266

**ENTERAL STENTS FOR THE PALLIATION OF MALIGNANT GASTRIC AND DUODENAL OBSTRUCTION**

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Introduction: Gastric outlet and duodenal obstruction are common complications of advanced upper gastrointestinal malignancy. Relief of obstruction to allow continued enteral feeding and early discharge is the primary therapeutic goal. Surgical bypass has a high success rate, but is not appropriate or feasible in all patients. The endoscopic placement of expandable metal stents has been proposed as an alternative technique to achieve palliation in patients not suitable for surgery.

**Aim:** To review our experience with gastroduodenal metal stent insertion for the palliation of malignant gastric and duodenal obstruction in patients unsuitable for surgical bypass.

**Methods:** A retrospective review of the notes of all patients who had a gastroduodenal stent inserted in our unit between March 1999 and October 2002 was performed. In addition, the referring consultant and GP were contacted to obtain follow up information.

**Results:** 29 patients (17 male, 12 female) with a mean (range) age of 66 (43–93) underwent insertion of an enteral stent for malignant gastric or duodenal obstruction. The primary tumour was in the stomach in 14 (48%), the pancreas in 10 (34%) patients, and metastatic in 5 (17%) patients. A stent was successfully placed in all patients; the sites of placement included the stomach (n = 5), across the pylorus (n = 6), through a previous surgical anastomosis (n = 3), or the duodenum (n = 15). Two stents blocked after insertion, one required dilatation, and the other patient had a second stent inserted. No patients required surgery. 26 patients have subsequently died, the median (range) survival being 2.8 months (2 weeks to 10 months), 22 patients survived at least one month. 25 (86%) patients were discharged from hospital: 19 home, 6 to a hospice. During follow up 8 (27%) patients returned to a solid diet, 17 (59%) required a soft diet, and 3 (10%) patients tolerated liquids only.

**Conclusion:** The use of enteral stents achieves good palliation in the majority of patients with malignant gastric or duodenal obstruction, allowing discharge from hospital and re-introduction of an enteral diet.
**Aim:** To audit outcome measures in ERCP patients and assess the safety and efficacy of snare ampullectomy (SA).

**Methods:** Records of all patients undergoing ERCP in this hospital over 6 years (including 3 years of SA) were reviewed to assess indications, procedures, and outcome including complications (abdominal pain, pancreatitis, bleeding, perforation, delayed discharge, readmission within 7 days) and 30 day mortality.

**Results:** 724 patients (61% female, median age 67) underwent ERCP by a single endoscopist. Indications included biliary colic (49%), jaundice/abnormal LFTs (38%), and prior pancreatitis with gallstones. Overall success in intended duct was 88%. When precut was employed, the success rate was 58%, but with SA, this rose to 88%. The rate of any complication for all ERCPs was 6%, and of pancreatitis was 2%. There were no perforations and 7 bleed, none requiring transfusion. 30 day mortality was 5% with a median age of 79 years, 43 patients underwent SA including 3 for ampullary neoplasms. In a case with a polya gastrectomy, a stent was inserted to guide the snare, but was cut through by the heating. A stepwise logistic regression model was used to assess the contribution of ES (n = 256), precut (n = 19), and SA to all complications, and revealed significant effects for precut (p < 0.01 odds ratio [OR] 6.2, 95% CI 2.2 to 17.2), SA (p = 0.02 OR 2.9, 95% CI 1.2 to 6.8) and ES (p < 0.01, OR 2.9, 95% CI 1.5 to 5.7). Significant effects in pancreatic stent were found for precut (p < 0.01, OR 14.9, 95% CI 4.0 to 56.1), and SA (p = 0.03, OR 4.4, 95% CI 1.2 to 16.3) but not for ES. No significant effect in 30 day mortality was found for precut (p = 0.98), SA (p = 0.24) or ES (p = 0.79).

**Conclusion:** We feel SA is a safer procedure than precut when access to the bile duct is critical due to jaundice or stones, and appears more effective. It carries a risk of causing pancreatitis, but less so than precut.

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**268 ENDOSCOPICALLY PLACED METAL STENTS FOR THE PALLIATION OF MALIGNANT GASTRODUODENAL OBSTRUCTION: THE TREATMENT OF CHOICE**

A. Holt, C. Hulley, M. Ahmed. Good Hope Hospital, Sutton Coldfield, Birmingham, UK

**Introduction:** Self-expanding metal stents (SEMS) have been used to re-canalise a variety of obstructed tubular organs. Their use in the stomach and duodenum has recently been described. We report our single-centre experience with the technique in palliating malignant gastro-duodenal obstruction.

**Patients and Methods:** Stenting was attempted in 16 patients (11 male, 5 female; mean age 79 years, range 64–91 years). Eleven patients had inoperable gastric cancer, four patients presented with duodenal obstruction due to pancreatic cancer and one patient had tumour overgrowth of a gastro-jejunostomy. We employed SEMS (Schneider Enteral Wallstent™ in 15 cases and a Flamingo stent in one case, Boston Scientific) over a 0.035" Amplatz wire through a large channel gastroscopy or therapeutic duodenoscope. The uncovered Enteral Wallstents were 6 or 9 cm in length and 20 or 22 mm in diameter (after deployment). Positioning of the stent was monitored by fluoroscopy.

**Results:** Gastro-duodenal stenting was technically successful in 14/16 patients and 3/16 patients also had metal biliary stenting. The two failures were due to kinking of the stent assembly in one case and complete duodenal obstruction preventing passage of the guidewire in the other. There were no immediate or late stent related complications. The 14 successfully stented patients all experienced relief from vomiting. 11 patients tolerated semi-solid diet and 3 tolerated liquid diet. 13 patients had inoperable gastric cancer, four patients presented with gastroduodenal obstruction. The 14/16 patients and 3/16 patients also had metal biliary stenting. The single-centre experience with the technique in palliating malignant gastroduodenal obstruction has recently been described. We report our single-centre experience with the technique in palliating malignant gastro-duodenal obstruction.

**Conclusion:** Gastro-duodenal stenting allows effective, minimally invasive palliation of malignant gastroduodenal obstruction. With careful patient selection and appropriate timing, stents relieve the distressing symptom of vomiting and allow safe discharge. The majority of patients tolerate a near normal diet.

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**269 PROSPECTIVE AUDIT OF ERCP OUTCOMES**

J.E. Mawdsley, P. Manoey, A.P. Catterall, P. McIntyre, S.M. Greenfield. QEII Hospital, Howlands, Welwyn Garden City, Herts, UK

**Background:** East and North Herts trust serves 500,000 patients; 350 ERCP procedures are performed/year. We present the largest UK prospective audit of 215 ERCPs.

**Methods:** Data were collected using a standard proforma completed at the time of endoscopy (99% completion). Patients were phoned at 3 and 30 days, or discussed with their medical team if an inpatient, to assess for a procedure related complications.

**Results:** Cannulation of the desired duct achieved at first attempt in 79% and 82% when the distal duodenum was reached. This improved to 85% with a repeat procedure. Biliary drainage was achieved in 64% of jaundiced patients (44/69). CBD stones were successfully removed in 71% at first procedures and 92% after a second procedure. Bile cytology was positive in (6/110) and bile brushings was positive in 32% (6/19).

**Findings:** CBD normal (61), CBD stones (58), CBD dilatation only (29), CBD stricture (29), duodenal obstruction (7), other (13).

**Procedures:** Diagnostic (90), standard/needle knife sphincterotomy (50/17), stent insertion (27), CBD stone removal (53).

**Complication Rates:** Mild pancreatitis occurred in 3 cases (1.5%). Mild haemorrhage at the ampulla was reported in 7 (3.3%) but did not require admission or transfusion. Overnight observation was required in 4 patients (1.9%). Procedure related mortality occurred in 2 cases (0.9%); one patient with pancreatic cancer and liver metastases died from haemorrhage and the second from perforation of the duodenum due to peptic ulceration. Seven deaths (3.3%) occurred within the 30 day follow up period attributable to other causes.

**Conclusions:** Complication rates were low and similar to other studies. Biliary cytology is worthwhile and more sensitive than brushings. Cannulation rates were similar to recommended JAG guidelines but drainage rates were lower and JAG recommendations may need to be reviewed. Pure diagnostic procedures were common and MRCP was used as a pre-procedure imaging modality in only 10%. This audit might be suitable as a template for the BSG to follow in its proposed prospective National Audit of ERCP.

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**270 CAN A COLONOSCOPY COMPUTER SIMULATOR DIFFERENTIATE BETWEEN A NOVICE AND EXPERT?**

S. Thomas-Gibson, M.E. Vance, B.P. Saunders. Wolfson Endoscopy Unit, St. Mark’s Hospital, London, UK

**Background:** Computer simulators are being developed as a training tool in colonoscopy. We aimed to establish whether a computer simulator could differentiate between novices and experienced colonoscopists.

**Methods:** Eight novice and 4 experienced endoscopists took part in the study. Novices (5 nurses, 3 junior doctors) had no previous practical endoscopy experience. Experienced endoscopists were senior doctors (2 consultants, 1 SpR) or nurse consultant (n = 1) (no previous significant simulator experience). All novices were given group teaching in principles of colonoscopy, functions of a colonoscope, and an introduction to the simulator (Immersion Medical). Both groups were given a standard practise case (SPC) with tutoring, then performed the standard test case (STC) without help. Insertion was terminated at 15 minutes if the caecum had not been intubated.

**Results:** 7 novices (88%) and all experienced endoscopists achieved caecal intubation. Terminal ileal intubation (TI) was achieved in 3 novices (38%). At 5 min the novices were in sigmoid (n = 4) descending (n = 1) splenic flexure (n = 2), and transverse colon (n = 1); all the experienced had intubated the TI and were extubating. There was no difference in percentage time in "no discomfort" or in "moderate/severe discomfort" between the two groups. See Table.

<table>
<thead>
<tr>
<th>Abstract 270</th>
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<tbody>
<tr>
<td><strong>Simulator data</strong></td>
</tr>
<tr>
<td>Novices</td>
</tr>
<tr>
<td>Experienced</td>
</tr>
</tbody>
</table>

**Values = Mean (SD) *p < 0.0001 **p = 0.0042 significant n=7**

**Conclusions:** This simulator can differentiate between novices and experienced endoscopists, novices take longer to achieve caecal intubation and are less likely to achieve TI. However, not all parameters automatically measured by this colonoscopy simulator differentiate.
THE DEVELOPMENT OF A MULTIPLE CHOICE QUESTION PAPER FOR TRAINING AND ASSESSMENT IN COLONOSCOPY

S. Thomas-Gibson, M.D. Rutter, N. Suzuki, M.E. Vance, C.B. Williams, B.P. Saunders. Wolfsion Unit for Endoscopy, St Mark's Hospital, London, UK

Background: Core knowledge is fundamental to good colonoscopy practice. A "curriculum" of topics relevant to colonoscopy was drawn up including gross and endoscopic anatomy; embryology of the colon; patient preparation; instrument functions; technique; endoscopic clinical conditions; complications; and patient follow up. Several hundred questions were designed in MCO, true/false format. Senior endoscopists performed initial selection and verification of questions. Ambiguous questions were excluded or replaced. Two 30 question papers were formulated; papers A and B, and were combined as a 60 question paper, AB. Each question had 5 stems (a total of 300 questions). Question papers were negatively marked (one mark for a correct answer, minus one mark for an incorrect answer, no marks for a question left blank). 3 groups sat the MCQ: 9 endoscopy nurses (novices), 8 colonoscopy trainees (previous experience of 50–500 colonoscopies) and 3 experienced endoscopists (1 nurse, 2 physicians; 500–5000 previous colonoscopies). The trainees sat paper A or B before an intensive week of colonoscopy training and paper AB at the end of the week.

Results: In the trainee group there was no significant difference in the mean scores for papers A and B pre-training 60.5% versus 49% (p = 0.189).

Conclusions: This MCQ paper can differentiate between endoscopists of different standards. A week of intensive training brings moderately experienced trainees up to the standard of knowledge of experienced endoscopists. This MCQ can be used as a training and assessment tool.

POST-PYLORIC ACCESS ON THE ICU: ENDOSCOPIC PLACEMENT OF THE BENGMARK TUBE

G. Constable, J. Pappachan, M.A. Stroud. Institute of Human Nutrition, Southampton General Hospital, UK

Introduction: Gastroparesis, high gastric aspirate volumes and retrograde peristalsis are common on the intensive care unit (ICU) and often thwart attempts at enteral feeding. This may result in a higher incidence of nosocomial pneumonia, increased mortality, longer ICU stay and prolonged periods of parenteral nutrition. Postpyloric feeding improves nutrient delivery and may reduce time to achieve feeding goal rates, but tubes are frequently difficult to place, requiring multiple attempts, endoscopy, and fluoroscopy. Furthermore, transfer of patients to the x-ray department is often not possible and fluoroscopy on the ICU is not practical.

Bengmark Tube: The bengmark tube (BT), a self-locating naso-jejunal tube designed for placement at the bedside, is reported to achieve over 90% spontaneous trans-pyloric passage and stay in position longer than alternative tubes. The principle is based upon a preformed large diameter coil that facilitates movement beyond the pylorus and limits regurgitation back through the pylorus, but spontaneous passage requires adequate gastric emptying. In an attempt to overcome the practical difficulties of obtaining post-pyloric access in the ICU we have used a simple technique of endoscopic placement of the BT that takes advantage of the preformed to prevent displacement of the tube as the endoscope is withdrawn, thereby obviating the need for screening, and also to reduce the risk of reflux into the stomach following successful placement.

Method: A suture is applied to the distal end of the BT, which is then flushed with water prior to complete insertion of the wire. The BT is then transferred from nose to mouth by means of laryngoscope and McGills forceps. The BT is grasped at the mouth with forceps deployed in the therapeutic channel of an endoscope and then carried into position under direct vision. Within D2 the wire is partially removed and the coil observed to form. The endoscope is then withdrawn fully prior removal of the wire to prevent tube displacement. Final tube position is confirmed by abdominal radiograph.

Results: This technique has been used successfully in 8/8 patients without procedure related complication. One tube was displaced within 24 hours while turning the patient and required repositioning. One tube became blocked 10 days after placement but was no longer required. The remaining facilitated uncomplicated enteral feeding for a mean of 12 days.

CLINICAL OUTCOME FOLLOWING INSERTION OF STENTS FOR THE PALLIATION OF PATIENTS WITH LARGE BOWEL OBSTRUCTION. A DGH EXPERIENCE

I. McNamara, M. Tremainling, I. Dunkley, P. Roberts, R. Dickenson. Department of Gastroenterology and General Medicine, Hinchingbrooke Hospital, Huntingdon, Cambridgeshire, PE29 6NS, UK

Background: The deployment of self expanding enteral stents via endoscopic and fluoroscopic guidance has emerged as effective treatment of large bowel obstruction in both the acute and elective setting.

Methods: 20 consecutive patients (10 male), with a median age of 72 years were studied between 1997 and 2002 on an intention to treat basis. All patients had symptomatic large bowel strictures.

Results: 26 procedures were performed on 20 patients. A total of 15 stents were inserted with successful placement on the first attempt in 13 procedures. One patient was stented on the second occasion and one patient was stented on the fourth occasion. In 5 patients (6 procedures) a wire could not be passed due to complete occlusion of the lumen or due to the position of the carcinoma which prevented viewing "en face". The remainder of the failures were due to poor preparation of the colon, or the stenosis being too lax to be amenable to stenting. The cause of the stenosis was malignant in 19 cases with the sites being rectosigmoid (45%), sigmoid colon (40%), splenic flexure (10%), transverse colon (5%). Symptoms improved in all patients successfully stented but in one patient there was distal migration of the stent 3 days later. In the others good palliation was obtained with a median symptom free survival of 7 months. 14 patients died in follow up due to causes unrelated to stent insertion.

Conclusion: Colonic stricts have an important role in the management of large bowel obstruction and palliation of colonic carcinoma and should be available in any district general hospital. Despite small numbers we have shown that with experienced endoscopists this is a feasible proposition.

PRE-CLINIC SELF-ADMINISTERED HEALTH ASSESSMENT EVALUATION FORMS COULD SAVE TIME AND RESOURCES

P.G. Hardo. Gastroenterology Unit, Benenden Hospital, Kent, UK

Background: The use of self-administered health assessment questionnaires maybe a useful instrument in an outpatient setup, especially when the general practitioner’s (GP) referral letters contain insufficient information. They can also improve doctor–patient communication. We therefore routinely use an in-house designed health assessment form (HAF) in the outpatient’s clinic.

Aims: To evaluate patient satisfaction with the HAF.

Methods: The two page HAF contains questions on common GI symptoms/signs together with information on previous tests, operations, family and social history, drug history and the impact of current

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Abstract 271

<table>
<thead>
<tr>
<th>Group (Paper)</th>
<th>Novices (AB)</th>
<th>Trainees-before (A or B)</th>
<th>Trainees-after (AB)</th>
<th>Experienced (AB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean score (SD)</td>
<td>23% (14.0)</td>
<td>54.8% (11.9)</td>
<td>64% (7.4)</td>
<td>74.9% (9.7)</td>
</tr>
</tbody>
</table>

Novices vs trainees p = 0.0001. Novices vs experienced p = 0.0009. Trainees pre vs experienced p = 0.046. Trainees post vs experienced ns.
illness on quality of life. Enough space is left for comments. All patients completed the HAF before they were assessed. When a GP letter was lacking information, a HAF was sent to the patient to be returned by post for prioritisation. A total 173 consecutive patients (111F/62M) were anonymously asked to evaluate the value of HAD before leaving the hospital. They completed a simple questionnaire about its relevance, usefulness, clarity, and ease of completion. A satisfaction scale from: 1 = not at all to 5 = yes, definitely, was used and a space for comment was allocated.

**Results:** 36% were male and 64% female. The very small proportion (2-3%) who felt that the HAF was not very relevant or useful [score 1] were mostly patients with minor or no GI problems. The majority of patients liked the HAF and wrote constructive comments.

### Abstract 276

**Colonoscopy Training: 90% Caecal Intubation—How Easy? How Long?**

A. Kumar, W. Ashraf. King George Hospital, London, UK

**Background:** JAG and ASGE recommended guidelines advocate over 90% caecal intubation rate for successful colonoscopy training. Most GI fellows in structured training programmes in the USA achieve this in 2–3 years. There is a lack of structured colonoscopy training programmes in the UK, hence a poor overall caecal intubation rate in the UK (57–77% at best).1

**Aim:** To determine the time and effort needed to achieve required competence in colonoscopy with structured training.

**Method:** A trust registrar in surgery who had no previous endoscopy experience underwent formal training offered by an experienced and well trained colonoscopist. Training was offered for one NHS session per week. The training programme included formal training in Upper GI endoscopy and flexible sigmoidoscopy (8 months) followed by colonoscopy training. Each procedure was recorded on computer Endoscopy Reporting System (version S1.05/F13 1204/1999).

**Results:** There was one significant post-polypectomy bleed (10th day). There were no perforations.

**Conclusion:** 90% caecal intubation rate at colonoscopy is easily achievable with a structured training programme utilising only one NHS session per week. A very low risk of complications with fully supervised training. Training non-gastroenterologists is an attractive option to deal with long waiting lists and impending CRC screening programme.


### Abstract 274

**Audit of Therapeutic Pancreatic Endoscopy**

A.L. Thuraisingham, H.L. Smart. Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP, UK

**Background and Aims:** Therapeutic pancreatic endoscopy is a specialised technique used to treat a range of pancreatic disease. There are few prospective, randomised studies of pancreatic endotherapy and most data are derived from uncontrolled series. We assessed current practice relating to pancreatic endotherapy at ERCP in a regional teaching hospital and examined our procedural outcomes.

**Methods:** A retrospective case note audit was undertaken of all patients, over a three and a half year period, in whom therapeutic endoscopy was attempted or performed. Data were collected regarding patient demographics; endoscopists; indications; use of pre-procedural imaging; procedure performed; success rate; 30 day complication rate; and 1 year outcome.

**Results:** Sixty-three out of 1906 ERCPs (3.3%), performed in this period, involved pancreatic endotherapy. These were undertaken in 32 patients by 5 principal endoscopists. There were 21 men and 11 women with a mean age of 49 years (range 11–74 years). Incomplete data were available for one patient. Imaging in the 3 months prior to endotherapy included: 43 CT scans; 27 ultrasounds; 25 ERCPs; 5 endoluminal ultrasounds; and 2 MRIs. The procedural indications were: 25 for pseudocyst drainage (9 with another indication); 26 for stent change; 8 for pancreatic duct stent; 7 for pancreaticocutaneous fistula; 3 for pancreatic ascites; and 3 for pancreatic duct traumatisation/disruption. Overall 49 of 63 procedures (78%) were completed successfully, with 2 patients having repeated failed procedures. 19 of 32 patients required more than one procedure. Complications included one episode each of pancreatitis, infection, perforation, and bleeding. There was no 30 day mortality. 18 of 21 patients followed up for over 1 year were alive.

**Discussion:** Pancreatic endotherapy remains an uncommonly performed specialised procedure. The predominant indications in this series relate to complications of pancreatic ductal disruption in chronic pancreatitis. Patients often undergo multiple imaging investigations and may require repeat procedures for treatment. Endoscopic management can be effective and our data compares well with the available evidence.

### Table 1

<table>
<thead>
<tr>
<th>Training period</th>
<th>Cols.</th>
<th>No. of Colonoscopies</th>
<th>Completion rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>at 4 mths</td>
<td></td>
<td>First 50</td>
<td>42</td>
</tr>
<tr>
<td>, 10 mths</td>
<td></td>
<td>51–100</td>
<td>20</td>
</tr>
<tr>
<td>, 17 mths</td>
<td></td>
<td>101–200</td>
<td>19</td>
</tr>
<tr>
<td>, 24 mths</td>
<td></td>
<td>201–300</td>
<td>8</td>
</tr>
<tr>
<td>, 28 mths</td>
<td></td>
<td>301–400</td>
<td>8</td>
</tr>
<tr>
<td>, 30 mths</td>
<td></td>
<td>401–500</td>
<td>Independently 98%</td>
</tr>
</tbody>
</table>

**Conclusion:** Most patients found the HAF valuable in preparing them for the consultation and a useful way to think about their problems before seeing the doctor. Based on our 6 years experience with the HAF (which we have modified as a result of this audit) we found it particularly helpful for: prioritising the urgency for consultation; speeding up the consultation process; and avoiding duplication of investigation. We achieve 99% patients’ compliance in completing the HAF. We recommend the use of a “self-administered health assessment questionnaire” as an integral part of the outpatient GI assessment.
Follow-up audit of colonoscopy completion rate: it takes time to improve

P.J. Mullen. The Princess Elizabeth Hospital, Guernsey

Background: An initial audit of 357 colonoscopies demonstrated what was thought, at the time, to be a well below par overall completion rate of 73.9%, adjusted to 80.5% if operator independent failures (eg poor bowel preparation, stricture, obstructing tumour) were excluded.

Action undertaken: Efforts were made to improve by: more frequent alteration of patient position; better loop avoidance; the use of "jiggling"; earlier and repeated de-looping manoeuvres; and increased use of manual abdominal pressure.

Methods: The records of all procedures performed by the same operator over the 4 years following the previous audit were reviewed retrospectively. The prime data collected were patient demographics, completion rate type of colonoscope used, and total procedural time ("door-to-door").

Results: There was no significant difference in patient demographics of the 653 procedures. The completion rate was significantly improved to 85.9% overall and 90.2% adjusted (p < 0.005). This improvement was still seen when comparing only procedures done with a CF230L colonoscope: 85.9% cf. 74.5% overall (p < 0.001) and 89.7% cf. 81.3% adjusted (p < 0.005). There were significantly more procedures taking 40 min or more (21.6% cf. 14.2%, p < 0.05) in the second audit period.

Conclusion: While certain aspects of technique are clearly important, it may be that workload constraints are primarily responsible for low completion rates. More acceptable standards appear feasible if time is made available for the difficult cases.


Colonoscopy completion rates: a comparison between standard and variable stiffness colonoscopes

P.J. Mullen. The Princess Elizabeth Hospital, Guernsey

Introduction: Faster caecal intubation times and reduced patient discomfort have been reported with the variable stiffness colonoscope when compared to a C200L colonoscope. In this study of 100 cases, there was no demonstrable difference in completion rates.

Aim: To compare the CF240AL variable stiffness and standard CF230L colonoscopes with respect to completion rates and total procedural time.

Method: The records of all colonoscopies undertaken by a single operator since the purchase of a CF240AL colonoscope in April 2000 up until the end of September 2002 were reviewed retrospectively. Prime data collected were: patient demographics, completion rates (overall, and adjusted for operator independent failures such as poor bowel preparation, stricture, obstructing tumour), and total procedural time ("door-to-door").

Results: There were 191 procedures with the CF230L and 214 with the CF240AL. There was no difference in either the patient demographics, the overall (86.4% cf. 86.9%) and adjusted (91.7% cf. 91.6%) completion rates, or the procedural times. Over the past 12 months, however, the completion rates were better with the CF240AL than the CF230L: 92.7% (97.8%) cf. 90.2% (93.2%) (difference NS).

Conclusion: This study reveals no difference in completion rates or procedural times between the two types of colonoscope. This unexpected result probably reflects a learning curve with the CF240AL and a type 2 statistical error.

**CLEANING AND DISINFECTION OF GASTROINTESTINAL ENDOSCOPES: CURRENT PRACTICE IN THE UK**

L. Gilby, M. Mulcahy, M.C. Allison. Gastroenterology Unit, Royal Gwent Hospital and St Joseph’s Hospital, Newport, South Wales, UK

**Introduction:** Until recently most endoscopy units in Europe and the USA have employed glutaraldehyde based disinfectants. Occupational exposure to glutaraldehyde is associated with hypersensitivity reactions prompting one manufacturer (Johnson & Johnson) to withdraw one of its widely used products (Cidex®). The Medical Devices Agency has recently revised its recommendations for endoscope decontamination. There have also been concerns about possible transmission of prion proteins by endoscopes, prompting the recommendation that enzymatic detergents are used during mechanical precleansing.

**Methods:** We undertook a telephone survey of 107 hospitals in the UK to gather information on decontamination practice and the range of disinfectants and detergents in current use. A range of size of hospital was chosen, including seven private hospitals. Of the NHS hospitals there were 60 from England, and 20 each from Scotland and Wales.

**Results:** All units surveyed perform manual cleaning before automatic endoscope disinfection. Manual cleaning is done using an enzymatic detergent by 63 (59%) of units and using ordinary detergent or soap solutions such as washing-up liquid by 28 (26%). The type of detergent used was unknown for 16 units. Aldehyde based disinfectants are used by 69 (64%); within this group 48 continue to use glutaraldehyde based solutions, 2 use diodehydes and 19 use ortho-phthalaldehyde (an aldehyde with greater mycobactericidal activity and lower sensitisation risk than glutaraldehyde). Of the remainder 20 units use peracetic acid disinfectants, 11 use superoxidi-dised saline, and 8 use chlorine dioxide. We identified 20 different brands of automatic endoscope reprocessors. 20 different brands of automatic endoscope reprocessors.

**Conclusions:** Mechanical cleaning followed by automatic endoscope reprocessing is now standard practice. Recommendations for the use of enzymatic detergents are only partly being adhered to.

**ENZYMATIC DETERGENTS ARE ONLY PARTLY BEING ADHERED TO.**

Abstract 281

<table>
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<tbody>
<tr>
<td>median</td>
<td>19</td>
<td>14</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>7.5</td>
<td>5</td>
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</table>

Correlation coefficient: $R^2 = 0.9$.

**Conclusion:** There is a year by year, significant decreasing trend in the publication rate of SpRs’ at the time of their consultant appointment. This could reflect diminished research funding opportunities, changing ratios of trainees to posts, or the impact of the Calman SpR system.

**SAFE EARLY DISCHARGE OF PATIENTS WITH LOW RISK UPPER GASTROINTESTINAL HAEMORRHAGE—A CHANGE IN PRACTICE**

R.S. Hodgson, M.J. Carter, A.A. Barrett, A. Ainsworth, A.P. Catterall, P.B. McIntyre, S.M. Greenfield. Queen Elizabeth II Hospital, Herts, UK

Approximately 650 bed days are used by patients admitted with upper gastrointestinal haemorrhage (UGIH) per annum in this hospital serving a population of 250 thousand. 145 of these are for patients with low risk UGIH (pre-endoscopy Rockall scores 0 and 1). There are few data on clinical outcomes and no published prospective studies on the impact of hospital policy on the outcome of patients with low risk UGIH. We investigated the outcome of patients with low risk UGIH.

**Methods:** Hospital policy was changed from 1 June 2002 to avoid admission of patients presenting with low risk UGIH. An UGIH clerking proforma was developed to aid and direct assessment of patients and for audit purposes. All patients with UGIH have a pre- and post-endoscopy Rockall score calculated. Low risk patients (score of 0 or 1) are assessed by a senior member of the on-call medical team before discharge. Emergency outpatient UGIH endoscopy is arranged on the next working morning. All patients are phoned 30 days later.

**Results:** In 18 weeks 53 patients presented with UGIH. 26 had pre-endoscopy scores of 0 or 1 (49%), 14M:12F, age range 18–78 years (mean 50). 13/26 were discharged (50%), only one did not present for UGIH as planned. None required admission following endoscopy. 7/13 (58%) had a normal endoscopy, 2 required OPA, 1 further investigations. 5 had ongoing melaena at 30 days in spite of OPA review (had not taken prescribed medication). Of the 13 low risk patients admitted, 11 had UGIH endoscopy, 3/11 (27%) were normal. All admissions were for other medical issues. The median length of hospital stay was 5 days.

**Conclusions:** Discharge from A&E of low risk patients presenting with UGIH with plans for early emergency outpatient UGIH endoscopy appears safe and cost effective. An estimated 72 bed days may be saved per annum in this hospital. In a UK population of 58.8 million this represents potentially a saving of 17 thousand bed days per annum.

**ADULTS WITH FOREGUT DUPLICATION CYSTS DIAGNOSED BY ENDOSCOPIC ULTRASOUND (EUS) CAN BE SAFELY MANAGED WITH AN EXPECTANT POLICY**

L. Langmead, S. James, I.D. Norton, D.B. Jones. Department of Gastroenterology, Concord Hospital, University of Sydney, Australia

**Background:** Enteric duplication cysts (EDC) are rare congenital anomalies that lie within or adjacent to the wall of the gastrointestinal tract. The majority of EDC have characteristic sonographic patterns on EUS. Because the management for adults diagnosed with foregut EDC at EUS is controversial, we aimed to assess their long term outcome.

**Methods:** We reviewed the indications and EUS findings for patients diagnosed with EDC over 5 years. Outcome was established from medical records and/or a questionnaire sent to referring physicians.

**Results:** Of 768 EUS examinations, 27 patients (10 males) were diagnosed with probable EDC. Median age was 51 years (range, 21–77). Presenting symptoms included dysphagia (n = 7), dyspepsia (6), reflux symptoms (5), and chest pain (2). Abnormal upper GI endoscopy (n = 21), with possible extrinsic compression (10) or submucosal tumour (8), was the commonest indication for EUS. Other prior investigations were CT (n = 7), barium meal (2), MRI (1) CRX (1), abdominal US (1). At EUS, most EDC were in the oesophageus (proximal (n = 4), mid (7), distal (11)). Other sites were proximal stomach (2) and duodenum (3). Maximal diameter ranged from 10–60 mm. Septation was seen in 2 cysts, sediment in 3, and probable haemorrhage in 4. Follow up data were available in 21 of 27, with diagnosis of EDC subsequently revised in 5/21. 3 patients had surgery after further imaging. In a patient with early oesophageal cancer, coincident EDC was not confirmed. A leiomyoma and a bronchial inclusion cyst were found in the others. CT after EUS suggested an alternative diagnosis in 2 patients (1 leiomyoma and 1 partial situs inversus with anomalies of azygous vasculature). In 16 patients (including 4 in whom follow up imaging supported the initial diagnosis of EDC) an expectant policy was employed. All 16 patients remain well 6 months to 4 years after EUS without development of new symptoms or complications related to the EDC.

**Conclusion:** Adult patients with asymptomatic, uncomplicated EDC of the foregut at EUS can be managed expectantly.

**INPATIENT COLONOSCOPY AND FLEXIBLE SIGMOIDOSCOPY—AN INFERIOR SERVICE?**

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**Introduction:** A recent retrospective audit of 3455 colonoscopies within our unit found that nonelective inpatient procedures were less likely to be completed to the caecum (77%) than in outpatients (89%). Despite this finding, abnormal examinations were more common in inpatients. Endoscopists and nursing staff have long suspected that inpatients might be less adequately prepared and informed than outpatients. We therefore conducted a prospective audit to investigate such disparities.
Aim: To compare the quality of inpatient to outpatient lower gastrointestinal endoscopy.

Method: A prospective audit was performed using standardised questionnaires completed by patients, endoscopy nursing, and medical staff. Bowel preparations used were Fleet Phospho-soda (colonoscopy: COJ) and phosphate enema (flexible sigmoidoscopy: FS). All outpatients received procedural information leaflets, while all inpatients had access to ward based information sheets. Statistical analyses employed were the students t-test and chi-square test.

Results: Procedures audited were 183 COL and 111 FS (34 inpatient, 260 outpatient). Inpatients were less likely to understand the indication and reason for the procedure or to recall receiving an information sheet (p < 0.05). For both COL and FS the bowel was less well prepared in inpatients (COL p < 0.03, FS p < 0.001). Inpatients had a higher mean American Society for Anesthesiology score (p < 0.001). There was no difference between the two groups with regards to side effects of the bowel preparation, sedation used, and duration or discomfort of the procedure as assessed by patient, endoscopy nurse, or endoscopist.

Conclusions: Inpatients are frailer and less well prepared for lower GI endoscopy in terms of both the quality of the bowel preparation and information they receive. This has implications regarding the consenting process and procedural completion rates. Endoscopy units should consider new ways of working in order to improve inpatient preparation.

Pancreas posters 286–288

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A COMPARISON OF THE PANCREOLAURYL RATIO WITH FECAL PANCREATIC ELASTASE-1 FOR ASSESSING PANCREATIC EXOCRINE FUNCTION

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Introduction: An ELISA kit for measurement of Faecal Pancreatic Elastase-1 (FE1) has recently been introduced for the investigation of pancreatic insufficiency. We compared this test with the urine pancreolauryl ratio (PLR). The clinical response to pancreatic enzyme supplements is used as the standard against which they are compared.

Methods: 45 patients under investigation for chronic diarrhoea were included in the study. All had urinary PLR measured as an outpatient. This has been the standard investigation for pancreatic insufficiency in our hospital to date. These patients also had a FE1 level measured. 33 patients (with either a high clinical suspicion of pancreatic insufficiency, a PLR < 20 or a FE1 < 200 µg/l) were given a trial of pancreatic supplements (Creon) at standard dose, and their clinical response assessed. A subjective improvement in diarrhoea and objective evidence of weight gain (at least 5% gain over 6 months) was required to record a positive response.

Results: We found a strong correlation between FE1 level and clinical response to Creon (p = 0.013 by χ² analysis).

<table>
<thead>
<tr>
<th>Response To Creon</th>
<th>FE1 &lt; 200</th>
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<tr>
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<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>11</td>
<td>33</td>
</tr>
</tbody>
</table>

However, a similar analysis yielded no significant correlation between PLR and clinical response to Creon (χ² p = 0.15).

Conclusion: FE1 more accurately predicts response to pancreatic enzyme supplements than PLR. This may be due to the inaccuracy inherent in performing the urine PLR as an outpatient. We have now adopted the FE1 for assessment of pancreatic exocrine function.

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COMPARISON OF URINARY PANCREOLAURYL AND FECAL ELASTASE-1 TESTS IN THE ASSESSMENT OF EXOCRINE PANCREATIC INSUFFICIENCY

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The urinary pancreolauryl (UPL) test is used widely for the non-invasive diagnosis of exocrine pancreatic insufficiency, but is time consuming and reported to be unreliable in mild to moderate exocrine insufficiency. A highly sensitive enzyme linked immunosorbent assay for faecal elastase-1 (FE1) using two specific monoclonal antibodies is now commercially available.

Aim: To compare UPL and FE1 test results in a group of patients with well characterised [CT, MRCP ± ERCP] chronic pancreatitis with and without overt exocrine pancreatic insufficiency.

Methods: Paired UPL and FE1 data were obtained in 51 patients (36 M, 15 F; mean age 52 year, range 29–77 year). Standard cutoff values for the UPL test (< 20% fluorescein recovery from the orally administered ester abnormal, 20–30% equivocal) and FE1 test (< 200 µg/g faeces abnormal) were used.

Results: There was concordance between the two tests in 31 (61%) patients (both UPL and FE1 normal in 12, abnormal in 19). Two of the 12 patients with normal UPL/FE1, and all 19 in whom both tests were abnormal, had moderate or severe morphological changes in the pancreas on CT/ERCP (Cambridge classification). Six patients had equivocal UPL results, none of whom had overt exocrine insufficiency and only one of whom had a low FE1. Two patients (4%) had normal UPL but low FE1 (both had moderate/severe morphological changes), while 12 (24%) had low UPL but normal FE1 (2 moderate/severe).

Conclusions: The FE1 test is simpler to perform than the UPL test, and correlates well with abnormalities of the pancreas seen on structural imaging. There was a disparity between FE1 and UPL results in patients with structurally mild disease, but FE1 appears to be a sensitive and specific indirect test for mod/severe pancreatic insufficiency.

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PROPHYLACTIC PANCREATIC DUCT STENTING IN PATIENTS WITH SUSPECTED SPHINCTER OF ODDI DYSFUNCTION BUT NORMAL SPHINCTER OF ODDI MANOMETRY

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Background: Although post-ERCP pancreatitis is a well recognised complication among patients with sphincter of Oddi dysfunction (SOD), preliminary data suggest that the rate of pancreatitis could be as high as 10% to 15% even among patients suspected to have SOD but have normal sphincter of Oddi manometry (SOM) studies. The aim of this study is to determine if placement of a temporary pancreatic stent in patients with suspected SOD but normal SOM reduces pancreatitis rates.

Methods: Evaluation of all patients who underwent ERCP for suspected SOD but had a normal SOM study (both biliary and pancreatic) over a 4 year period (1998–2002). If SOM was normal (basal sphincter pressure < 40 mm Hg), the decision to place a temporary, 3 Fr, single pig-tail pancreatic stent (Wilson-Cook, Winston-Salem, NC) was made by the individual endoscopist. Patients who underwent any therapeutic intervention, such as stent extraction or orifice dilatation, during the same setting were excluded from the study. Post-ERCP pancreatitis was defined as per standard consensus criteria. Abdominal x ray was done routinely after 14 days to verify spontaneous stent passage.

Results: A total of 147 patients with normal biliary and pancreatic manometry studies were identified from the ERCP database. The rate of post-ERCP pancreatitis was 0% (0/26) among patients who underwent prophylactic pancreatic duct stenting compared to 10.7% (13/121) among those who were not stented. No pancreatic stent induced complications were encountered.

Conclusions: Routine temporary pancreatic duct stenting appears to decrease the rate and severity of pancreatitis among patients suspected to have SOD but have normal SOM studies. The procedure appears safe. A randomised controlled trial is warranted to confirm these findings.
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**289 VARIATION IN HELICOBACTER PYLORI STRAINS FROM IRAN AND ZAMBIA**

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Different genotypes of H pylori have been observed in different locations of the world and identification of these genotypes may be important for understanding the clinical outcome of infection, the efficacy of antibiotic treatment, laboratory diagnosis, and possibly human migration patterns. Data on the vacA diversity from Iran and Africa are sparse. We compared the vaculating cytotoxin alleles (vacA) and the cytotoxin associated gene A (cagA) in H pylori isolates from Iran and Zambia by means of PCR. A total of 31 H pylori isolates were studied from Iranian dyspeptic and 23 from Zambian dyspeptic patients. There was an equal distribution of s1 and s2 alleles in Iran, where s1c was the predominant s1 subtype (10 of 16 s1 strains) with the m2 region predominating (26 out of 26 strains, with 5 strains unable to be typed in the “m” region). Isolates from Zambia mostly carried the s1 allele (21 out of 23) with the s1 allele being the most frequent (18 out of 21) and m the region the m allele predominating (17 out of 21) with the cagA marker typed (19 of 113). Using primer pairs for cagA, the percentages of cagA positive strains in Iran and Zambia were 41% (13 out of 31) and 86% (20 out of 23), respectively. Most of the cagA positive strains (85%) from Iran were of the non-Asian type and only two isolates were of the pure East Asian type. All of the 20 cagA positive strains from Zambia were of the non-Asian type and had the s1 allele. In Iran the cagA gene was found at a higher frequency in the s1 allele type (11 out of 16) as compared to the s2 strains (2 out of 15). Overall, there was a strong association between the cagA marker and the s1 allele (p < 0.001).

**Conclusions:**

H pylori serology is an unreliable test for predicting H pylori infection. This is particularly so in a multiethnic population where the specificity is much lower. Therefore, other non-invasive, more reliable ways of diagnosing H pylori infection should be used preferentially.

**Abstract 291**

<table>
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<th>Caucasians</th>
<th>Non Caucasians</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
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<td>85%</td>
<td>89%</td>
</tr>
<tr>
<td>Specificity</td>
<td>61%</td>
<td>36%</td>
</tr>
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<td>Positive predictive value</td>
<td>45%</td>
<td>62%</td>
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<tr>
<td>Negative predictive value</td>
<td>91%</td>
<td>75%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>27%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Conclusions:**

H pylori serology is an unreliable test for predicting H pylori infection. This is particularly so in a multiethnic population where the specificity is much lower. Therefore, other non-invasive, more reliable ways of diagnosing H pylori infection should be used preferentially.
than after the other beverages (p < 0.01), independently from the insulin response, not significantly different during the four tests. Triglycerides were slightly higher after ingestion of the alcoholic beverages than after water, but were markedly reduced after dealcoated wine compared with the other beverages (p < 0.05 for all contrasts). Both alcohol containing beverages produced a highly significant post-prandial increase of serum glucose, only minor wine constituents reduce that of triglycerides.

Conclusions: Red wine produces a marked delay in gastric emptying, only partially explained by its alcoholic content. Moreover, red wine, alcohol, and minor wine constituents reduce the postprandial increase of serum glucose, only minor wine constituents reduce that of triglycerides.

Introduction: To date only a few H pylori isolates have been demonstrated to colonise Mongolian gerbils. The aims of this study were to establish stable colonisation of strains of H pylori from China in Mongolian gerbils and to assess the function of the cag pathogenicity island of infecting strains.

Methods: Fresh clinical H pylori isolates from Chinese patients were inoculated into gerbils. At 4 to 6 weeks post-inoculation, infection status was evaluated by microbial culture, biopsy urease test and pathology. Sequencing of glmM and random amplified polymorphic DNA (RAPD) fingerprinting of DNA from cultured H pylori were used to evaluate the genetic identity of pre-inoculated and post-inoculated strains. The ability of pre- and post-inoculated strains to stimulate IL-8 transcription in human gastric epithelial cells was analysed using an IL-8 luciferase reporter assay.

Results: Three of five inoculated clinical isolates colonised the Mongolian gerbil and induced chronic antral gastritis by 4 weeks post-infection. Each of the three pre- and post-inoculation cagA+ strains had identical glmM sequences and RAPD profiles, and stimulated luciferase secretion from LSFT1 epithelial cells. The strain, which caused severe pathological changes, was selected for repeat infection to prove reproducible and stable colonisation. The cagA+, vacA s1/c2 Chinese strain 42GX gave stable colonisation in the Mongolian gerbil and induced severe gastritis.

Conclusions: This study demonstrates that low passage H pylori clinical isolates will successfully colonise Mongolian gerbils and the ability of the strains to stimulate IL-8 transcription in human gastric epithelial cells is maintained following infection in the Mongolian gerbil.

Aims: The aim of our study was to determine the outcomes of patients admitted to hospital as emergencies with acute complications of their undiagnosed cancers, and to compare their outcomes with those of patients diagnosed via conventional outpatient referrals.

Methods: Eighty-eight patients (median age 73 years, 55 months) admitted to hospital as emergencies with acute complications of their undiagnosed gastric cancers were studied prospectively and compared with 170 patients (71 years, 114 months) with gastric cancer diagnosed as outpatients or open access endoscopy.

Results: In a multivariate analysis, acute presentation (HR 2.70, 95% CI 2.07 to 3.33, p = 0.002) and the stage of gastric cancer (HR 1.773, 95% CI 1.457 to 2.089, p < 0.0001) were found to be significantly and independently associated with poor survival.

Conclusion: Although the one in three patients presenting acutely had not suffered undue diagnostic delay, they were less likely to undergo potentially curative surgery and to survive long term. Acute presentation with gastric cancer remains common, and if the findings of this study are representative, is an independent and significant prognostic marker of an aggressive form of gastric cancer.

Methods: A simulation model of 72 alternative management strategies for a dyspeptic patient was constructed. The model simulated the flow of individual patients with potential upper GI disorders through potential investigations and therapies, including endoscopy, non-invasive testing for H pylori, acid suppression therapy, and H pylori eradication. Epidemiological data and meta-analyses were used to specify parameters within the model. The model was used to establish the important comparisons for future research and to establish likely effect sizes in terms of cost and efficacy. Sensitivity analysis explored potential effect modifiers and the MRC-CUBE study was designed and powered on the basis of the model.

Results: Recent trials have supported some of the model’s findings, in that only empiric acid suppression with either an antacid or a PPI, or H pylori “test and treat”, followed by acid suppression were cost effective. Test and treat was more effective, but more costly than empiric acid suppression alone. Based on the model, the minimum effect size would be 7%, assuming a maximum willingness to pay for a patient free of dyspepsia for a year of 100, and a control event rate of 70%. 1940 patients would be required for an alpha of 0.05 and 0.1.

Conclusions: The MRC-CUBE trial is about to start recruitment in 60 practices, a large, multicentre trial being justified on the basis of the model. As well as informing the selection of appropriate comparisons, pre-trial modelling enables cost effectiveness trials to be powered for cost as well as effectiveness outcomes.
dyspepsia) but in 15 (38%) there was no compelling indication (NSAID with no peptic ulcer disease, alcohol abuse, on clopidogrel). 22 patients (55%) were on healing doses of PPI. In 6 (15%) this was for an appropriate reason (active peptic ulcer, uncontrolled reflux symptoms). 16 patients (40%) were prescribed inappropriately high doses (NSAID prophylaxis, controlled dyspepsia with no attempt made to reduce to maintenance doses). 22 patients (55%) had previous upper GI endoscopy, 10 (25%) were unfit for investigation, 1 (2%) had not attended, 7 (18%) were suitable but had no previous investigations performed. 12 patients had a diagnosis of gastritis, duodenitis or peptic ulcer disease made at endoscopy. Of these 2 were not tested for Helicobacter pylori infection.

**Conclusion:** A substantial proportion of patients were prescribed PPI therapy with no clear indication, or in inappropriately high doses. 7 patients were on long term PPIs without a confirmed clinical diagnosis. It is with possible H. pylori associated pathology were not tested. The NICE guidance on the use of PPIs is not followed in clinical practice.

**THE VALUE OF DRUGS TO TREAT UPPER GASTROINTESTINAL SYMPTOMS: WHAT ARE PATIENTS WILLING TO PAY?**

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**Introduction:** Over £500 000/year is spent on anti-secretory therapy in the UK and until recently they were the most expensive drug class in the NHS budget. The treatment of upper gastrointestinal symptoms is such an integral part of life so we need to be sure that this money is being spent appropriately. We have previously shown that quality adjusted life years are not sufficiently sensitive to measure the value of treating dyspepsia symptoms. We have therefore assessed directly how much dyspepsia patients are willing to pay for cure of their symptoms.

**Methods:** Unselected patients with dyspepsia attending for endoscopy were interviewed. Demographic and income data were collected and also a validated dyspepsia questionnaire was administered. Patients were asked to place a monetary value on a hypothetical drug that had a 20, 50, or 80% chance of curing their symptoms. The patient bid higher or lower from a randomly selected starting point between £5 and £100 until they were satisfied that the correct price had been reached.

**Results:** 193 patients completed the interview (mean age = 50, range 19–76 years; 89 [46%] male). Patients were willing to pay £11.52 (95% CI = 9.60 to 13.45) for a drug with a 20% chance of curing their symptoms, £20.24 (95% CI = 18.15 to 22.34) for a 50% chance of curing their symptoms and £30.13 (95% CI = 27.88 to 32.37) for a drug with an 80% chance of curing their symptoms. These costs did not statistically significantly alter with increasing severity of dyspepsia symptoms, in a multiple regression model including age, sex, income, educational status, endoscopy diagnosis, dyspepsia score, most troublesome symptom, and starting bid the only significant predictor of the amount patients were willing to pay was the starting bid (0.23; 95% CI = 0.09 to 0.37 per unit increase in starting bid).

**Conclusions:** These data suggest lower priced drugs such as generic H2 receptor antagonists and proton pump inhibitors are too expensive when the probability of cure is low but these are at an acceptable cost when the chance of success is more than 50%.

**CAN PATIENTS WITH AN UPPER GI BLEED BE DISCHARGED?**

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There are various scoring systems for upper GI bleeding to predict mortality, including the Rockall score. The newer Blatchford score predicts the need for intervention. These scores help in management of patients with least intervention requirement who are otherwise investigated including endoscopies after hospitalisation, has not been studied in district general hospital setting where most of the patients are managed.

**Aims:** To validate the Blatchford scoring system in a different population group and also compare it with the Rockall scoring system, in identifying the population at least risk, of requiring intervention.

**Methods:** All patients presenting to the hospital with the diagnosis of upper GI bleeding during a 12 month period were included in this study. They were scored using Blatchford and Rockall systems and the results compared with the outcome.

**Results:** Of 17 249 general medical patients admitted, 225 had upper GI bleeding. As in other studies there was a close correlation between mortality and the initial Rockall score (eg Score 2 in this study mortality was 5.6%; in this study 12.1%. Score 5 in his 39.6%; in this 30% mortality). Surprisingly a relationship also existed between the Rockall score and the need for intervention and length of stay, not found in previous studies. As in the original study the Blatchford score predicted the need for intervention and length of stay. With a Blatchford score of 0, the need for intervention in this study was 3.8% versus 18.8% in the Blatchford study; a score of 6 was associated with intervention in 62.5% versus 50.4% in the Blatchford study.

As suggested in the Blatchford study group of patients with Hb > 13.0 g/dl in men and > 12.0 g/dl in women, urea < 6.5mmol/l, systolic BP > 110 mm Hg, and pulse < 100, (15.56% of patients) the need for intervention is low at 2.8% and in those < 65 years of age (8.9% of patients) is 0%. Similarly no intervention is needed in patients with value of 0 in both Blatchford and initial Rockall scoring system.

**Conclusion:** The Rockall scoring system is useful for assessing risk of mortality while the Blatchford scoring system predicts the need for intervention. A combination of them could help in early discharge of some 9% of patients with less intervention requirements.

**IMPROVEMENT OF DYSEPSIS SYMPTOMS AND QUALITY OF LIFE IN HEALTHY INDIVIDUALS AFTER ADMINISTRATION OF ARTICHOKE LEAF EXTRACT (ALE)**

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**Background:** Dyspepsia is a common condition but can be a difficult symptom to treat although antacids or prokinetics are often used. Recent data from Germany suggest that high doses of artichoke leaf extract (ALE) can reduce symptoms of dyspepsia. Aim: To investigate the efficacy of low dose intervention with ALE on amelioration of dyspeptic symptoms and improvement of quality of life.

**Design of Study:** Open, dose ranging postal study in patients with self-reported dyspepsia recruited through the media (articles in local and national newspapers).

**Methods:** The Nepean Dyspepsia Index and the State-Trait Anxiety Index were assessed at baseline and after 2 months of treatment with ALE to assess the efficacy of the intervention. Volunteers were randomly allocated to receive either 320 or 640 mg of the extract daily.

**Results:** Of the 516 participants, 454 completed the study. In both dosage groups, there was a significant reduction in all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. There were no differences in the outcome measures between the two groups. Health related quality of life was significantly improved in both groups.

**Conclusion:** This open study demonstrated that ALE may ameliorate upper gastrointestinal symptoms and improve quality of life in healthy subjects suffering from dyspepsia. Further double blind, placebo controlled studies are needed to confirm these results. Nevertheless, these results hold promise of a safe new approach to dyspepsia in primary health care.

**DIAGNOSTIC DELAY IN GASTRIC CANCER IS RELATED TO BOTH INDICES OF DEPRIVATION AND BLIND ACID SUPPRESSION**

G. Blackshaw1, P. Edwards1, J. Barry1, C. Gent1, M. Allison2, W. Lewis1. 1Department of Surgery, 2Department of Gastroenterology, Royal Gwent Hospital, Newport, UK

**Aims:** To examine the time taken to diagnose gastric cancer, identify the source of delay, and assess its clinical importance.

**Methods:** Two hundred and fifty eight consecutive patients (median age 73 years, 55 months) with cancer of the stomach were studied prospectively. The main measures of outcome were the interval from the onset of symptoms to histological diagnosis, final pathological stage of the tumour, and whether potentially curative resection was...
Antibiotic resistance to helicobacter pylori in north wales


Background: Resistance to antibiotics can be a major problem in the treatment of bacteria infections. As the use of antibiotics increases, bacterial resistance to these agents is rising and in many cases is responsible for the failure of treatment regimes. Although the treatment of H pylori infection requires the use of more than one antibiotic to obtain adequate eradication rates, the efficacy of currently used antibiotic combination has been shown to be reduced by resistance to one of the antibiotics used.

Aim: To evaluate the antibiotic resistance to H pylori in the past 4 years in North Wales.

Method: Central database of all patients who are H pylori positive over the past 4 years in two district general hospitals in North Wales. Minimum inhibitory concentration (MIC) of amoxycillin, metronidazole, tetracycline, and erythromycin were determined by agar dilution method.

Results: A total of 888 H pylori organism isolated. Of those, 147 had no sensitivities due to failure of the organism to grow on subculture. Primary resistance rates were: metronidazole 12.6%, erythromycin 6.7%, amoxycillin 0.6%, and tetracycline 0.7%. There was an overlap with organisms resistant to both metronidazole+erythromycin (6.8% of total of these groups); metronidazole+tetracycline (2.3% of total of these groups) and erythromycin+amoxycillin (1.9% of total of these groups).

Conclusion: A proportion of patients from North Wales were infected with resistant strain of H pylori. The higher resistance rate to metronidazole and this used in combination with erythromycin have both proved not to be effective for eradication therapy of H pylori. Amoxycillin and tetracycline are useful component of treatment regimens in this area. No significant change in resistance rates during the period of investigation were observed. Antibiotic resistance monitoring is very important to ensure effective eradication of H pylori infection.

Patient and gp use of nsaid: In musculoskeletal pain: Misperceptions of risk

A.L. Blower, A.D. Woolf, N. Amin, A.I. Carr [introduced by M Guslandi] on behalf of the Arthritis Action Group. Royal Albert Edward Infirmary, Wigan, UK; Royal Cornwall Hospital, UK; White Lodge Medical Practice, UK; University of Nottingham, UK; Istituto Scientifico S. Raffaele, Italy

Background: In the UK, up to 2000 NSAID users a year die from gastrointestinal (GI) side effects. Little is known about the perceptions of risk and benefit associated with NSAID management of musculoskeletal pain (MP) in primary care. The Arthritis Action Group (AAG) survey was undertaken to increase understanding of the management of MP in 8 European countries. Data from UK GPs and patients are presented here.

Methods: A telephone survey was conducted with 1483 doctors and 5803 chronic pain sufferers in 8 European countries. In the UK, 200 GPs and 7% of MP sufferers were surveyed. All doctors and patients were randomly selected. The survey was based on a structured questionnaire that asked about health status (SF-12), usual management of MP, risks and benefits of treatment and beliefs about treatment.

Results: Arthritis is the most common cause of MP. In first line management of MP, 61% of GPs use analgesia alone and 35% use NSAIDs alone. Cox-2 NSAIDs are used by 2% of GPs. 26% of patients taking prescription NSAIDs supplement with OTC medication. Most GPs (85%) are concerned about NSAID related side effects and routinely screen patients for some known risk factors but only tell patients about the most common side effects (64%). Most patients who are taking NSAIDs (71%) are unconcerned about side effects and only 51% are aware of any side effects of NSAIDs. However, among those who change medications, 42% do so because of GI side effects. Patients’ perceptions of their risk of serious GI side effects is poor: 44% of patients who are at increased/critical risk of side effects perceive their risk as moderate or high. GPs and patients believe that the side effects of NSAIDs can be worse than the condition and few believe that they are safe from side effects if they take NSAIDs as prescribed. Patients are concerned about tolerance and addiction to NSAIDs.

Conclusion: Many patients remain unaware of their personal risk, despite general concerns about NSAIDs. They require more and better information about the specific personal risks and benefits of treatment.

Intensive study of serial endoscopic and histological changes occurring over 48 hours in humans given naproxen

M.W. James, J.R. Bebb, C.T. Atherton, N. Bailey-Flitter, A. Zaitoun, C.J. Hawkey. Division of Gastroenterology, University Hospital, Nottingham, UK

Introduction: Animal studies support a central role for leukocytes in acute NSAID associated injury, which can be abrogated by pre-treatment with anti-leukocyte antibodies. However, with chronic human use inflammatory cells are seldom seen without H pylori infection. Because appreciation of a role for leukocytes in early human pathogenesis would be important and to test the relevance of animal models of NSAID damage to humans we performed an intensive endoscopic and histological evaluation of the acute effects of naproxen in humans.

Methods: Eight healthy H pylori –ve human volunteers were randomised to receive naproxen 500 mg twice daily or no treatment for 48 h. Endoscopy was performed before and 3, 12, and 48 hours after dosing. Serial antral biopsies were analysed by blinded histology.

Results: Increased neutrophil margination and vascular plugging were not seen over a time course in which they are prominent in animal models. Any changes were mild and showed no evidence of progressive evolution, with no differences between naproxen and placebo. The table shows the number of subjects with individual changes at any time point.

Abstract 303

<table>
<thead>
<tr>
<th>Feature</th>
<th>Control</th>
<th>Naproxen</th>
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<tbody>
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</tr>
<tr>
<td>Capillary vasodilatation</td>
<td>4</td>
<td>4</td>
</tr>
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</table>
Aims: To establish the prevalence of PPI prescription in patients admitted to medical and surgical wards, indication for PPI use, applicability of prescription, and potential cost savings.

Methods: Subjects attending for gastroscopy were recruited. Two fundic biopsies were taken for RNA extraction and two antral biopsies for H pylori status. RNA was reverse transcribed and cDNA subject to quantitative real-time PCR with results normalised for the housekeeping gene hHPRT. Ghrelin primers were: Fwd: 5'-ACAACCTCTTGACGCTCC-3'; Rev: 5'-ATCTTCATGAAGGTAGRCAGTC-3'.

Results: Nine subjects (4 HpPos) have been studied so far (Age: 32-73 years; BMI 23-32 kg/m2). A trend towards lower median expression (ghrelin/HPRT ratio) in H pylori positive versus negative subjects is apparent (p = NS).

Conclusions: Based on these preliminary findings, H pylori infection may be associated with downregulation of fundic ghrelin expression. If this observation is confirmed (and is associated with reduced gastric ghrelin secretion) this phenomenon may contribute to extraintestinal manifestations of the infection via reduced GH release and/or via disturbances in the regulation of appetite and energy homeostasis.

305 PREVALENCE AND APPLICABILITY OF PROTON PUMP INHIBITOR PRESCRIPTION IN SECONDARY CARE

R. Hebbar, Z. Ahmed, M.S. Zulliker, S. Scott-Thomas, N.D. Hawkes. Department of Medicine, Prince Charles Hospital, Merthyr Tydfil, UK

Introduction: NICE has issued guidance on the prescription of proton pump inhibitors (PPIs), which play an important role in managing the dyspeptic patient but constitute a major expenditure for the NHS.

Methods: A 1 month, prospective, proforma based study. A team of pharmacists reviewed daily all patients admitted to the designated study wards and noted details of PPI prescription. A trial investigator further reviewed the indication and applicability of prescription according to agreed criteria based on evidence from the British National Formulary (No. 44). Statistical analysis was performed using SPSS version 11.0.

Results: Of the 960 admissions, 98 (10.2%) were taking PPI medication, 36 males, mean age 68.4 years (range 18-94). 60/98 (62%) were long term prescriptions and 42/98 (42.9%) did not follow NICE guidance. Endoscopic investigation increased the proportion of appropriate prescriptions compared with clinical based decisions (z = 14.5, p < 0.001). Details are shown for each indication (see table). Estimated annual savings for this cohort over a 12 month period were £13,420. Assuming constant admission and PPI prevalence rates, this represents a potential annual saving of £161,042 for the community drug budget.

Conclusions: We found a prevalence of 10.2% of patients on PPI medication. NICE guidance was not followed in 43% of this inpatient cohort taking PPIs. Specialist review of inpatients can play a significant role in reducing overall cost of long term PPI therapy in the community.
down staged sufficiently to allow a surgical resection to be undertaken. Patients were followed up until death or for a minimum of 45 months.

Results: The overall mean survival in the patients who underwent a resection was 33.1 months (8.1–81.8 months), whereas in the non-resected patients the mean of survival was 13.2 months (3.5–55 months). In the resected group 9 died of disseminated malignancy and 4 remain disease free 41.3–66.6 months following surgery. Of the 13 non-resected patients 1 remains alive after 55 months. The remainder have died of progressive local (n = 5) or disseminated disease (n = 6).

Conclusion: In a subgroup of patients with locally advanced oesophageal cancers, surgical resection following down staging with combination chemotherapy can provide long term survival. It is likely that this is due to better local disease control.

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**308 IDIOPATHIC SLOW TRANSIT CONSTIPATION: A RARITY IN MALES**

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Colonic transit is delayed in about half of patients presenting to specialist units with severe constipation. Most patients are female, and a majority (about two thirds) have no identifiable cause. There is almost no information regarding males with slow transit constipation. We reviewed the records of patients with constipation referred to two large centres specialising in functional bowel disorders, over 4 years (Centre 1) and 8 years (Centre 2) respectively. Colonic transit was assessed by validated radiological marker studies. Constipation was considered idiopathic when dilated bowel (megarectum) and neurologic injury (central, spinal, or pelvic) were excluded. See Table 1. Not only were the minority of patients referred for constipation male, but proportionally fewer males than females had slow colonic transit (p < 0.05). Of males with slow transit, only 8 from Centre 1, and 2 from Centre 2, were idiopathic (10 of 43, or 23%) (see Table 2).

In the small number of males presenting with constipation, colonic transit is delayed in the minority, and most of these have an identifiable cause, in distinction to women. Either men are less exposed to insults that impair colonic function, or have a greater reserve in resisting their effects.

<table>
<thead>
<tr>
<th>Abstract 308 Table 1</th>
<th>Centre 1</th>
<th>Centre 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number with constipation</td>
<td>1323</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1243 (94%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow colonic transit</td>
<td>741 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>715 (58% of females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (33% of males)*</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Abstract 308 Table 2</th>
<th>Centre 1</th>
<th>Centre 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow transit males</td>
<td>26</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>Dilated bowel</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Neurologic injury</td>
<td>14</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>8 (31%)</td>
<td>2 (12%)</td>
<td>10 (23%)</td>
</tr>
</tbody>
</table>

**309 EVIDENCE FOR INCREASED POST-PRANDIAL PLASMA 5-HYDROXYTRYPTAMINE (5-HT) CONCENTRATION IN FUNCTIONAL DYSPSYETICS AND RELATIONSHIP TO GENDER AND SYMPTOMS**

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Recent studies suggest that patients with irritable bowel syndrome (IBS) have elevated levels of plasma 5-HT following meal ingestion compared with healthy controls. Moreover, patients who exhibit post-prandial symptoms have higher plasma 5-HT levels compared with those who do not, suggesting a possible relationship between post-prandial symptoms and abnormalities in 5-HT release. Given functional dyspepsia (FD) belongs to the same family of disorders as IBS, the aims of this study were to assess platelet depleted plasma (PDP) 5-HT concentrations under fasting and fed (760 kcal meal) conditions in 11 patients with FD (aged 30–61 years; 6 males) and 12 healthy volunteers (aged 20–48 years; 5 males) and assess any relationship to gender and epigastric pain/discomfort (p/d).

Results: Under fasting conditions FD patients had similar levels of PDP 5-HT to controls (FD (n = 11): 4.65 ng/ml (geometric mean) vs controls (n = 12): 4.57 ng/ml; ratio FD:controls (95%CI), 1.02 (0.14,1.26)). However, under fed conditions, although the peak PDP 5-HT concentration for the whole group of FD patients was not significantly different from the controls (n = 11): 8.43 ng/ml vs 8.43 ng/ml; 1.33 (0.69, 2.54); p = 0.37, patients who reported post-prandial p/d had a higher PDP 5-HT peak (n = 8: 14.74 ng/ml) than both patients who did not report p/d (5.36ng/ml; ratio with:without p/d 2.75[1.24, 6.10]; p = 0.02) and controls (8.43 ng/ml; ratio FD with p/d:controls, 1.75 (0.79, 3.87); p = 0.14). This was as a consequence of a higher 5-HT peak in the female FD patients with p/d (36.56 ng/ml), as all other females (FD and controls (n = 9): 7.71 ng/ml; ratio FD with p/d:FD and controls, 4.74 (2.5, 9.0); p < 0.001) and all males (FD and controls (n = 11): 8.07 ng/ml; ratio female FD with p/d: all males, 4.53 (2.19,9.35); p = 0.001) had lower PDP 5-HT peaks. Lastly, symptom severity tended to correlate with peak PDP 5-HT concentration (rho = 0.37; p = 0.08).

Conclusions: These data provide evidence for a role for 5-HT in post-prandial symptoms in patients with FD, particularly females.

**310 SMOKING IS ASSOCIATED WITH THE DEVELOPMENT OF POST-INFECTIONOUS IRRITABLE BOWEL SYNDROME**

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Introduction: Irritable bowel syndrome (IBS) can be triggered by psychological stress, alterations in gut motor function and/or visceral perception. Previous studies suggest 4–32% of people develop IBS after bacterial gastroenteritis but the exact mechanisms underlying post-infectious IBS are not clear.

Aim: To look into the role of possible causative factors in the development of post-infectious functional gastrointestinal disorders, namely IBS, functional dyspepsia, or functional diarrhoea.

Methods: A prospective cohort study. There were 128 subjects without a prior FGID under study and with recent stool positive bacterial gastroenteritis who consented to participate. The presence or not of IBS, functional dyspepsia or functional diarrhoea was diagnosed at the start and on follow up at 6 months using self-complete Rome II modular questionnaires. Data on demographics, social class, infecting organism, smoking and alcohol use, anxiety, depression (via Hospital Anxiety and Depression Scale) and life events and impact (via Life Events Survey) were collected at the start of the study.

Results: One hundred and seven Rome II questionnaires were returned at follow up. Twenty-five subjects developed a FGID, 16 who
had symptoms consistent with IBS. Of the factors mentioned, only smoking was significantly associated with the development of a post-infectious FGID (odds ratio 4.1; CI 1.4 to 11.6). The odds ratio of a smoker developing post-infectious IBS was 3.6 (CI 1.12 to 11.60). The odds ratios of a smoker developing functional diarrhoea or functional dyspepsia were not statistically significant.

Conclusion: Post-infectious IBS appears to be associated with smoking and we did not find evidence of association with life events, anxiety, or depression. Smoking is known to moderate gut immunity in other disorders such as ulcerative colitis and Crohn’s disease. Our study adds to increasing evidence for an organic basis to post-infectious IBS, perhaps moderated via inflammatory pathways.

MEDICINES TAKEN BY PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS)

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Introduction: Many studies have evaluated the prescribed medicines taken by patients with IBS. However, there is a paucity of information about over-the-counter and complementary therapies taken. This study describes medicines taken by patients with IBS from a self-administered diary and evaluates differences in medication taken by those referred to secondary care and those not referred.

Method: A self-selected group of patients with IBS (n = 595) submitted a daily diary for 6 months. The cohort was stratified by those who reported a referral to secondary care (n = 381) and those who did not report referral (n = 203) at baseline evaluation. Eleven patients could not be stratified and were excluded from analysis. Medicines taken at any time during the study period were evaluated and were defined as prescribed or non-prescribed (including herbal).

Results: At any time over the study period 425 of 595 people took a “medicine”. In total there were 1589 “medicines” taken, 1335 (84%) had a BNF identifiable ingredient. Of the 381 secondary care patients, 280 (73%) patients were taking “medicine”. The majority of patients (58%) were taking an antispasmodic (161/280). Other medicines include laxatives (35%), and antidiarrhoeals (29%), and analgesics (18%). There were 145 (71%) patients taking “medicines” of the 203 patients treated in primary care. The most frequently taken medicines were antispasmodics (75% 110/145), laxatives (36%), antacids (18%), and analgesics (14%). Herbal and non-prescribed therapies were used similarly proportion (31%) in each group (88/280 referred, 45/145 not referred) with Acidophilus, aloe vera and garlic supplements being the most frequent.

Conclusions: “Medicine” usage is similar whether or not IBS sufferers are managed in primary or secondary care. A larger proportion of patients treated in primary care took antispasmodics, but use of other medicines was similar. A significant number of IBS patients take non-prescribed or herbal products, the proportion using these was the same in both groups. Study was funded in part by GlaxoWellcome.

ROLE OF HEPATOBILIARY SCINTIGRAPHY IN THE MANAGEMENT OF SPHINCTER OF ODDBY DYSFUNCTION


Sphincter of Oddi dysfunction (SOD) is a cause of post-cholecystectomy pain. Current gold-standard diagnosis is by measurement of basal pressure by sphincter of Oddi manometry (SOM), and if elevated an endoscopic sphincterotomy (ES) is performed. Both these procedures carry significant complication rates. Hepatobiliary scintigraphy (HBS) was performed using a standard protocol. A semi-quantitative scoring system classified scans as positive (SOD) or negative (no SOD). Two observers reviewed all 21 scintigrams. SOM was regarded as diagnostic of SOD if sphincter base pressure was > 40 mmHg. If elevated, an ES was performed and a successful result was defined as an improvement in symptoms.

Results: 17 of our patients were female, average age 42.4 ± 4.0 years. Agreement was 100% between observers.

<table>
<thead>
<tr>
<th>Abstract 312 Table 1</th>
<th>HBS results vs SOM results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOM result</td>
<td>improvement</td>
</tr>
<tr>
<td>HBS result &gt; 40 mmHg</td>
<td>positive 3</td>
</tr>
<tr>
<td></td>
<td>negative 4</td>
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</table>

Kappa: 0.00. Sensitivity: 100%, specificity: 100%; PPV: 1.0, NPV: 0.75.

Conclusions: HBS can be interpreted reliably between observers. HBS is a poor screening tool in isolation, but may prove a useful adjunct to manometry in predicting ES outcome.

ALTERED BOWEL HABIT DUE TO TIME ZONE SHIFTS: A PILOT STUDY

S.K. Arthur1, D.F. Evans1, P. Farrand2, E. Yazaki1. 1Department of Adult and Paediatric Gastroenterology, Barts and the London School of Medicine and Dentistry; 2Institute of Health Studies, University of Plymouth

Introduction: Circadian rhythms for protein transcription have recently been identified in the gut. Environmental synchronizers may exist between biological clocks, leading to alteration in gut functions, but alteration in bowel transit due to time zone shifts experienced in long haul flight is yet to be reported.

Methods: Six men (Age 33.2 +/- 7.2 years) and 3 women (36.7 +/- 7.2) (mean +/- 1 SD) flew from London to California, USA, back. As a pre-condition to joining the study, they were on no drugs +/- 7.2) (mean +/- 1 SD) flew from London to California, USA, back. As a pre-condition to joining the study, they were on no drugs. Pre-, in-, and post-flight abdominal symptoms were used to examine significant changes in sleep and stool form scale from the pre-flight level. Stool form scale may be used as a guide to intestinal transit time.

Results: Sleep duration and times pre-flight, during foreign stay and post-flight were not significantly different (p > 0.05). Additionally, there was no reason to believe that the stool changes were attributable to a drastic change in diet. Abdominal symptoms were unremarkable and did not change during foreign stay or on return home from abroad. All our subjects were normal and had an uneventful stay abroad. Average stool consistency changed significantly (p < 0.01) from a lumpy to smooth consistency to a smooth to soft consistency during foreign stay and persisted 4–5 days into postflight. The respective stool form scales were pre-flight 2.8 +/- 1.0, foreign stay 3.5 +/- 1.1, post-flight 3.7 +/- 1.2.

Summary and Conclusion: During a time zone shift of +/- 8h, while the sleep clock was synchronized with the external clock, gut transit, as measured by the stool form scale, failed to synchronize with the external clock, leading to altered bowel habit. Biologic clocks that regulate gut functions may not adapt as readily to time shifts, as does the sleep clock.

**314 ASSESSMENT OF REFUX IN NEUROLOGICALLY-IMPAIRED CHILDREN USING THE MULTIPLE INTRALUMINAL IMPEDANCE PROCEDURE**

M. Thomson, D. Rawat, G. Ball, T. Wenzl, R. Del Buono. Centre for Paediatric Gastroenterology, Royal Free Hospital, Pond Street, London, NW3 2GQ, UK

Background: In addition to acid gastro-oesophageal reflux (GOR), non-acid GOR (pH > 4) may be clinically relevant in neurologically impaired children. However, standard pH meter can only detect the former. We have therefore used the pH independent technique of intraluminal electrical impedance to quantify all reflux events.

Aim: The aim of this study was to quantify acid and non-acid reflux in a group of these patients using a new catheter related technique.

Methods: Ten children (9 cerebral palsy, 1 Trisomy 21) fed intragastrically underwent 12 h studies of intraluminal 6 channel impedance and dual channel pH monitoring. All patients were off medication influencing gastric pH. Recordings were analysed for the frequency of acid and non-acid GOR and the height reached by the refluxate.

Results: 369 reflux events were detected with the combined technique. 191 (51.8%) were non-acid events (mean pH 5.6) and of these 138 (72.2%) reached the uppermost (1) impedance channel. Of the 178 acid reflux events (mean pH 3.1), 81.5% reached the uppermost channel.

Conclusions: Over half of reflux events in neurologically impaired children are non-acidic and therefore are missed using standard pH meter. Most of these refluxes reached the upper oesophagus. Simultaneous intraluminal oesophageal impedance and pH measurements to give valuable information that may improve therapeutic management in this patient group.

**315 SIGNIFICANCE OF ANXIETY IN IBS OUTPATIENTS: RELATION TO BOWEL SYMPTOMS AND FINAL DIAGNOSIS**

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Introduction: Although it is well recognised that the probability of consultation with irritable bowel syndrome (IBS) is increased by anxiety, it is unclear what influence anxiety has on severity of symptoms.

Aims: To prospectively evaluate the relationship between anxiety, symptoms, and final diagnosis in patients presenting with symptoms of IBS.

Methods: Hospital anxiety and depression (HAD) scores were measured prospectively in 178 new outpatients referred with symptoms consistent with IBS. Investigations to exclude other diagnoses were instituted as clinically indicated. The final diagnosis was obtained from review of electronic records 3–3 years later. Patients were categorised by mode of onset (post-infectious (PHIBS)), or predominant bowel habit (diarrhoea (DIBS), constipation (CIBS), alternating (AIIBS)). The anxiety and depression scores were compared for each group. A healthy control group (n = 40) was included.

Results: 28 patients had alternative diagnoses made including: bile salt malabsorption (5), lactose intolerance (4), microscopic colitis (4), ulcerative colitis (1), pancreatic disease (3), and collagen disease (2) and coeliac disease (1) leaving 150 patients with IBS (38 c-IBS, 49 d-IBS, 20 alt-IBS, 37 PHIBS, 6 IBS unspecified). Abnormal anxiety levels were present in 68.6% (severe in 12%, moderate in 22.4% and mild in 34.4%). Raised depression scores were detected in 26.3% (severe in 2.5%, moderate in 10.7% and mild in 13.1%). The mean A and D scores were 9.3 ± 0.35 and 4.5 ± 0.32 respectively for all IBS patients, which was significantly greater than values in control patients (4.0 ± 0.4 and 1.6 ± 0.33, p < 0.001). There were no significant differences in anxiety depression scores between the subtypes of IBS. Anxiety scores did not correlate with number of stools passed or days per week of bloating or pain.

Conclusions: Anxiety is common in patients presenting with IBS-type symptoms but this does not differentiate them from those with underlying organic disease. There is no significant relationship between severity of reported symptoms and anxiety.

**316 INVESTIGATION OF THE REPRODUCIBILITY OF CEREBRAL ACTIVITY TO OESOPHAGEAL STIMULATION**

S.J. Coen1, L.J. Gregory1,2, D. Hall1, L. Yaguz1, E. Amaro1, S. Smale1, S.C.R. Williams1, D.G. Thompson1, G. Aziz2. London, UK; 1GI Sciences, University of Manchester, UK; 2King’s College Hospital, London, UK

Introduction: The cerebral activation during functional magnetic resonance imaging (fMRI) sessions can be influenced by many variables, including scanner noise, subject movement, and cognition, such as habituation and learning; although the cerebral processing of visceral sensation has been studied, information regarding the trial re-trial reliability is not available.

Aims: The purpose of this study was to assess the reproducibility of the functional neural correlates of oesophageal sensation, using fMRI.

Methods: 7 healthy volunteers participated in the study. The protocol consisted of two conditions; non-painful (50% of the difference between sensory and pain thresholds) and painful (pain threshold) stimulation intensities using phasic balloon distension in the distal oesophagus. The order of presentation of these intensities was counterbalanced. A modified block design was employed for each intensity where “active” and “rest” phases were repeated five times. This experimental procedure was repeated on two additional occasions (three scans in total) to investigate the consistency of cerebral activation over time.

Results: In response to painful stimulation, highly reproducible activation was seen in the anterior cingular gyrus (ACG) (BA24, 32), bilateral insula, supplementary motor cortex (SMA), thalamus, primary and secondary sensory cortices (SI and SII) and dorsolateral prefrontal cortex. Further analysis revealed a significant (p < 0.05) decrease in cerebral activity from the first to the final scan in the anterior cingular (ACG), SMA and SI. Activation in response to non-painful stimulation was seen in similar regions to those seen during painful stimulation, with the exception of the thalamus, but was found to be more variable in the ACC, SI, SII, and SMA in comparison to painful stimulation.

Conclusions: Painful stimulation of the oesophagus produces robust activity in many brain regions previously associated with visceral pain. Non-painful stimulation results in a similar pattern of cerebral activation, but is variable between scan time, possibly suggesting that individuals are more likely to habituate to a non-painful stimulus, rather than a more salient painful stimulus.

**317 EVIDENCE OF OESOPHAGEAL STIMULUS INTENSITY DEPENDANT RESPONSE IN THE HUMAN ANTERIOR CINGULATE AND PRIMARY SOMATOSENSORY CORTEX**

S.J. Coen1, L.J. Gregory1,2, D. Hall1, L. Yaguz1, E. Amaro1, S. Smale1, S.C.R. Williams1, D.G. Thompson1, G. Aziz2. 1Institute of Psychiatry, London, UK; 2GI Sciences, University of Manchester, UK; 3King’s College Hospital, London, UK

Introduction: Functional Magnetic Resonance Imaging (fMRI) can be used to objectively quantify perception of visceral sensation. However, the neural correlates of varying, quantifiable, intensities of visceral stimulation have remained unclear, and the regions involved in encoding of stimulation intensity are not fully understood.

Aims: To determine the neural correlates of varying intensities of oesophageal stimulation using fMRI.

Methods: 7 healthy volunteers participated in the study. The protocol consisted of four conditions. During each condition one of four balloon distension intensities, obtained by dividing the difference between sensory (0%) and pain thresholds (100%) into 4 levels at 25% increments ie 25%, 50%, 75%, and 100% were used to stimulate the oesophagus using fMRI. Encoding of stimulation intensity are not fully understood. However, the neural correlates of varying, quantifiable, intensities of visceral pain. Non-painful stimulation results in a similar pattern of cerebral activation, but is variable between scan time, possibly suggesting that individuals are more likely to habituate to a non-painful stimulus, rather than a more salient painful stimulus.

Results: VAS scores increased progressively with increasing stimulation intensities (p < 0.001). In response to 100% and 75% stimulation intensity, activation was seen in the anterior cingulate gyrus (ACG) (BA24, 32), bilateral insula, supplementary motor cortex (SMA), thalamus, primary and secondary sensory cortices (SI and SII) and dorsolateral prefrontal cortex (DLPFC). 50% and 25% intensity (non-painful) stimuli activated the same regions to a lesser extent, with the exception of the thalamus, and SII, and additional activation in the inferior frontal gyrus. Further analysis revealed that there was a significant trend (p < 0.05) of an increase in cerebral activity with an increase in stimulation intensity, in the ACG (BA24), and SI (bilateral).
Conclusions: Visceral stimulation results in a complex pattern of cerebral activation that is similar across varying levels of stimulation intensity. The ACG and SI, both show evidence of stimulus dependent response, which may be a result of encoding of stimulus intensity, unpleasantness of the stimulus, or levels of attention.

318 INCREASED EXPRESSION OF GALANIN IN MUCOSAL NERVES OF PATIENTS WITH PAINFUL DIVERTICULAR DISEASE

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Background: Galanin is a neuropeptide distributed widely throughout the central and peripheral nervous system. In particular, its presence has been demonstrated in dorsal root ganglia, spinal dorsal horn neurones and enteric nerves. It is known to have a regulatory function on nociception and peripheral nerve injury has been shown to upregulate its synthesis. We have previously shown that resection sections for complicated diverticular disease shown evidence of neural damage and regeneration within the enteric nervous system (ENS).

Aim: To quantify the level of galanin expressed by mucosal nerves in patients with symptomatic and asymptomatic diverticular disease.

Method: Ten symptomatic and ten asymptomatic patients underwent flexible sigmoidoscopy and multiple peridiverticula biopsies were obtained. Standard fluorescent immuno-histochemical methods were used. Mucosal nerves were identified using PG99.5 and peripherin. Using digitised image analysis, the level of galanin immunoreactivity within mucosal nerves was expressed as percentage area of lamina propria.

Results: Median age was 68.5 years (range 49–70) with no difference between groups. Symptomatic patients experienced recurrent abdominal pain on a median of 6 (range 3–12) days/month. Duration of the pain was 4 (0.75–12) hours. No pain was experienced by the asymptomatic group. The percentage area of galanin immunoreactivity within the lamina propria was 0.155% in symptomatic patients compared with 0.004% in controls (p < 0.0001, Mann-Whitney).

Conclusion: There is an increased expression of galanin within colonic mucosal nerves in patients with painful diverticular disease. Although the direct effect of this change in the development of abdominal pain is as yet unclear, the increased expression implies previous or ongoing injury to the ENS in symptomatic patients, possibly due to inflammation.

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319 METHODOLOGICAL STUDY TO ASSESS REPEAT PLANAR WHITE CELL SCANNING IN MONITORING THE EFFEICACY OF TREATMENT IN INFLAMMATORY BOWEL DISEASE

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Introduction: Radio-labelled white cell scans (WCS) provide non-invasive and accurate quantification of inflammatory bowel disease (IBD) activity in both large and small bowel and may be useful in the objective evaluation of treatments for IBD. Clinical activity scores are partly subjective and do not accurately reflect underlying inflammation.

Aim: A methodological study to assess the efficacy of repeated planar WCS in monitoring the response to treatment of active IBD and comparing to clinical activity scores.

Patients: 9 subjects with active ulcerative colitis (UC) (5 mild, 3 moderate, 1 severe) and 9 subjects with active Crohn’s disease (CD) (5 mild, 3 moderate, 1 severe) were recruited.

Methods: 99mTcHMPAO WCS were carried out immediately before and 2 weeks after treatment. Prior to each scan disease activity scores for UC (Powell-Tuck index (PTI) and Mayo clinic score (MCS)) or CD (Crohn’s disease activity index (CDAI), Harvey Bradshaw index (HBI) and van Hees activity index (VHAI)) were calculated. Scan scores for total bowel activity were calculated by using a validated visual grading system at 1 hour. Two independent observers scored each scan and the final score was agreed by consensus.

Results: In IBD subjects following anti-inflammatory treatment 11/18 (61%) of WCS improved, 4/18 (22%) remained unchanged and 3/18 (17%) deteriorated. In UC subjects there was agreement for direction of change in scan score and PTI in 4/9 (44%) and MCS in 3/9 (33%). In the CD subjects there was better agreement between WCS score and clinical scores (CDAI in 7/9 (78%); HBI in 5/9 (56%); VHAI in 5/9 (56%).

Conclusion: Clinical scores in IBD agree poorly with objective measures of bowel inflammation, and while valuable in assessing the patients general well being have limited application in assessing the anti-inflammatory effect of therapeutic agents. Non-invasive white cell scanning is a more reliable method to monitor the anti-inflammatory efficacy of treatments for active IBD.

320 PERCEIVED PREOPERATIVE STAGE OF OESOPHAGEAL CANCER. PROSPECTIVE EVALUATION OF EUS AND SPECIAL INTEREST CT

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Aims: Endoluminal ultrasound (EUS) has been championed as the answer to the limitations of computed tomography (CT) in assessing tumour infiltration (T stage) and lymph node involvement (N stage) in patients with oesophageal cancer. However, the precise strength of agreement between EUS, special interest CT, and the true histopathological stage has not been reported.

Abstract 320

<table>
<thead>
<tr>
<th>Stage</th>
<th>CT</th>
<th>EUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>N</td>
<td>TN</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>89</td>
<td>80</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>77</td>
<td>63</td>
</tr>
<tr>
<td>Kw</td>
<td>0.24*</td>
<td>0.44*</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Methods: Sixty consecutive patients (median age 61 year, 35 m, 41 adenoma, 19 squamous cell) with oesophageal cancer were studied prospectively. Each patient underwent preoperative CT (Siemens Somatom +4) performed by the specialist multidisciplinary team consisting of radiologist, and EUS (Olympus U-M20, and MH-90B). The strength of the agreement between the perceived radiological stage and the true histopathological stage of the resected specimen was determined by the weighted Kappa statistic (Kw).

Results: When CT and EUS concurred, the accuracy of the radiological stage was enhanced twofold (T Kw 0.51, N Kw 0.80, p < 0.0001).

Conclusion: These data reinforce the fact that the modalities of CT and EUS are complimentary, and highlights the value of multidisciplinary teams in refining preoperative diagnoses and optimising the treatment of patients with oesophageal cancer.

321 RENDEZVOUS PROCEDURE OR PTC AND METAL STENT FOR BILIARY OBSTRUCTION—IMPLICATIONS FOR PROCEDURAL COSTS AND DURATION OF INPATIENT STAY

G.R. MacFaul1, R. Mathiakalagan1, M. Gibson1, P. Torrie1, A.S. Mee1. 1Department of Gastroenterology, 2Department of Radiology, Royal Berkshire Hospital, Reading, UK

Background and Aims: After failed endoscopic treatment for malignant biliary obstruction, non-surgical approaches include a rendezvous (combined) procedure (CP) incorporating percutaneous cholangiography (PTC) then ERCP, or initial PTC and insertion of a metal stent. We hypothesised that PTC and stenting would lead to reduced procedural costs, morbidity, and duration of inpatient stay.

Methods: Between 1994 and 1998 15 patients had a CP, and between 1998 and 2000 15 patients went onto PTC and stenting, following failed ERCP(1). Notes of both groups were analysed for diagnosis, duration of stay including delay from definitive procedure to discharge/death, and individual procedural costs.
Results: Full data were available on 14 patients in each group. The average length of stay from first ERCP to discharge or death was 11.2 days (5–26) in the CP group, with a delay from CP to discharge of 4.7 days (1–19). Similar durations in the PTC group were 10.4 days (2–34) and 5.6 days (2–12), respectively. Average procedural costs were 1752 with CP (6 patients required two ERCPs prior to the CP), and 1548 for PTC and stenting. Average age was 71.8 years (41–89) and 78.5 years (55–94), respectively. Obstruction was due to proven pancreatic cancer in 86% of the CP group and 50% of the PTC group. Cholangiocarcinoma was found in 4 patients (26%) who had a metal stent. 2 patients from the CP group died (at 2 and 8 days) and 1 from the PTC group (day 5 post-PTC).

Conclusion: PTC and metal stenting lead to decreased procedural costs and length of inpatient stay compared to the rendezvous procedure. It was also safely undertaken in a more elderly cohort of patients and we therefore suggest it should be the procedure of choice in the relief of malignant biliary obstruction after failed ERCP.

322 SEGMENTAL ASSESSMENT OF COLONIC TRANSIT STUDIES: AN INDICATOR OF EVACUATORY DISORDERS?

M.T. Eltringham, E. McCauley, I.M. Bain, J.Y. Yiannakou. University Hospital of North Durham, Durham, UK

Background: Colonic transit study is a widely used investigation in patients with chronic constipation. It has been suggested that it is possible to determine from the distribution of markers in various regions of the colon whether the patient has an evacuatory disorder or colonic inertia. The aim of the study is to assess whether this is the case.

Methods: 40 patients who attended a specialist constipation clinic were investigated using colonic transit studies and radionuclide proctography. The patients all had prolonged transit and were divided into 2 groups, normal or prolonged evacuation rate on the basis of the proctogram. The transit studies from the 2 groups were assessed by two different methods: number of markers in the left and right colon; and number of markers in 3 regions (right colon, proximal left colon and rectosigmoid).

Results: 17 patients had prolonged evacuation rates and 23 were normal. The mean values for numbers of transit study markers on the whole left colon (TSMPL), proximal left colon (TSNL), and rectosigmoid (TSMRS) are shown in Table 1. The number of markers in the rectosigmoid is also expressed as a percentage of the total number of markers retained throughout the colon (RS%TC) and percentage of total left colonic markers (RS%L).

<table>
<thead>
<tr>
<th></th>
<th>Mean TSMPL</th>
<th>Mean TSMRS</th>
<th>Mean TSM total</th>
<th>RS%TC</th>
<th>RS%L</th>
</tr>
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<tbody>
<tr>
<td>Normal ER</td>
<td>23.29</td>
<td>13.81</td>
<td>36.29</td>
<td>18.86</td>
<td>34.01</td>
</tr>
<tr>
<td>Abnormal ER</td>
<td>22.27</td>
<td>16.81</td>
<td>39.18</td>
<td>25.89</td>
<td>40.72</td>
</tr>
</tbody>
</table>

Discussion: There is no significant difference between the abnormal and normal evacuation rate groups in terms of total numbers of left sided or rectosigmoid markers. This indicates that the segmental method of assessing radiological marker transit studies is no more accurate in indicating an evacuatory disorder than the left or right method.

Neoplasia posters 323–339

323 ‘THE 2 WEEK UPPER GI CANCER RULE.’ HOW SUCCESSFUL IS THIS? A RETROSPECTIVE AUDIT IN A DISTRICT GENERAL HOSPITAL

R.J. Warner, D. Das. Department of Gastroenterology, Stepping Hill Hospital, Stockport, UK

Introduction: The NHS Executive introduced a 2 week standard for cancer referrals in an attempt to speed up diagnosis and improve patient care. This has now been implemented, but are we improving our care because of it, or is it just an additional headache for endoscopy units?

Aims: To assess how many referrals: 1) were endoscoped (OGD) within 2 weeks, 2) identified cancer, 3) for upper Gastrointestinal (GI) cancer came via our cancer office—the Bobby Moore Oncology Unit.

Methods: We performed a retrospective audit of all patients referred via the Bobby Moore unit in a 12 month period. Faxed referrals were made on a standard proforma that was distributed to all local GPs. Data were collected looking at referral information and OGD results.

Results: 146 referrals were received (age range 23–92), of which 144 (98.6%) were offered OGD within 2 weeks. 10 patients did not attend 1st appointment. 10/146 (6.8%) had cancer, 6 oesophageal, 2 gastric, 1 pharyngeal and 1 direct spread from transverse colon. Of the same period 61 oesophageal and 43 gastric cancers were identified via alternative routes, ie only 7.7% of upper GI cancers came on the cancer proforma. Recent onset dysphagia in patients > 45 years as the only symptom (28/146) yielded 0 cancers, whereas 11% of patients with dysphagia had cancer.

Conclusions: We only detected 7.7% of upper GI cancers via our cancer proforma. Patients who did not attend in our study did not have cancer on subsequent OGD. Dysphagia alone did not yield any cancers. Although offering this rapid access service we may be delaying OGDs for patients with cancer referred from other sources.

324 TAPE RECORDED ENHANCED OESOPHAGOGASTRIC CANCER CONSULTATIONS FACILITATE PATIENTS’ MEMORY AND PERCEPTION OF TREATMENT OPTIONS

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Background: Consultations to convey a diagnosis of oesophagogastric cancer may be a difficult and traumatic time for patients. Indeed, as many as 50% of patients are displeased with the information received. One of the key recommendations of the Bristol report was the provision of audio tape recording facilities. The aim of this study was to assess the value of tape recording the first consultation, to determine whether re-listening to the information given, might aid patients’ memory of key facts, and reduce anxiety prior to therapy.

Methods: Two groups of patients were studied: a historical control group of 15 patients (median age 66 years, 8 months, 5 oesophageal, 10 gastric cancers) who did not receive tape recordings of their consultations was compared with 10 consecutive patients (median age 68 years, 8 months, 6 oesophageal, 4 gastric cancers) who had their consultations tape recorded. All patients completed a hospital anxiety and depression (HAD) questionnaire 1–2 weeks after the consultation.

Results: Patients who had received tape recordings of their consultations were less likely to forget key facts regarding their diagnosis and treatment options (0 patients) compared with patients who had not received a tape [5 patients, \( \chi^2 = 4.167, \) df 1, \( p = 0.04 \)]. HAD questionnaire scores were also lower in patients who had received a tape compared with patients who had not (median [range] HAD A 5.5 (0–160) v 6 (2–14), HAD D 3.5 (0–13) v 4.5 (1–11), respectively, \( p = n.s. \)).

Conclusion: All patients who received a tape found that listening to the consultation again with relatives was helpful. Tape recorded enhanced interviews improved patients factual memory and in general reduced levels of anxiety prior to therapy.

325 AUDIT OF THE 2 WEEK RULE (TWR) FOR SUSPECTED UPPER GASTROINTESTINAL (UGI) CANCER AND THE PATHWAYS TO DIAGNOSIS

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Aims: To audit TWR for UGI cancers in a north east district general hospital (DGH) and to determine the proportion of UGI cancers diagnosed outside the TWR referral system.

Methods: Prospective audit of all TWR over a 20 week period (Oct 2001 to March 2002) in our DGH (catchment population approximately 250,000). All upper GI cancers diagnosed over the same time period were also audited.

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Results: 172 patients (mean age 62 years, range 17–89 years, 84 male, 88 female) were referred for suspected UGI cancer under the TWR referral system during the audit period. The mean delay from faxed referral to endoscopy was 11 days (range 1–30 days), with 86% of referrals assessed within 2 weeks. A total of 35 UGI cancers were diagnosed in our DHU during this period. Of those, 17 (49%) were diagnosed within the TWR referral system (mean delay 11 days, range 4–18) and 11 (31%) following emergency admission (mean delay from admission to endoscopy 5 days, range 1–12). Of the remaining 7 patients with UGI cancers, 2 were picked up by appropriate surveillance, 1 did not follow the TWR referral pathway due to an administrative error (delay 86 days) and 4 patients were referred by the GP outside TWR referral pathway despite having suspicious symptoms and were seen in the outpatient clinic first (mean delay from clinic to endoscopy 45 days, range 24–83, principally due to investigations requested prior to endoscopy).

Conclusion: 86% of referrals under the TWR system for UGI cancers in our hospital were assessed within 2 weeks. All cancer patients other than those diagnosed through surveillance had suspicious symptoms. Delay can be reduced by GPs and hospital consultants using the TWR referral system for all patients with suspicious symptoms.

326 IMPACT OF 2 WEEK WAIT REFERRAL ON THE MANAGEMENT OF UPPER GASTROINTESTINAL MALIGNANCY

M.S. Aung, J. Vuovicj, S. Anwar, M.H. Shiwani. [Introduction by M. Hayat]
Barnsley District General Hospital, Gawber Road, Barnsley, UK

Objective: To audit 2 week wait referral (TWR) for suspected upper gastrointestinal malignancy (UGIM) and also to evaluate whether this system identifies patients with suspicion of cancer at early stage of the disease.

Method: In a district general hospital all patients referred through TWR desk from September 2000 to December 2001 were studied. All newly diagnosed patients with UGIM referred through the conventional routes in the same period were included. Case notes of all the patients with proven UGIM were studied and data were collected.

Result: Of the 307 TWR only 29 (9.4%) patients were diagnosed with UGIM and the majority, 91.6% patients, have alternative diagnosis. Total number of patients diagnosed with UGIM through TWR and conventional routes were 105. Of these 105 UGIM, the majority 76 (72%) patients were referred through conventional routes including A&E: 43 (57%), clinic: 20 (26%) and direct access endoscopy: 13 (17%). Median appointment time, referral time to diagnosis, and waiting time to treatment were 12, 21, and 35 days, respectively for TWR group and 25, 34, and 55 days, respectively for conventional group. Staging of the disease and treatment offered was noted using various modalities (see Table).

Conclusion: TWR standards are achievable. This system generates more work but does not provide any benefit to diagnose disease at early stage, hence does not have any impact on long term survival.

327 RAPID ACCESS UPPER GI CANCER SERVICE (RAUGICS): WORKLOAD, NON-ATTENDANCE, AND PREDICTIVE VALUE OF REFERRAL CRITERIA

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Background: The NHS 2 week rule requires rapid evaluation of patients with suspected upper GI cancer based on the presence of pre-determined alarm features. We report a single centre experience of implementing a RAUGICS in a university hospital serving a population of 330,000.

Methods: Details of all referrals to the RAUGICS were recorded prospectively on a dedicated database, including demographics, referral indications (from standard referral proforma), OGD results, and outcome. DNA rates (failure to attend) were also monitored. Accuracy of GP stated referral criteria were verified by self-administered symptom questionnaire in a sample of patients.

Results: Predictive value of referral criteria for cancer (18 month data; 1852 patients; mean age 59 years; cancer yield: 3.8%); Logistic regression analysis revealed that dysphagia (OR 3.1), weight loss (OR 2.6) and age > 55 years (OR 9.5) were significant predictors of cancer, whereas so-called “high-risk dyspepsia” had negative predictive value within this cohort (OR 0.1). Workload data (12 month period): 1207 patients were referred. All initial non-attenders were sent a 2nd appointment, hence 1462 slots (121% of referral numbers) were allocated. 1137 patients (94.2%) attended for OGD (74% being undertaken by nurse endoscopists). There were 53 cases of cancer (yield: 4.6%). Of 1030 patients who were allocated a follow up clinic appointment after OGD, 240 (23%) failed to attend. The presence of significant pathology at OGD did not influence subsequent clinic DNA rate (serious disease: 20% vs normal OGD: 24%). GP stated referral criteria: symptom questionnaires confirmed the presence of designated alarm features in 97% of patients (n = 65).

Conclusions: Despite effectively targeting rapid access diagnosis to a high risk population for cancer (4.6% prevalence), the high workload of our RAUGICS is compounded by a DNA rate of 21%, with similar levels of non-attendance at the follow up clinic. Application of narrower referral criteria for “2 week rule” investigation (eg exclusion of “high risk dyspepsia” alone), more selective targeting of patients for follow-up clinic, and strategies to reduce DNA rate may improve cost effectiveness while maintaining yield of cancer. As expected, most of the activity of RAUGICS involves dealing with benign conditions as the referral criteria have poor sensitivity and specificity for cancer.

328 ANGIOGENESIS IN RECTAL CANCER: CAN PREOPERATIVE ENDOSCOPIC BIOPSY PREDICT TUMOUR BEHAVIOUR?

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Introduction: Preoperative radiotherapy is now the accepted treatment for a subgroup of patients with rectal cancer who are at high risk for local recurrence and poor survival. At present cross-sectional imaging is the only preoperative means of identifying this high risk subgroup. Rectal tumours with high microvessel density (MVD) in the resected specimen have been shown to be associated with poor survival. The aim of this study was to compare angiogenesis using MVD in preoperative endoscopic rectal cancer biopsy specimens (PERCBS) with the corresponding resected cancer specimen.

Methods: Immunohistochemistry using CD31 monoclonal antibody was undertaken on paraffin sections from preoperative biopsies and microvessel density was compared with corresponding resected tumours from 25 patients with rectal cancer. Statistical analysis was done using linear regression and paired t test.

Results: In patients who had not undergone radiotherapy prior to surgery there was a highly significant correlation (p < 0.0001; r² = 0.812) between MVD in biopsies (range 35–231/µm²; median 118) and resected tumour specimens (range 27–177/µm²; median 112). MVD was significantly lower in post radiotherapy resected specimens compared with PERCBS (p < 0.0255).

Conclusion: Our results suggest that MVD in PERCBS is a reliable predictor of tumour MVD and could also provide useful prognostic tool with implication for planning of adjuvant radiotherapy. Also in this study preoperative radiotherapy appears to downstage angiogenic activity as assessed by MVD, the significance of which will need further investigation.

<table>
<thead>
<tr>
<th>Stage of Malignancy</th>
<th>Number of Patients Total: 105</th>
<th>Two Week Referral Total: 29 (28%)</th>
<th>Conventional Route Referral Total: 76 (72%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>28 (27%)</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Advanced</td>
<td>77 (73%)</td>
<td>22</td>
<td>55</td>
</tr>
</tbody>
</table>

Proportion of the patient diagnosed with early disease in TWR group was 24%, compare to conventional referral group, which was 28%.
GI SYMPTOMS DEVELOPING AFTER PELVIC RADIOThERAPY REQUIRE GASTROENTEROLOGICAL REVIEW


Background: After pelvic radiotherapy, at least 30% patients develop permanent change in bowel habit affecting quality of life. Most are never referred to a gastroenterologist.

Aims: To analyse the cause for GI symptoms following pelvic radiotherapy we prospectively recorded all final diagnoses from a consecutive series of patients with symptoms starting at any time after their treatment referred over 24 months to a gastroenterology clinic.

Results: 167 patients have completed investigations. 51 women, median age 62 (22–81 years), 116 men, median age 70 (31–85 years). Radiotherapy ended 2.5 years (0–13) earlier in women and 2 years (0–21) in men. Primary tumours were urological (n = 117), gynaecological (n = 43), and gastrointestinal (n = 9). Reasons for referring were: rectal bleeding (n = 109), loose stool or incontinence (n = 69), tenesmus or discomfort (n = 33), change in habit (n = 18), vomiting (n = 13), or other (n = 4). After investigation, diagnoses could be grouped into 3 categories, definitely related, possibly related or clearly unrelated to previous radiotherapy. Diagnoses directly related included proctitis (n = 2), sigmoid ulceration (n = 2), and obstruction (n = 4). Findings possibly related included hyperplastic polypsis (n = 13), bacterial overgrowth (n = 7), squamous polyps (n = 3), fatty acid malabsorption (n = 2), pancreatic insufficiency (n = 2), bile salt malabsorption, collagenous colitis, and relapsing ulcerative colitis (n = 1 each). Diagnoses unrelated to radiotherapy included a new primary tumour (n = 6), relapse of the primary cancer (n = 7), adenomatous polyps (n = 19), diverticular disease (n = 37), hypothyroidism (n = 2), infection (n = 2), irritable bowel syndrome (n = 2), alcohol (n = 2), rectal mucosal prolapse, and bleeding piles (n = 1 each). In 2 patients, no diagnosis was made. Gastroenterological referral changed the diagnosis in 64% and allowed institution of curative therapy in 27%.

Conclusion: Untreatable radiation toxicity must not be assumed to be the cause for GI symptoms after pelvic radiotherapy. Evaluation of new GI symptoms arising after pelvic radiotherapy by an experienced gastroenterologist is mandatory as it allows diagnostic investigations to be performed and appropriate treatment to be instituted.

IS SURVIVING SIGNIFICANT IN THE p53 APOPTOTIC PATHWAY AFTER SHORT COURSE RADIOThERAPY?

H. Ishikawa1,2, I.C. Talbot1. 1First Department of Surgery, Nara Medical University, Kashihara, Japan; 2Academic Department of Pathology & ICRF, St. Mark’s Hospital, Harrow, UK

Aim: We have shown the significance of the p53 apoptotic pathway in short course radiotherapy. Recently, survivin, a novel anti-apoptotic gene, has been identified but its role in vivo is still unclear. We have examined the role of survivin with reference to apoptotic cell death and the expression of apoptosis regulating proteins in short course radiotherapy.

Methods: 26 patients underwent operation from June 1982 to October 1984 after short course radiotherapy (15Gy). Patients were aged between 27 and 77 years (median 57). Eleven were male. Tumour stages were (Dukes A) 2 (2), B (11), C (13). Sections of paired biopsies and post-irradiated surgical specimens of each tumour were immunohistochemically stained for p53, Bcl-2, BCL-XI, Bax, P21/WAF1, and survivin. The percentage of positive tumour cells was measured using the TUNEL method.

Results: After radiotherapy, the average AI increased significantly (2.2 vs 7.5; p < 0.01). Survivin immunostaining was positive in 15/26 (57.7%) of biopsies and in 8/26 (30.8%) of surgical specimens. Bax immunostaining was positive in 3/26 (11.5%) of biopsies and in 15/26 (57.7%) of surgical specimens. There were no correlation of expression between survivin and other proteins in both biopsies and surgical specimens. In surgical specimens, the average AI of survivin-negative subgroup (n = 8) was higher than that of negative one (n = 18) (7.87 vs 6.7; p > 0.05). In biopsies the average AI was almost equal irrespective of survivin expression. However, in surgical specimens, the combination of p53-low/survivin-negative expression formed a group with the highest AI of all other subgroups.

Conclusion: Apoptotic cell death and down-regulation of survivin protein were induced by radiation in vivo. These results suggest that survivin has a role, possibly regulatory, in the p53-apoptotic pathway after short course preoperative radiotherapy.

LATE TOXICITY FOLLOWING SHORT COURSE PREOPERATIVE RADIOThERAPY FOR OPERABLE RECTAL CANCER

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Introduction: Short course preoperative radiotherapy (SCPRT) reduces local recurrence following total mesorectal excision (TME). In the Dutch TME trial the absolute reduction was 5.8% at 2 years (2.4% vs. 8.2%). This benefit should be weighed against acute and late side effects following combined treatment. We have previously reported acute toxicity in a series of 176 consecutive patients. The purpose of this study was to report late side effects in the same cohort of patients.

Method: The hospital notes of 176 patients who underwent TME preceded by SCPRT were examined. Side effects occurring more than 3 months after the start of SCPRT were graded using the EORTC/RTOG late radiation toxicity system. A multivariate analysis was performed to identify associated factors.

Results: Of 176 patients, 15 died within 3 months of SCPRT and 3 patients were lost to follow up. At a median follow up of 40 months (Grade 3–4) toxicity was seen in 20 (13%) of 158 assessable patients (gastrointestinal 13 (8%); urological 3 (2%); thromboembolic 3 (2%); musculoskeletal 11 (7%)). On multivariate analysis, abdominal-perineal resection (p < 0.001) and Dukes A tumours (p = 0.05) were associated with less severe toxicity.

Conclusions: In this retrospective series the rate of late grade 3–4 toxicity following SCPRT and TME was 13%. Although AP resection is associated with a lower incidence of late physical side effects this may be counterbalanced by the impact of a stoma on quality of life. These factors should be considered when deciding on the most appropriate management for operable rectal cancers.

TNF α MODULATION OF E-CADHERIN IN AN EX VIVO MODEL OF BARRETT’S METAPLASIA

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Introduction: The majority of oesophageal adenocarcinoma arises from the Barrett’s metaplasia-dysplasia-carcinoma sequence. E-cadherin expression is down regulated along this progression, and TNFα expression is increased. We have demonstrated in an intestinal cell culture model that TNFα stimulation results in down regulation of E-cadherin. We aim to investigate the modulation of E-cadherin by TNFα in an ex- vivo tissue culture model.

Methods: Specimens of Barrett’s metaplasia were obtained endoscopically. Each biopsy was divided, half for histology and half for tissue culture. Matched normal squamous and duodenal epithelium was also taken from each patient. Biopsies were divided and randomly assigned to culture with or without TNFα at 50 ng/ml by standard tissue explant methods. Samples were then harvested at time points and processed for Western blotting. LDH levels in the culture media were used as a measure of viability, along with morphological assessment and immunohistochemistry (IHC) with Ki-67 antibody.

Results: Nine sets of biopsies were cultured. LDH assay, morphology and Ki-67 IHC confirmed viability at 18 hours. By 24 hours media LDH levels had increased and there was evidence of necrosis, with reduced Ki-67 expression indicating a reduction in cell division. E-cadherin protein expression as assessed by Western blotting did not show any evidence of down regulation in response to TNFα when compared to uncultured specimens or those cultured in TNFα free media. This was also true for normal squamous and duodenal mucosa.

Conclusion: We demonstrate the short life span of explant tissue samples ex vivo. In addition the effects of TNFα on E-cadherin expression are in contrast to our previous work. This may reflect the fact that BM has a TNFα rich microenvironment and that its receptors are already maximally stimulated. It is also possible that ex vivo TNFα does not modulate E-cadherin expression within the period of experimentation.
**333 EXPRESSION OF C-KIT (CD117) IN NEUROENDOCRINE TUMOURS—A TARGET FOR THERAPY?**

K. Khan, V. Kastoula, K. Savage, M. Stubbs, M. McStay, A.P. Dhillon, M.E. Caplin. Royal Free and University College Medical School, London, UK

**Introduction:** Gliovac (mastinib mesylate) is currently being used in clinical trials for the treatment of gastrointestinal stromal tumours and is known to specifically inhibit the tyrosine coupled receptor encoded by the c-kit proto-oncogene. Gliovac is currently being assessed as a therapeutic possibility in other c-kit positive tumours.

**Aim:** To assess the expression of c-kit (CD117) in neuroendocrine tumours.

**Methods:** Immunohistochemistry was performed on paranfin embedded sections from 62 consecutive NEPT patients: 36 carcinoid, 16 NET and 10 paraganglioma. Somatic mutations in 56 carcinoid tumours, 6 NET and 4 paragangliomas were identified. Corresponding normal tissues were used as controls.

**Results:** 36% of carcinoids and 18% of pancreatic NET demonstrated expression of c-kit (CD117). No staining was observed on paragangliomas and medullary carcinoma of thyroid.

**Conclusion:** Immunohistochemical studies have demonstrated the presence of c-kit (CD117) in carcinoid and pancreatic neuroendocrine tumours, with the most expression observed in carcinoid. With limited treatment availability, Gliovac may have therapeutic efficacy in the treatment of selected tumour patients.

**334 GERMLINE MUTATIONS IN THE BASE EXCISION REPAIR GENE MYH—A NEW POLYPOSIS DISORDER**

R. Davies1, N. Al-Tassan1, S. Jones1, N.H. Chmiele1, J. Maynard1, N. Fleming1, A.L. Livingston2, G.T. Williams2, A.K. Hodges1, S. Dolan1, S.S. David2, J.P. Cheadle1, J.R. Sampson1. University Hospital of Wales, Cardiff, UK

**Background:** Multiple colorectal adenoma families have been identified that do not conform to classical FAP or HNPCC. We studied the somatic mutation profile of adenomas from affected siblings in one such family to establish the nature of their inherited defect.

**Method:** Family ‘N’ consisted of seven siblings, 1 with colon cancer at the age of 46, which was associated with adenomas. Screening his siblings identified two with approximately 50 adenomatous colorectal polyps at the ages of 59 and 55, respectively. 11 tumours from these 3 affected siblings were screened for somatic APC gene mutations.

**Results:** 18 somatic inactivating APC gene mutations were identified in these 11 tumours. Remarkably, 15 of these were G:C to T:A transversions. This type of mutation was significantly over-represented when compared to somatic mutations so far described in sporadic and FAP associated adenomas / adenocarcinomas. Similar mutations had previously been reported in DNA repair deficient yeast and bacteria.

**Conclusion:** Germline mutations of the base excision repair gene MYH—A NEW POLYPOSIS DISORDER

**335 VEGF-C EXPRESSION AND TUMOUR SPROUTING ARE USEFUL INDICATORS FOR NODAL INVOLVEMENT IN SUBMUCOSAL INVASIVE COLORECTAL CARCINOMAS**

H. Ishikawa, H. Fujii*, F. Kayama*, T. Mukogawa*, H. Matsumoto*, T. Kobayashi, H. Kuniyasu*, Y. Nakajima*. First Department of Surgery, Nara Medical University, Kashihara, Japan; *Oncological Pathology, Nara Medical University, Kashihara, Japan

**Introduction:** VEGF-C expression and tumour sprouting along with clinicopathological factors, the ratio of nodal involvement of polypoid tumours [1/33] was lower than that of non-polypoid [6/35; p = 0.044]. Tumours were divided into sm1[14], sm2[29], sm[32] in the depth, sm[18], sm[27], sm[23] in the width. There was no nodal involvement in sm1 and sm2[6]. As tumour invasion increased in depth and width, positive cases of UI, venous invasion (VI) and nodal involvement increased. VEGF-C expression showed positive correlation with UI, VI and nodal involvement and tumour sprouting showed positive correlation with UI and nodal involvement. Both VEGF-C expression [6/7, 85.7%] and tumour sprouting [5/7, 71.4%] showed high specificity for nodal involvement.

**Conclusion:** VEGF-C expression and tumour sprouting are useful in predicting nodal involvement in SICC.

**336 EXPRESSION AND UPTAKE OF PARATHYROID HORMONE RELATED PEPTIDE IN HEPATOCELLULAR CARCINOMA**

M. McStay, K. Savage, M. Stubbs, K. Khan, A. Dhillon, M. Caplin. Royal Free and University College Medical School, London, UK

**Introduction:** Glivec (imatinib mesylate) is currently being used in clinical trials for the treatment of gastrointestinal stromal tumours and has been classified as a polyposis disorder. In colorectal adenomas and biallelic germline MYH mutations, confirmatory. Since then, it has been found to be expressed in malignancies such as breast and prostate cancer, which are not commonly associated with HHHM, and has been found to regulate their growth. Preliminary studies have suggested a role for PTHrP in hepato-cellular carcinoma.

**Aim:** To assess the expression of PTHrP and its corresponding receptor (PTH[1–10]R) in human hepatocellular carcinoma resection specimens and cell lines.

**Methods:** Immunocytochemical localisation of PTHrP and PTH[1–10]R was performed by the APAAP method on paraffin sections from 16 consecutive, pre-operatively eucalemic, patients with well-defined hepatocellular carcinoma, and on the hepatocellular carcinoma cell lines, PLC/PRF/5, HepG2 and MCA RH 7777. Murine monoclonal antibodies to PTHrP(1–10) and PTH[1–10]R were used, and specificity was confirmed by Western blotting, using the cell lines, PLC/PRF/5, HepG2 and MCA RH 7777. As tumour invasion increased in depth and width, positive cases of UI, venous invasion (VI) and nodal involvement increased. VEGF-C expression showed positive correlation with UI, VI and nodal involvement and tumour sprouting showed positive correlation with UI and nodal involvement. Both VEGF-C expression [6/7, 85.7%] and tumour sprouting [5/7, 71.4%] showed high specificity for nodal involvement.

**Conclusion:** VEGF-C expression and tumour sprouting are useful in predicting nodal involvement in SICC.
addition to hamartomatous gastrointestinal polyps and pigmented perioral lesions, PJS is associated with an increased risk of tumours at multiple sites. Follow up information on carriers is limited. Genetic heterogeneity makes counselling and management in PJS difficult. Here we report the analysis of the LKB1 locus in 33 PJS families, and estimation of cancer risks in carriers and non-carriers.

Methods: Germline mutations of LKB1 were identified in 52% of cases. This observation reinforces the hypothesis of a second PJS locus. In carriers of LKB1 mutations the risk of cancer was markedly elevated. The risk of developing any cancer in carriers by age 65 was 47% (95% CI: 27 to 73%) with elevated risks of both gastrointestinal and breast cancer.

Conclusion: PJS with germline mutations in LKB1 are at a very high relative and absolute risk of multiple gastrointestinal and non-gastrointestinal cancers. To obtain precise estimates of cancer risk associated with PJS requires further studies of genotype-phenotype especially with respect to LKB1 negative cases as this group is likely to be heterogeneous.

338 EFFECT OF FIBRE DIET ON NEOPLASIA; CELL PROLIFERATION AND CRYPT FISSION IN MIN MICE

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Background: The precise nature and magnitude of the relationship between specific fibre intake and risk of colorectal cancer have not been clearly established. Some studies have shown increased risk rather than protection in man and in animals. One possible explanation is that dietary fibre can modify the process of crypt fission, by which crypts can duplicate themselves, and increase cell proliferation which, can be a promoter of carcinogenesis.

Methods: We have used the Min mouse (C57BK/6J-ApcMin) to investigate the actions of a cow diet, a fibre-free semi-synthetic diet and semi-synthetic diets supplemented with apple fibre or wheat bran fibre on polyp progression, cell proliferation and crypt fission. Forty Min mice, 4 weeks old, were divided into 4 groups and fed the four diets for 8 weeks. The number and size of polyps in the small and large intestines were scored as were the number of native mitoses and the percentage of branching crypts.

Results: The guts of Min mice fed the fibre-free semi-synthetic (SS) diets were lighter than those of the Chow fed. There were fewer polyps in the semi-synthetic diet compared to the Chow fed (p < 0.05). There were more polyps in small intestine of the Min mice fed apple fibre (p = 0.07) and bran (p = 0.014). In the colon there were 50% more polyps in the apple fibre group (NS) and 188% more in the bran fed. There was a significant increase in cell proliferation in the colon of the apple fed group with little change in colonic crypt fission. Crypt fission in the small intestine was significantly decreased by the apple and bran fibres (p < 0.05).

Conclusion: Both apple fibre and bran were associated with increased polyp number in the small intestine and colon but the actions of altered crypt fission are still not clear.

339 ANALYSIS OF BILE IN PATIENTS WITH AND WITHOUT PANCREATICOBILIARY MALIGNANCY BY IN VITRO 31-PHOSPHORUS NMR SPECTROSCOPY

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Background: Mortality rates for cholangiocarcinoma have been widely reported to be increasing. In vitro phosphorus (31P) NMR spectroscopy can be used to analyse body fluids for metabolite abnormalities and the presence of xenobiotics. Several NMR spectroscopy studies on organs and tissue extracts have highlighted differences in the ratio of phospholipid metabolites (phosphodiesters, PDE and phosphomonoesters, PME) between individuals with and without cancer. Decreases in resonances contributing to the PDE region are typically seen in malignancy, often with increases in resonances from the PME region, reflecting increasingly rapid cell turnover of tumour cells. Such a study has not previously been performed on bile.

Methods: 31P NMR spectra were obtained from bile samples from 24 patients, collected at ERCP. 13 patients had an underlying malignancy: pancreatic carcinoma, cholangiocarcinoma, or metastatic liver disease. 11 cases had non-malignant pathology.

Results: A combination of a reduced glycerophosphorylcholine (GPC) signal from the PDE region with the presence of a resonance from the PME region, was seen in bile in 38% of cancer patients, but in only 25% of non-cancer patients. A low or absent GPC signal level was present in 77% of samples from cancer and only 50% of non-cancer patients.

Conclusion: Although the difference in PDE/PDE resonances between cancer and non-cancer patients did not reach statistical significance, the patterns found are consistent with previous NMR studies of changes in PDE/PDE resonances and their constituent components in organs and tissue extracts. This is the first study to show that 31P NMR spectroscopy of bile can potentially be used to assess differences in phospholipid content between cancer and non-cancer patients. This has implications for the development of novel diagnostic and prognostic strategies.

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340 RENAL TUBULAR PROTEINURIA IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Introduction: The irritable bowel syndrome (IBS) is a heterogeneous disorder involving many possible factors: infection, mucosal inflammation, and visceral hypersensitivity. We have previously demonstrated tubular proteinuria in patients with inflammatory bowel disease (IBD). This study examined whether tubular proteinuria may be a feature of IBS.

Methods: 53 control subjects (age range 20–65 years) and 21 patients with IBS (M:F 9:12 age range 16–64 years (NS)) were recruited. Subjects with known renal disease, hypertension, diabetes, or microbiological evidence of urinary infection were excluded. The IBS group patients all fulfilled the Rome II criteria for diagnosis. None gave a history of preceding gastroenteritis. Many patients underwent radiological or endoscopic evaluation. All subjects provided the second voided urine of the morning. Urinary concentrations of the protein α1-microglobulin (α1-M) were measured using rate nephelometric immunossay and corrected for urinary concentration by measurement of creatinine (upper reference limit 1.5 mg/mmol). Blood was analysed for biochemical and haematological indices including C-reactive protein. Statistical analysis was by unpaired T-test.

Results: None of the IBS patients over a 3 year follow up period were reclassified with IBD. All had normal haematological parameters. Mean (+/- SD) urinary α1-M concentrations were significantly higher in IBS than controls (IBS (1.17 +/- 0.65 mg/mmol); controls 0.75 +/- 0.36 mg/mmol, p < 0.01) and exceeded 1.5 mg/mmol in 7 patients.


341 CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHOEA (CDAD), ONSET IN THE COMMUNITY AND HOSPITAL

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CDAD is usually considered to be a problem that develops in patients following hospitalisation for another condition that requires administration of antibiotics. Little is known about patients that require admission to hospital following the onset of CDAD in the community. We
have compared patients that developed CDAD following admission to hospital with those in whom the diarrhoea started in the community.

**Method:** Patients admitted to hospital or developing diarrhoea as inpatients were studied. CDAD was diagnosed in the presence of diarrhoea (> 3 liquid motions in 24 h) and either positive stool C difficile cytotoxin test or pseudomembranes were seen at sigmoidoscopy and the diarrhoea responded to vancomycin or metronidazole.

**Results:** Over a period of 30 months, 136 patients with CDAD (50 male and 86 female) of median age 82 year (range 24 – 97 year) were studied, of which 131 (96%) had taken broad spectrum antibiotics in the community with those in whom the diarrhoea started in the community. Of the patients admitted with diarrhoea, 33 (86.8%) had been hospitalised over the preceding 12 months compared with 56 (57.1%) that developed diarrhoea as inpatient (p < 0.001). Prior to treatment, patients who developed diarrhoea in the community had a higher daily stool frequency (7.2 ±0.8) vs 4.6 ±0.2, p < 0.001) and shorter period of hospitalisation (23 ±3) vs 49 ±4 days, p < 0.001, but there was no difference in age, the duration of diarrhoea, CRP, or WBC. Of the patients who developed diarrhoea in the community, 21 (55.3%) were admitted from their own home with 23 (60.5%) returning there on discharge. Respective figures for patients that developed CDAD in hospital: 68 (69.4%) and 30 (30.6%, p < 0.001).

**Conclusions:** Of hospitalised patients with CDAD, a significant proportion developed the disease in the community. A majority of these had been hospitalised over the preceding 12 months, raising the possibility of acquisition of toxigenic C difficile during a previous hospital admission, with the development of CDAD following the administration of antibiotics in the community.

**Abstract 342**

**RAPID DIAGNOSIS OF GI INFECTION FROM FLATUS**

C.S. Probert1, P. Jones2, N. Ratcliffe2. 1University of Bristol, UK; 2UWE, Bristol, UK

Clostridium difficile affects ca.15,000 people pa in England and Wales and results in 2100 bed days lost per DGH pa costs. Part of the problem is the delay in treatment—8.2 days in a recent series. Small round structured virus (SRSV/Novark) outbreaks result in ward closures. Early diagnosis will facilitate treatment or isolation.

We have undertaken a study of the volatile compounds in stool of patients with diarrhoea (38) and healthy controls (6). Using a novel solid phase microextraction technique linked to gas chromatography and mass spectroscopy, we have characterised the key volatile compounds in normal stool and diarrhoea due to C difficile, SRSV, rotavirus, and Campylobacter jejuni. Diagnostically useful volatiles were: indole, 3-methylindole (3MI), 2-furancarboxaldehyde (2FC), 3-methyl-2-furancarboxaldehyde (3M2FC), ethyl dodecanoate (EDD), ammnia (Amm), the terpenes, and hydrocarbons (HC). The strength of association is shown using χ² test, sensitivity and specificity, positive predictive value (PPV) and negative predictive values (NPV). Grouping some compounds increased their diagnostic value.

These observations suggest that volatiles from stool samples could be used to rapidly diagnosis the cause of infectious diarrhoea. A device based on a portable MS machine could be used or an e-nose built. Our observation may lead to near patient testing on wards or in the field.

<table>
<thead>
<tr>
<th>Marker</th>
<th>χ²</th>
<th>P</th>
<th>Sens %</th>
<th>Spec %</th>
<th>PPV</th>
<th>NPV</th>
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<td>2FC pos.</td>
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<td>8.6E-8</td>
<td>83</td>
<td>97</td>
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<td>C. diff. (ii)</td>
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<td>1.3E-7</td>
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<td>Camp. jej.</td>
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<td>Rotavirus</td>
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<td>SRSV (ii)</td>
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<td>25.6</td>
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</tbody>
</table>

**Abstract 343**

**FAECAL CALPROTECTIN LEVELS ARE ALTERED IN NEONATED WITH ACUTE NECROTISING ENTEROCOLITIS**

D. Carroll, R.D. Spicer1, P. Cairns1, A. Corfield1. 1Department of Paediatric Surgery, Bristol Children’s Hospital, UK; 2Institute of Child Health, St Michael’s Hospital, UK; 3Division of Medicine, University of Bristol, UK

**Introduction:** Faecal calprotectin levels are known to be markedly elevated in children and adults with inflammatory bowel disease. Faecal calprotectin levels are an indirect marker of gastrointestinal inflammation. Necrotising enterocolitis (NEC) is a severe condition of neonatal like characterised by gastrointestinal inflammation and ischaemia. Optimal management for this condition relies upon prompt recognition and early institution of conservative treatment. This study aims to evaluate the potential usefulness of faecal calprotectin levels to diagnose NEC.

**Methods:** Stool samples were collected from neonates with written parental consent on D1, D7 and D14 of life. Any children with suspected NEC had additional stool samples collected. Feed type, gestational age, and postnatal age were recorded. Stool samples were stored frozen at –20°C and analysed using the PhlCal EUSA based kit. Faecal calprotectin levels for each patient were calculated against a standard curve run with each assay. Statistical analysis of data was performed using SPSS for Windows version 10.

**Results:** The presence of NEC is associated with a statistically significant increase in faecal calprotectin levels compared to matched controls (p < 0.001). Faecal calprotectin levels in infants are considerably higher than the reported adult reference range. This is most marked in stool samples collected on the first day of life. Faecal calprotectin levels fall as postnatal age increases.

**Conclusions:** Faecal calprotectin levels are a useful tool for diagnosing NEC in infants. Faecal calprotectin levels are significantly higher in neonatal life than in healthy adult controls.
than the other three isomers [EC50 17.6±3.7 mM; p < 0.01]. Furthermore, this was also more potent than methoxamine racemate and phenylephrine (p < 0.01). This stereoisomer has been synthesised by a novel chemical synthetic pathway, which retains the potency of the chromatographically separated fraction [EC50 10.5±2.0 mM].

Conclusion: L-erythro methoxamine is a possible treatment for incontinence and is four times more potent than phenylephrine. This compound has potential to produce more substantial rises in anal resting pressure with fewer local side effects. Further trials are underway examining the efficacy of L-erythro methoxamine in vivo.

345 ACUTE APPENDICITIS—A DISEASE IN DECLINE: A STUDY OF HOSPITAL ADMISSIONS IN ENGLAND

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Background: The incidence of acute appendicitis declined in Western countries from the 1930s to the 1980s. However, it has been argued that this could in part be due to some patients being reclassified as having non-specific abdominal pain (NSAP) or mesenteric lymphadenitis (ML).


Methods: Hospital episode statistics for admissions were obtained from the Department of Health.

Results: Between 1989/90 and 1999/2000, age-standardised hospital admission rates for acute appendicitis decreased by 12% for males and 19% for females. The admission rates for ML decreased by 40% and 41%, respectively. Coding for NSAP was changed in 1995/1996. From 1989/90 to 1994/1995, NSAP admissions increased by 4.7% for males and 4.9% for females. Over the same period admissions for acute appendicitis decreased by 8.3% for males and 11.4% for females. The increase in NSAP admissions occurred among subjects aged > 34 years, with a decline among those aged 5–19 years. There was a decline in appendicitis among generally elderly patients with significant co-morbidity.

Conclusions: Admission rates for acute appendicitis have continued to fall in the 1990s. This fall cannot be accounted for by an increased tendency to diagnose ML or NSAP.

346 COST COMPARISON OF TREATING EARLY AND LATE COLORECTAL NEOPLASIA

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The objective of this paper is to compare the cost of treating early colorectal neoplasia, to that of late neoplasia with an attempt to show that treating early colorectal neoplasia is more economical in comparison to late colorectal neoplasia. While we are debating the most effective method of screening in order to improve survival, very few people have explored the economical aspects of treating colorectal cancer (CRC) at different stages of its progression. In current literature there is no evidence to suggest that treating early CRC is more cost economical. The majority of the medical literature concerning the treatment of CRC concentrates on the best available options in terms of patient outcome rather than the cost incurred. While this should inevitably be the case, it is important that in an increasingly cost conscious health service, the price of the treatment must also be a consideration. A retrospective analysis of 471 patients over a 3 year period was performed by calculating the cost of inaugural treatment and the subsequent management during a 5 year follow up phase or until the death of the patient with CRC or polyps. Among these, 304 had adenomatous polyps or early carcinoma (adenomas, Duine’s A and B) and 167 had late stage cancer (Duine’s C, D and T4). The median cost of treatment and follow up was significantly lower for early than late stage colorectal neoplasia (10 607 and 13 891), respectively, Mann-Whitney U test, p = 0.0002. The main contributors to the high cost of the late stage cancer were oncological treatment, more admissions with complications, more local recurrences, non-clinical cost (eg stoma care, palliative care), and in certain cases, oncological surgery. In view of these findings, early detection is certainly the desired goal. The growing popularity of screening is justified considering it would be both instrumental in decreasing the mortality as well as the cost of treatment of CRC.

347 THE USE OF METALLIC STENTS IN LARGE BOWEL OBSTRUCTION

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Introduction: There has been an expansion in the use of metallic stents in the management of large bowel obstruction.

Aims: To evaluate results of colonic stent placement in our centre.

Methods: We reviewed all patients who underwent colonic stent placement at our hospital between March 2000 and August 2002. Enteral Wallstents (6 cm or 9 cm long × 20–22 mm diameter, uncovered, Boston Scientific) were used in the majority. All patients had intravenous midazolam (mean dose 4.7 mg).

Results: There were 13 patients (7 female, mean age 74.4 years, range: 42–92 year) undergoing 14 procedures. All patients presented with large bowel obstruction. The sites of obstruction were rectum (n = 1), rectosigmoid (n = 9), descending colon (n = 2), and ascending colon (n = 1). 9/13 patients had adenocarcinoma, the others had colonic obstruction due to ovarian cancer (2), Non-Hodgkin Lymphoma (1), and diverticular stricture (1). The mean length of the obstructing lesion was 6.2 cm (range 3–14.5 cm). Technical success was achieved in 12 stenting attempts. One patient had 2 stents placed sequentially for a long rectosigmoid tumour, another had 2 successive stents (3 months apart) for recurrent tumour. Of these technical successes, 10 had sustained clinical and radiological improvement. One patient had early bleeding (requiring transfusion) and subsequent stent migration. 6/13 patients also underwent adjuvant chemoradiotherapy. In the 10 patients with technical and clinical success, stenting was the definitive palliative procedure. The length of hospital stay was 1–5 days. Mean survival was 128 days in those who received adjuvant chemoradiotherapy and 40 days in those who did not. The remaining 4 with technical or clinical failure underwent emergency surgical decompression.

Conclusions: Metallic stents are effective, safe and minimise hospital stay. Stenting obviates the need for emergency surgery in a group of generally elderly patients with significant co-morbidity.

348 MONOCYTE CHEMOTACTANT PROTEIN-1 (MCP-1/CCL2) AND THE MACROPHAGE INFILTRATE ASSOCIATED WITH HUMAN COLORECTAL CANCER

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The chemokines are a group of more than 40 chemoattractant cytokines that are responsible for leukocyte trafficking under normal and pathological conditions. They are small molecules (~70 kDa) that show structural similarities both at the primary and tertiary levels. In particular they are characterised by conserved amino terminal cysteine residues that may be single (C), adjacent (CC) or separated by another amino acid (CXC). Chemokine signalling is mediated via serpentine receptors. Many human tumours contain a leukocyte infiltrate, including colorectal cancer, of which macrophages may form a significant part. In the 1980s and 1990s a variety of tumours were found to express chemokines that may account for the type and distribution of these infiltrates. In particular another epithelial cancer, ovarian, was found to express and produce monocyte chemotactic protein-1 (MCP-1/CCL2), a potent chemoattractant/macrophage chemotactic agent. MCP-1/CCL2 is expressed predominantly by tumour cells but also by some infiltrating macrophages. We have examined MCP-1/CCL2 production in human colorectal cell lines by specific ELISA and have found constitutive or inducible expression (in response to TNF-a) in 2/3. MCP-1/CCL2 expression has also been examined in RNA extracted from whole tumours and was present in 7/7. In the cell line

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that did not express MCP-1/CCL2, HT-29, monocyte chemoattractant activity was still present when supernatants were tested using the monocyte cell line THP-1 in Boyden chamber migration assays. We have demonstrated that MCP-1/CCL2 can be produced by colorectal cell lines and is expressed by tumours. MCP-1/CCL2 may therefore be involved in determining both the type and distribution of the leukocyte infiltrate in these malignancies.

**Abstract 349**

**DIVERTICULAR DISEASE: RACIAL DIFFERENCES IN PREVALENCE**

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**Introduction:** Diverticular disease (DD) is said to be uncommon in Africans and in Asians.

**Aim:** To determine if patients of Indian subcontinent racial origin (ISC Asians) have a lower prevalence of DD compared to other patients (non-Asians).

**Method:** All colonoscopies performed at St George’s Hospital from October 1999 to October 2002 were studied. ISC Asians were identified by name.

**Results:** 3013 patients were included. There were 245 ISC Asians and 2768 non-Asians. ISC Asians were younger and more likely to be male (mean age 55.1 years, M:F = 1:0.7) compared to non-Asians (mean age 60.1 years, M:F = 1:1.2). ISC Asians and non-Asians with DD had similar sex ratios (1:1.2 and 1:1.1, respectively). Indications for colonoscopy were similar in the two groups.

<table>
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<th>Abstract 349</th>
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<th>NON Asians</th>
<th>P-value</th>
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<tr>
<td>Age</td>
<td>DD Total</td>
<td>DD Total</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>11</td>
<td>245</td>
<td>604</td>
</tr>
<tr>
<td></td>
<td>45.65</td>
<td>6</td>
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<tr>
<td></td>
<td>65.85</td>
<td>5</td>
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</table>

**Conclusions:** There is a lower prevalence of DD among ISC Asians presenting for colonoscopy, compared to non-Asians. This cannot be explained by sex or age differences. If confirmed, our findings may provide opportunities for research into the pathogenesis of DD.

**Abstract 350**

**COLORECTAL MICROFLORA METABOLITES ALTER THE PROTECTIVE CAPACITY OF THE COLORECTAL MUCUS LAYER IN VIVO**

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This study aimed to determine the effects of reactive oxygen species (ROS) and butyrate on the protective capacity of the colonic mucus layer in vivo. An intravital microscopy technique was used to measure the maximal thickness and replenishment rates (rate of mucus secretion after partial removal of the layer by suction) of the colonic mucus layer of anaesthetised male Wistar rats (n = 5 for each treatment) over 5 h under 7 mM butyrate (normal concentration in the rat colon), as well as ROS solutions containing 0.5 mM Fe2+/EDTA mixed with 5–50 mM H2O2. These effects were compared to saline controls (n = 5). Maximal mucus thickness was not affected by 7 mM butyrate or 10 mM H2O2, but 5 mM H2O2 significantly increased maximal mucus thickness, whereas ROS solutions containing more than 10 mM peroxide (i.e. 17.5, 25, and 50 mM) significantly reduced the thickness of the mucus barrier (50% in the case of 50 mM H2O2). 7 mM butyrate significantly increased mucus layer replenishment rate over the first hour of measurement (30% faster than the saline control). Measurement of the effect of ROS on the colonic mucus layer replenishment was hampered by release of plasma exudate and red blood cells from the colonic mucosa. This suggests that low millimolar concentrations of butyrate and ROS may increase the protective capacity of the colonic mucus layer, possibly as a cytoprotective response. Higher levels of ROS appear to be damaging to both the mucus layer and mucosa, especially once the mucus layer is depleted. This study shows that bacterial metabolites may alter the protective potential of the colonic mucus barrier.

**Abstract 351**

**THE RISK OF DYSPLASIA IN POST-SURGICAL COLORECTAL MUCOSA IN ULCERATIVE COLITIS**

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**Background and Aim:** Although panproctocolectomy (PPC) is the operation of choice in longstanding extensive ulcerative colitis (UC), other procedures are occasionally chosen, leaving the patient at risk of dysplasia/cancer in the colorectal remnant. We aimed to assess this risk.

**Methods:** Operative details of all patients in a major UC surveillance programme were reviewed. All patients undergoing surgery other than PPC were studied. Follow up data were obtained from our prospective surveillance database, case notes, colonoscopy and histology reports, GPs, other hospitals, and the Office of National Statistics. Details included indication for surgery, surgical procedure, and post-surgical outcome.

**Results:** Twenty-one patients were studied (11 male, 10 female). Mean post-surgical follow-up was 6.3 years. Median age at operation was 50 (range 28–80). Median duration of colitis was 21 years (range 9–52). Indication for surgery was dysplasia (3), cancer (7), and symptomatic colitis/bleeding (11; surgical specimen showing cancer in 1, dysplasia in 2, and no dysplasia in 8). Nine patients had UC coexistent with ileostomy, 8 patients colectomy with ileorectal anastomosis, and 4 had segmental resection of neoplasia. Eleven patients remained well with no dysplasia. Four underwent surgical resection of the rectal remnant due to symptoms, no dysplasia being found. Six patients died: one from metastatic progression of initial初uke’s C cancer, and 5 from unrelated causes, one of whom had had post-operative rectal high grade dysplasia but had refused further surgery. This solitary patient with post-operative dysplasia had originally undergone ileorectal anastomosis for high grade dysplasia in the sigmoid, but had also had rectal high grade dysplasia 2 years previously.

**Conclusion:** Patients with ulcerative colitis who retain part of the colorectum post-operatively remain at risk of cancer; however this study suggests the risk is low, even in patients with previous colorectal neoplasia.

**Abstract 352**

**HISTOLOGICAL PREDICTORS OF SURVIVAL IN RECTAL CANCER IN THE SHORT TERM**

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**Introduction:** Rectal cancer is associated with poor overall survival at 05 years. We aimed to explore the histological features associated with poor survival in the short term, in patients having an operation for rectal cancer between March 1995 and September 2002.

**Patients and Methods:** 84 patients (40 male, 44 female, median age 55 years, range 22–85) with rectal cancer situated (median, range) 6 cms, (1–15) from the anal verge underwent anterior resection (n = 60), abdomino-perineal resection/total reconstruction (n = 7), Hartmann operation (n = 3), restorative proctocolectomy (n = 7), and subtotal colectomy (n = 7). All specimens were evaluated by a single pathologist after haematoxylin and eosin staining of paraffin sections. The following data were obtained: TNM stage, serosal involvement by tumour, involvement of resection margins—radial, mesorectal excision, and distal resection, angioinvasion, lymphatic, and perineural involvement. The association between histology and survival was evaluated by Cox’s regression and Kaplan Meier analysis.

**Results:** The median follow up was 18 months (range 5–86 months). Overall operative mortality was 4 (4.7%). Cancer related mortality has been 26 (31%) of 84. Independent predictors of poor survival were; T stage (p = 0.028 Cox regression) and presence of metastasis (p = 0.02). Nodal involvement alone was not an independent predictor of survival (N0, p = 0.48; N1, p = 0.42). Similarly, invasion of blood vessels, lymphatics, and nerves around tumour were not independent predictors of short term survival (p = 0.64, p = 0.64, p = 0.28, respectively).

**Conclusion:** Patients with rectal cancer were likely to have reduced short term survival in rectal tumours, which invaded beyond the...
submucosa, and in those with tumour involving peritoneum. The combined presence of metastasis with tumour beyond submucosa further reduced survival. Lymph node involvement by tumour reduced survival only if combined with any of the above predictive parameters; they were not independent predictors of survival.

### 353 HISTOLOGICAL AGREEMENT BETWEEN PATHOLOGISTS FOR DIAGNOSING COLORECTAL NEOPLASMS: THE EFFICACY OF THE VIENNA CLASSIFICATION

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**Background:** The use of different nomenclature and differences in histological interpretation between Western and Japanese pathologists have caused considerable problems in the diagnosis, treatment and outcome for gastrointestinal epithelial neoplasms. In order to resolve this discrepancy, the Vienna classification (VC) has been developed.

**Aim:** To clarify the discrepancy between UK and Japanese pathologists and to assess the efficacy of the VC for the diagnosis of colorectal neoplasms.

**Methods:** 350 colorectal neoplasms (340 polypectomy and 10 biopsy specimens) were examined by two British (UK1, UK2) and two Japanese (J1, J2) pathologists using both conventional (mildly, moderately, or severely dysplastic adenomas and cancer) and the VC.

**Result:** Under conventional classification, there was moderate to good agreement ($\kappa = 0.63$, 0.56) between the pathologists within each country compared to only fair to moderate agreement ($\kappa = 0.29–0.52$) between UK and Japanese pathologists. By adopting the VC a better mutual agreement was established between the UK and Japanese pathologists ($\kappa = 0.50–0.64$). Japanese pathologists tended to assign a higher grade of dysplasia in both classifications (see Table).

### Table

<table>
<thead>
<tr>
<th>Pathologists</th>
<th>Conventional (Odds)</th>
<th>Vienna (Odds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>UK2</td>
<td>1.54</td>
<td>1.08</td>
</tr>
<tr>
<td>J1</td>
<td>2.68</td>
<td>1.79</td>
</tr>
<tr>
<td>J2</td>
<td>3.88</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Odds: a polyp being graded in the next highest category relative to pathologist UK1.

**Conclusions:** The discrepancy caused by different nomenclatures with their possible knock-on differences for clinical management was improved by using the VC. The reason for the higher grading made by Japanese pathologists needs analysis but might be related to more reliance on cytological parameters.

### 354 AWARENESS AND KNOWLEDGE OF COLORECTAL CANCER: IMPLICATIONS FOR FUTURE COLORECTAL CANCER SCREENING PROGRAMMES

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**Introduction:** Cancer screening is rarely successful in populations with little knowledge of the disease being screened. CRC screening will likely be implemented in many countries over the next 10 years, requiring accompanying educational programmes. Data are unavailable from any country on awareness and knowledge of CRC within the general population.

**Aim:** To determine awareness and knowledge of CRC in the Irish population.

**Methods:** A nationwide survey of 2355 adults (1250 females), comprising almost 0.1% of the entire adult population. Survey conducted in all 26 Irish regions in 2001/2002. Patients completed a questionnaire with questions on different aspects of CRC. Questions were asked about heart disease and breast cancer to provide control data.

**Results:** Awareness of heart disease and breast cancer was high (73% and 81%, respectively, had heard of these diseases in the recent past). In contrast, only 40% had heard of CRC (14% magazines/newspapers, 12% TV/radio, 22% family/friends, 6% medical profession, 7% other sources). In relation to knowledge, 79% knew that a positive family history was associated with increased risk. However, irritable bowel syndrome (60%) and stress (62%) were thought to be greater risk factors for CRC than polyps (59%). 42% could name at least 1 colorectal cancer symptom, 53% thought that most patients were under 60 years of age at diagnosis, 61% were aware of surgery as a treatment, 45% estimated 5 year survival as above 40%, and 46% were aware that screening tests were available. Factors associated with CRC knowledge included having read about the disease in the recent past ($p = 0.01$), older age ($p < 0.001$), and higher educational status ($p < 0.001$).

**Conclusions:** This nationwide survey shows that awareness and knowledge of CRC is limited, especially in certain groups. This may have important implications for the success of future screening programmes and will allow us to target certain population groups for intensive education about CRC and the risks and benefits of screening.

### 355 IMPROVEMENT IN COLORECTAL CANCER SURVIVAL OVER THE PAST 20 YEARS: THERE ARE MORE QUESTIONS THAN ANSWERS

G. Bennett, J. Hyland, K. Sheehan, J.L. Murphy, A. White, D.P. O’Donoghue, H.E. Mulcahy. Centre for Colorectal Diseases, St Vincent’s University Hospital, Elm Park, Dublin 4

**Introduction:** There has been a 1000% increase in the output of colorectal cancer research over the past 30 years and many diagnostic, surgical, and oncological advances. These might be expected to have had a favourable impact on survival but it is not known if this is the case.

**Aim:** To determine colorectal cancer survival trends over a 20 year period in a single institution.

**Patients:** 1853 consecutive patients admitted to St Vincent’s University Hospital, Dublin between 1983 and 2002 were prospectively entered onto a database. Demographic, clinical, and pathological data were collected and patients were followed until death. For analysis, the study group was divided into tertiles based upon year of diagnosis.

**Results:** Age rose over the study period ($p < 0.001$) while the percentage of patients undergoing tumour resection decreased from 96% to 88% ($p < 0.001$). There were no changes in sex ($p = 0.35$), tumour site ($p = 0.52$), or overall tumour stage ($p = 0.58$). However, on subanalysis, the proportion of stage II tumours decreased and stage III tumours increased in frequency over time ($p = 0.02$). Cancer related survival improved over the period from 45% to 56% ($p = 0.005$). On subanalysis, only those with stage III cancers had a significant improvement in survival ($p = 0.05$).

**Conclusions:** There has been a modest improvement in colorectal cancer survival over the past 20 years that may be related to a number of discrete factors. The improvement appears greatest in stage III tumours but this is as likely to be related to stage migration over the 20 years as it is to any therapeutic advances.

### 356 PELVIC TRAUMA AND RECTOCELES: DO THEY CAUSE SEVERE CONSTIPATION?

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**Introduction:** There are a host of causes attributed to chronic constipation while some patients remain idiopathic. Labour, pelvic surgery, and consequent rectoceles have been seen as causes but this remains controversial and few studies have shown a definite link.

**Methods:** 53 consecutive female patients with severe constipation (SC) were assessed using a proforma including a detailed history of the effect, on their symptoms of pelvic trauma (PT) including childbirth, and pelvic surgery. Patients with PT were asked whether it had; triggered symptoms of SC, worsened them if present previously, or had no effect. All of the patients had radionuclide proctograms and data were obtained on the presence and size of rectoceles.

**Results:** 40/53 (75%) of patients with SC had experienced PT. Of these 12/40 (30%) felt their constipation was triggered by it, 10/40 (25%) had symptoms preceding PT but felt it worsened their symptoms, and 18/40 (45%) felt there was no relationship between PT and SC. Patients with a history of PT had a greater likelihood of having a rectocele (85%) compared with the group with no PT (52%). Rectocele size was significantly greater in the PT group, 3.1 cm versus 2.2 cm ($p = 0.02$). Rectocele size was no greater for patients in "triggered"...
(3.13 cm) or “worsened” (2.97 cm) groups than in those with “no effect” (2.95 cm) \( p = 0.96 \).

**Conclusions:** Pelvic trauma is a significant factor in the aetiology of SC. However, the mechanism of this is unclear. Rectoceles are a common finding in women with SC, and are likely to be greater in size if the patient has experienced pelvic trauma. However, it seems unlikely that the presence or size of rectocele is a major factor in the pathogenesis of SC.

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**ABDOMINAL SUTURE RECTOPEXY WITHOUT LARGE BOWEL RESECTION FOR RECTAL PROLAPSE DOES NOT RESULT IN CONSTIPATION; DATA FROM PROSPECTIVE BOWEL FUNCTION EVALUATION, ANORECTAL PHYSIOLOGY, AND TRANSIT STUDIES**

V.Y. Sabaratnam, G. Rathnayake, K.I. Deen. University Department of Surgery, Northern General Hospital, Sri-Lanka

**Introduction:** Traditionally, suture rectoectomy has been combined with sigmoid resection for rectal prolapse to prevent postoperative constipation. Furthermore, preservation of lateral ligaments will not result in constipation. Suture rectoectomy alone without resection is being popularised. No studies have shown the influence of suture rectoectomy without resection on colonic transit, and postoperative constipation.

**Patients and Methods:** Forty-six patients (median (range) age 32 (19–82) years) with rectal prolapse underwent suture rectoectomy alone without division of lateral ligaments from March 1999. Prospectively, bowel function and anorectal physiology (ARP) were evaluated before and after surgery in a subset of 15 patients. Follow up (median, range) has been 12 (1–42) months.

**Results:** Follow up was complete in 36 patients. Recurrent prolapse was seen in 5 (full thickness 3 (8.3%); mucosal prolapse 2 (5.5%)). Physiological data in a subset of 15 patients revealed no significant difference in anorectal physiology before and 3 months after the operation (see Table). Similarly there was no significant difference in the rate of evacuation of transit markers on day 3 and 5 (see Table).

**Conclusion:** Abdominal suture rectoectomy without resection for rectal prolapse improves constipation symptoms, and does not result in significant change in colonic transit. We recommend this procedure either by open operation or by laparoscopy.

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**Nutrition posters 358–363**

**358 A SIMPLE AND SAFE METHOD OF TRANSCUTANEOUS GASTROSTOMY REPLACEMENT**

M.B. Frenz1, G. Siuda1, A.S. McIntyre2, S.P.L. Travis1. 1Gastroenterology Unit, John Radcliffe Hospital Oxford, OX3 9DU, UK; 2Wycombe Hospital, HP11 2TT, UK

**Introduction:** The replacement of gastrostomy (PEG) feeding tubes often requires endoscopic procedures as the fistula closes soon after the accidental or elective removal of the PEG. Transcutaneous replacement of PEG tubes often leads to reduction in PEG size because of contraction of the fistula tract.

**Aim:** To assess the use and safety of a guide wire and vascular dilators for transcatheter PEG replacement.

**Methods:** Patients referred for either elective PEG replacement or re-insertion of accidentally removed PEGs received the new balloon PEG (MIC-Key PEG, Vygon UK, in 11 cases and Corflor, Merck UK in one case) using the transcutaneous approach. The gastrostomy fistula was dilated with vascular dilators after a standard ERCP guide wire was passed through the fistula. The replacement PEG was inserted over the guide wire and the position checked by aspiration of gastric contents.

**Results:** A total of 12 PEGs were replaced in 8 patients. In 9 episodes the PEG had been accidentally removed and patients presented after a delay of 16–24 hours. In 3 cases the PEG had to be replaced because of malfunction and the old PEG was removed using the cut and push technique. Sedation was only used in one patient. The gastrosytm fistula was dilated to 2 Fr larger than the replacement PEG. In 9 cases the size of the replacement PEG was identical to that of the old PEG (14 Fr in 8 patients and 10 Fr in one patient). In two cases the replacement PEG was smaller than the original PEG (9 Fr to 12 Fr). All patients tolerated the procedure well and had no complications except minor bleeding during dilatation, which was self-limiting. In 8 of the 12 patients the procedure was carried out as an outpatient procedure.

**Comments:** This technique of PEG replacement appears safe and well tolerated by patients. It reduces the need for repeat endoscopic procedures and sedation in most cases. Vascular dilators are easily available and less expensive than other dilators. It is a simple outpatient procedure and reduces both admission and endoscopy time for patients with PEG malfunction or accidental removal of their PEG.

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**359 IMPACT OF IMPLEMENTATION OF SPECIFIC FEEDING GUIDELINES ON THE 30 DAY MORTALITY AFTER PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG TUBE INSERTION) IN HOSPITALISED PATIENTS**

F. Mohammed1, J. Gassm2, S. Balakrishnan2, S. Hurst1, P. Conlong2, B. Rameh3. 1Birch Hill Hospital, Rochdale, OL12 ONB, UK; 2University Hospital Aintree, Liverpool, L9 7AL, UK; 3Royal Oldham Hospital, Oldham, OL1 2JH, UK

**Background:** A previous audit at the Royal Oldham Hospital done between March 1999 and June 2000 had shown that there was a 42% mortality at 30 days after PEG tube insertion in hospitalised patients. Several recommendations were made after this audit: patient’s head to be kept at an angle of 30–45 degrees when feeding; recheck gastric contents before feeds (if greater than 150 ml residue aspirated then withhold feeds); use of a gastroenterology specialist nurse to assess patients before and after PEG tube insertion. Our aim was to determine whether these measures led to a reduction in 30 day mortality in hospitalised patients.

**Methods:** Reviewed the medical records of hospitalised patients who underwent PEG insertion between June 2000 and December 2001. Cause of death was identified from clinical notes and death certificates for patients who died within 30 days of PEG insertion.

**Results:** 73 PEG tubes were inserted during the audit period. 73% of patients were more than 70 years of age (range 38–98). 51 patients (70%) had PEG tubes because of dysphagia secondary to a cerebrovascular accident. 58 patients (80%) had their PEG tubes inserted within one week of referral and 5 patients had insertion delayed because of the need for further assessment prior to PEG insertion. There were no immediate deaths during or within 24 hours of the procedure but there were 16 deaths (22%) within 30 days and 9 (12%) of these were PEG related. There was a statistically significant difference \( p < 0.05 \) in mortality compared to the previous audit period.

**Conclusions:** Careful assessment of patients before and after PEG tube insertion and implementation of specific feeding guidelines can decrease the 30 day mortality after PEG tube insertion.

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**Abstract 357**

<table>
<thead>
<tr>
<th>Median (Range)</th>
<th>BEFORE</th>
<th>AFTER</th>
<th>P VALUE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum squeeze pressure (mm Hg)</td>
<td>67.5 (19–130)</td>
<td>90 (28-157)</td>
<td>0.164</td>
</tr>
<tr>
<td>Maximum resting pressure (mm Hg)</td>
<td>25 (7-50)</td>
<td>33.2 (7-80)</td>
<td>0.026</td>
</tr>
<tr>
<td>Maximum tolerable volume (ml)</td>
<td>230 (180-340)</td>
<td>200 (50-290)</td>
<td>0.139</td>
</tr>
<tr>
<td>Transit – excretion percentage</td>
<td>Day 3</td>
<td>100 (3-100%)</td>
<td>100 (0-100%)</td>
</tr>
<tr>
<td>Transit – excretion percentage</td>
<td>Day 5</td>
<td>100 (21-100%)</td>
<td>100 (21-100%)</td>
</tr>
</tbody>
</table>

*Wilcoxon signed rank test. n = 15.
**Aims:** To establish attitudes and current practice regarding nutritional support in the ICU setting and to explore factors determining choice of feeding route.

**Methods:** A questionnaire was sent to 324 ICUs in the UK. It comprised an attitudinal survey assessing unit policy and opinion in relation to nutritional support, and a “snap-shot” survey of current patients to determine how this policy was implemented in practice. Completed questionnaires were returned by 112 units (35%), responsible for the care of 617 inpatients on the day of the survey. 416 patients (67%) were receiving artificial nutrition. 85% were on some form of enteral nutrition (EN) alone, 9% were receiving parenteral nutrition (PN) alone, and 6% were on a combination of EN and PN. Nasogastric (NG) feeding accounted for 90% of the EN group. In the attitudinal survey, most respondents (83%) agreed that NG feeding generally allowed patients to meet their nutritional requirements. However, frequent problems with NG feeding were reported in practice, with 30% needing tube replacement, 24% having absorption problems and 24% having unplanned interruptions to their feed. 51% of respondents agreed that those who fail NG will usually tolerate nasojejunal (NJ) feeding, yet only 15 patients had NJ tubes (2 with supplemental PN). Only 25% of units claimed to use NJ feeding regularly, whereas 18% units never use it. Of the 39 patients on NJ, only 14% appeared to have an accepted contraindication to NJ feeding. NJ tubes were placed endoscopically in 6/13 patients with 3 placed blindly, 2 with fluoroscopy and 2 during surgery. 45 units reported difficulty in arranging endoscopic NJ tube placement. 62/109 units felt that a reliable NJ tube placement service would probably decrease their use of PN.

**Conclusions:** EN is firmly established as the preferred choice for nutritional support in ICU patients. NG remains the main feeding route but is frequently associated with problems that may limit nutrient delivery. Many patients have difficulty arranging endoscopic NJ tube placement. Better access to the technique might decrease the use of PN.

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**NUTRITIONAL SUPPORT IN INTENSIVE CARE UNITS—NATIONAL SURVEY OF CURRENT PRACTICE IN THE UK**

N. Kapoor, H. Cooper, P. O'Toole. Aintree Centre for Gastroenterology, University Hospital Aintree, Liverpool, UK

**Dietary Fibre Modulates the Protective Potential of the Colonic Mucus Barrier and Mucosal Health**

I.A. Brownlee1, M.A. Atherton2, M.E. Havler2, P.W. Dettmar2, A. Allen1, J.P. Pearson1. 1Cell & Molecular Biosciences, Newcastle University, NE2 4HH, UK; 2Reckitt Benckiser Healthcare (UK) Ltd, Hull, HU8 7DS, UK

This study aimed to characterise the effect of dietary fibre type on levels of mucosal reddening and the protective capability of the colonic mucus barrier in an in vivo model. The effects of 8 week feeding of six different fibre containing diets were assessed on Wistar rats, and compared to control diets (standard chow). Each diet contained approximately 14% fibre by weight, except the fibre deficient diet. After this time, the maximal colonic mucin thickness and replenishment rates were measured in vivo using an intravital microscopy technique. Initial mucosal redness and intracellular mucin were assessed by densitometric image analysis of in vivo and histological microphotographs, respectively. Fibre deficient, pectin, and cellulose diets reduced maximal mucin thickness (> 100 µm thinner than 550 µm control) and mucin replenishment rates (by > 50%) compared with controls (p < 0.001), but not intracellular mucin. Pectin and cellulose diets significantly increased colonic mucosal reddening (p < 0.001). An ispaghula husk diet increased intracellular colonic mucin levels (p < 0.05) by 28% as a result of 1% alginate in the diet lead to an elevation of maximal mucin thickness (103 µm thicker than control) and a reduced level of mucosal reddening by 15% (p < 0.001). Higher levels of alginate (5%) had no effect. Dietary fibre types that caused a reduction in the protective capability of the intracellular (pectin and cellulose) of the colonic mucin layer lead to an increase in mucosal redness. These results suggest fibre type and inclusion in the diet modulates both the protective potential of the colonic mucin layer, and also levels of mucosal damage. Certain fibre types may be of benefit in the possible prevention and alleviation of certain diseases (e.g. IBDs, IBS), where colonic protection by the mucin layer is reduced.

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**Dietary fibre modulates the protective potential of the colonic mucus barrier and mucosal health**

I.A. Brownlee1, M.A. Atherton2, M.E. Havler2, P.W. Dettmar2, A. Allen1, J.P. Pearson1. 1Cell & Molecular Biosciences, Newcastle University, NE2 4HH, UK; 2Reckitt Benckiser Healthcare (UK) Ltd, Hull, HU8 7DS, UK

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**The Effect of Peanut Lectin on Intestinal Proliferation, ACF and Tumour Development in Colonic Carcinogenesis**

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**Background:** Peanuts lectin (PNA) is a highly specific carbohydrate binding protein found in the diet and PNA may be harmful, as it is mitogenic to the human colon. Aberrant crypt foci (ACFs) are early precursor lesions of the adenoma-carcinoma sequence. They are found in FAP and sporadic patients and maybe associated with the early stages of adenoma development.

**Aims:** To investigate intestinal growth, crypt fission (a process by which crypts split longitudinally to produce two new crypts), ACF, and tumour occurrence in rats.

**Methods:** Rats were given a small dose (40 µg/rat/day) of PNA for 28 weeks, with or without DMH (20 mg/kg weekly). Carnoy’s fixed tissue was stained with the Feulgen reaction and carefully microdissected to reveal individual crypts. Crypt cell production (following vincristine induced metaphase arrest) and crypt fission were scored. The number and size of polyps and ACFs in the colon were scored.

**Results:** PNA significantly increased crypt cell production in the distal colon (p = 0.02) with DMH having no effect on proliferation. DMH significantly increased crypt fission (p < 0.001), but PNA had no effect on fission. Tumour distribution revealed two sites of tumour development, poorly differentiated mucous adenocarcinoma (Gp 1) in the proximal colon, and well differentiated tubular adenocarcinoma (Gp 1) in the distal colon, but ACFs were mainly confined to the distal colon. ACF multiplicity varied an average of 2–4 crypts per focus.

**Conclusion:** Peanut lectin can have trophic actions on the colon but no effects on tumour and ACFs number were seen. ACFs may only be predictive of distal colon cancer.

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**Plasma Fatty Acid Composition and Nutritional Status in Paediatric Crohn’s Disease**

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Malnutrition and growth retardation is associated with increased disease activity in paediatric Crohn’s disease (CD). Adequate availability of essential fatty acids (EFA) (linoleic (LA) and α-linolenic acid (αLNA)) and their derivatives (arachidonic (AA) and docosahexaenoic acid) may be required for optimum childhood growth and development, and altered plasma levels may be associated with protein energy and oedematous malnutrition. In paediatric CD the relationship of plasma concentrations of EFA, and derived fatty acids, to disease activity, nutritional status and percentage total body water (%TBW) is poorly defined. Paediatric CD patients (10.3–17.0 years) were stratified by Paediatric Crohn’s Disease Activity Index as active (n = 15) and inactive (n = 15) disease groups, and assessed for nutritional status (anthropometry and bioelectrical impedance) and fatty acid composition of plasma phosphatidylcholine (PC) (by gas chromatography). Lower concentrations of αLNA were noted in active CD (0.26%) vs inactive CD (0.35%) (p = 0.044). Active CD was associated with lower triceps skinfold thickness and mid-arm muscle circumference and higher %TBW compared with inactive CD. On post hoc analysis, CD patients with a BMI centile < 50 vs > 50 demonstrated lower LA (23.3% vs 25.6%; p = 0.021) and αLNA (0.25% vs 0.34%; p = 0.025), but higher AA (9.68% vs 8.39%; p = 0.017) levels in plasma PC. Similar differences were noted in patients with a %TBW > 65 % vs < 65 %. There were no differences in habitual dietary fat or energy intake between CD patient groups stratified by PCDAI, BMI centile or %TBW. Disease activity and nutritional status in paediatric CD are associated with alterations in the availability of EFA and AA that cannot be simply explained by differences in habitual dietary intake but may reflect adaptive or pathological responses. Further investigation is indicated to determine the effect of dietary intervention on modulating plasma fatty acid profiles and nutritional status and growth, in paediatric CD.
Small bowel posters 364–374

364 B12 DEFICIENCY—AN AUDIT OF CURRENT PRACTICE
S.C. Cooper, N.C. Fisher. Department of Gastroenterology, Dudley Group of Hospitals, High Street, Pensnett, Dudley, West Midlands, DY1 2HZ, UK

Background: B12 deficiency is a common condition with variable presentation from differing pathological processes. We sought to audit the methods of investigating, diagnosing and managing B12 deficiency.

Methods: Retrospective case note analysis of 100 patients with the lowest B12 levels over an 18 month period 1999–2001, collected from a database of 953 B12 deficient patients (c.115 g/l). B12 levels correlated significantly with MCV (p < 0.001) but not with age (p = 0.54). Investigations were by the following groups: 35% general physicians, 24% gastroenterologists, 22% geriatricians, 15% haematologists, and 15% other (eg surgeons, obstetricians). 28% of low B12s were missed (mostly by the non-physician group 53%), 37% were investigated and treated, 22% were not investigated but just treated, and 8% were clinically diagnosed and treated. An age bias approach was taken to just treating without investigating (median age 84–80, 56% were diagnosed within physicians vs. non-physicians (n = 7), followed by surgical resection (gastricctomy n = 4, ileal ileum n = 4); coeliac disease was the cause in 2 patients. All Cronh’s patients had had surgical resections. Schillings test had the best positive yield of 56%, while GPC and IF antibody testing had a yield of 39%.

Conclusions and Recommendations: Too many low B12 levels are missed by all groups of doctors, but most noticeably by non-physicians. Laboratory alerts should therefore appear on results. A good history will often reveal the cause; if not, GPC, IF, gliadin, and endomyrial antibodies should be the first line tests. A high MCV should always lead to checking a B12 level. Referral to gastroenterologists should occur when symptoms suggest a GI cause.

365 DOES ADOPTION OF BSG GUIDELINES FOR MANAGEMENT OF IRON DEFICIENCY ANAEMIA (IDA) RESULT IN AN INCREASE IN UNNECESSARY DUODENAL BIOPSIES?
H.R. Ferguson, J. Sommerville, P. Murphy. CRA Margaret Area Hospital, Lurgan Road, Portadown, Northern Ireland

Introduction: The British Society of Gastroenterology guidelines for the management of IDA suggest that duodenal biopsy should be done as a routine at the time of OGD in all patients. These guidelines were adopted in our trust but there was concern that they may increase the workload of an already stretched histopathology service, without a significant increase in the rate of diagnosis of coeliac disease.

Aim: To determine the number of duodenal biopsies performed annually and the rate of diagnosis of coeliac disease, before and after publication of the BSG guidelines.

Methods: The histopathology laboratory indenfied all patients who had a duodenal biopsy performed from April 1998 to April 1999, and April 2001 to April 2002. Reports were reviewed and data collected included patient demographics, consultant requesting biopsy, indication, and result.

Results: 118 patients had duodenal biopsies performed in the year before adoption of the BSG guidelines. Mean age 49.3 years (range 4–86 years). 56% were female. 70% were referred by physicians, the indication in 30 patients (25%) had had surgical resections. Schillings test had the best positive yield of 56%, while GPC and IF antibody testing had a yield of 39%.

Conclusion: The number of duodenal biopsies substantially increased after implementation of the guidelines, however this was not primarily due to a large increase in biopsies for IDA. Furthermore this increase was accompanied by an increase in the rate of diagnosis of coeliac disease. Implementation of the BSG guidelines has not been associated with increased numbers of unnecessary biopsies.

366 MAKING THE DIAGNOSIS OF COELIAC DISEASE: IS THERE A ROLE FOR PUSH ENTEROSCOPY?
B.S. Höroldt, M.E. McAlindon, T.J. Stephenson, M. Hadjivassiliou, D.S. Sanders. Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK

Background and Aims: Previous investigators have suggested that the only role for enteroscopy in coeliac disease (CD) is in the assessment of refractory cases. We assessed the value of enteroscopy in making the diagnosis of CD.

Methods: 31 patients (22 female, 9 male) were recruited prospectively from September 2001 to October 2002. Mean age 52.7 years (range 20–80 years). Clinical indications for investigating for CD were anaemia (n = 12), diarrhoea (n = 9), irritable bowel syndrome (n = 7), family history of CD (n = 1), elevated transaminases (n = 1), and abdominal pain (n = 1). All patients were tested using a combination of immunoglobulins, IgG and IgA gliadin antibodies (AGA) and endomysial antibody (EMA). Of the 31 cases, 8 were EMA positive (alone or in combination with either AGA) and 23 had positive IgG and/or IgA AGA. Initial quadrantic duodenal biopsies showed intraepithelial lymphocytes in 16 cases and normal mucosa in the other 15. In view of the clinical indications and positive antibody titres we proceeded to enteroscopy with repeat quadrantic duodenal biopsies (4×) and separate distal small bowel biopsy (4×).

Results: A single investigator performed push enteroscopy. Mean depth of insertion was 115 cm beyond the pylorus (range 95–135 cm). All samples were reviewed by a gastrointestinal histopathologist and compared with the initial duodenal biopsy. The diagnosis of CD could not be confirmed from either the 2nd duodenal biopsy or small bowel biopsy in all 23 cases that were only AGA positive. For the 8 EMA positive cases, repeat biopsy proved the diagnosis of CD in 5 cases (AGA group vs EMA: Fisher exact test p < 0.0001). Of these 4 cases, 3 only had evidence of villous atrophy in the distal small bowel biopsy.

Conclusion: EMA positive patients in whom the diagnosis of CD has not been confirmed after duodenal biopsy may benefit from repeat biopsy. In 3 of the 5 cases the diagnostic information was only apparent in the distal small bowel. There may be a role for enteroscopy in making the diagnosis of CD, however larger prospective studies are required.

367 IgA ANTIBODIES TO HUMAN TISSUE TRANSGLUTAMINASE: ADVANCING THE DIAGNOSIS OF COELIAC DISEASE
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Introduction: We recently confirmed the superior diagnostic accuracy of tissue transglutaminase antibody (TGA), using human antigen, for the diagnosis of coeliac disease (CD) with selected samples. Here we report the first 6 months experience of TGA as our first line test for CD.

Methods and Serum Samples: TGA was measured using the Celikey kit with recombinant human tissue transglutaminase as antigen (Pharmacia Diagnostics, Milton Keynes, UK). Levels > 3 units/ml are considered abnormal. Endomysial antibody (EMA) was measured by indirect immunofluorescence on monkey oesophagus slides (The Binding Site, Birmingham, UK) at a 1:10 serum dilution on all samples with TGA > 2.9 units/ml. Serum samples received from April to Sept 2002 in the investigation of adults from primary or secondary care were included in this group.

Results: 1601 samples were analysed in this 6 month period, the median level was 0.6 units/ml; 1542 (96.3%) had results of < 3 units/ml. The table summarises the results and small bowel biopsy findings thus far. IgA deficiency can be suspected from a low optical density reading in the assay; 14% of all samples required total IgA measurement. 3 new case of IgA deficiency were detected.

Conclusions: TGA levels of twice the upper limit of normal (10 units/ml) are invariably diagnostic of CD raising the question whether biopsy is still essential for the diagnosis. Introduction of the assay has fulfilled expectations of high specificity and has significantly reduced the EMA workload. However, we appear to be missing the expected small proportion of subjects with CD who are EMA negative at diagnosis.

368 UPRGULATION OF DUODENAL PROTEIN EXPRESSION OF DIVALENT METAL TRANSPORTER 1 PROTEIN IN UNTREATED COELIAC DISEASE MAY BE DUE TO A SWITCH TO A MORE MATURE MUCOSAL EPITHELIAL PHENOTYPE

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Introduction: Not all patients with untreated coeliac disease (CD) have iron deficiency anaemia. Studies show that expression of iron cognate proteins involved in iron absorption is highest in the duodenal villi, with little expression in the crypts. In untreated CD patients with normal iron indices, we hypothesised that there may be a switch to a more mature phenotype among the mucosal and crypt epithelial cells resulting in up-regulation of expression of proteins involved in iron absorption.

Aims: To investigate the duodenal expression of iron cognate proteins in patients with untreated and treated CD with normal body iron indices.

Methods and Patients: Immunohistochemical methods were used to assess semi-quantitative protein expression of divalent metal transporter 1 (DMT1), transferrin receptor (TfR) and ferritin in distal duodenal mucosa of untreated CD (n = 5), treated CD (n = 6), and controls (n = 13).

Results: In both untreated and treated CD patients, crypt membranous, cytoplasmic, and nuclear expression of DMT1 (p < 0.04 to p < 0.0001) and crypt membranous expression of TfR (p = 0.0008) was higher compared to controls. In treated CD, villous expression of DMT1 and TfR was higher compared to controls (p < 0.0001). Expression of cytoplasmic and nuclear ferritin expression was lower in untreated and treated CD compared to controls (p < 0.026 to p < 0.0001).

Conclusions: This preliminary study has shown differences in duodenal mucosal expression of iron cognate proteins in untreated and treated CD with controls, despite similar body iron indices. Infiltration of DMT1 expression in untreated CD suggests the existence of a mature mucosal epithelial phenotype protecting against iron deficiency.

369 EFFECTS OF BACTERIAL ENTEROTOXINS ON DISTANT (NEUROGENIC) INTESTINAL FLUID AND ELECTROLYTE TRANSPORT

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We have shown previously that CT, LT, and STa have distal effects on intestinal fluid and electrolyte transport via neural mechanisms. Intestinal transection can abolish or reduce the remote effects of CT, LT, and STa by supporting a role in intrinsic neurones of the enteric nervous system.

Aim: To determine the role of vagotomy in the remote actions of CT, LT, and STa; and to determine the effects of granisetron, a selective 5-HT3 receptor antagonist, and PG 97–269, a selective VIP1 antagonist in CT induced effects on distant intestinal transport.

Method: A model of remote intestinal secretion was created in adult CD rats. Distal small intestine (stomach infused with saline) was ligated and infused with CT (50 µg/ml), LT (50 µg/ml), STa (2 ug/ml), and hyperosmolar mannitol (600 mM/Kg/ml), a control secretagogue, and saline (control) were placed independently in a proximal jejunal loop. A distal ileal loop was perfused with 2% PEG to measure changes in fluid and electrolyte transport. The experiment was repeated post-vagotomy. Intraperitoneal granisetron (75 µg/kg) and intravenous PG 97–269 were given independently prior to CT.

Results: Vagotomy completely inhibited STa induced ileal fluid and electrolyte transport changes but had no effect on CT and LT. Granisetron and PG 97–269 completely reversed the remote effects of CT (p < 0.05). Mannitol had no effect on distant intestinal fluid and electrolyte transport.

Discussion: STa is dependent on vagal activity to mediate distant intestinal fluid and electrolyte changes. CT and LT’s remote effects are independent of vagal activity but dependent on intestinal integrity and hence an intact enteric nervous system. 5-HT, and VIP receptors are involved in the neural pathway mediating the remote actions of CT. The neural mechanisms involved in the distal intestinal fluid and electrolyte transport are likely to have important pathophysiological implications as CT, LT, and STa can attenuate the distal intestine’s capacity to absorb excess fluid.

370 ROLE OF PRO-INFLAMMATORY CYTOKINES IN ENTEROCYTE MEDIATED ELIMINATION OF ENCEPHALITOZOON INTESTINALIS

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Introduction: E intestinalis, a microsporidian pathogen in man, has emerged as a serious opportunistic pathogen in HIV infected individuals. In this study the development of the parasite in different cell lines was investigated. In addition, the effect of pro-inflammatory cytokines on this development was analysed.

Methods: Seventy percent confluent monolayers of human (HT-29, Caco-2) colonic and murine (CMT-93) rectal adenocarcinoma cell lines were incubated with 4x10^6 E intestinalis spores at 37°C and the cells were examined for intracellular parasitic development after 24, 48, and 72h. In cytokine experiment cells were cultured in the presence of the cytokine(s) for 24 h prior to inoculation of E. intestinalis, and for a further 72h after inoculation in a concentration that was previously found not to damage the cells.

Results: Our results showed E intestinalis was able to establish considerable infection in CMT-93 but, surprisingly, not in the human cell lines. The different stages of intracellular parasitic development were clearly visible in the CMT-93 cell line, making it a suitable in vitro model to study the infection in intestinal epithelium. Our results showed even small concentrations of IFN-α inhibited the development of the parasite by more than 90%. TNF-α and IL-6 also significantly reduced the infection and a combination of both cytokines had significantly higher inhibitory effect than either cytokine alone, suggesting that they have a synergistic effect.

Conclusions: Observations from this study suggest that the CMT-93 cell line is appropriate for use in an in vitro model of E intestina- lis infection. The requirement for IFN-α indicates that a Th1 response is important in control of infection. Additionally, enterocyte derived cytokines TNF-α and IL-6 may have an important role in intes- tinal immunity to infection.

371 RETROSPECTIVE LONGITUDINAL STUDY ON GASTROINTESTINAL MORBIDITY IN VSO VOLUNTEERS WORKING ABROAD

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Introduction: Gastrointestinal illness affecting the short term traveller to the developing world has been well studied, yet little attention has been paid to the long term traveller or temporary expatriate. Voluntary Service Overseas (VSO) volunteers were studied as a representative cohort.

Objectives: To determine the incidence of gastrointestinal illness in a group of VSO volunteers and identification of associated risk factors.

Method: A retrospective analysis was carried out on pre-travel medicals and post-travel health questionnaires of 2230 VSO volunteers, employed on 6 month to 2 year postings abroad, between 1992–1998. Recording of data: Epi Info 6 database. Statistical analysis: SAS.

Results: 56% of volunteers were female. Median age was 28 years (range 19–73). Pre-travel, 4.8% reported a current and 71.9% a past abdominal problem. During travel, 77.6% of volunteers had diarrhoea, with 32% reporting more than 6 attacks during travel. Significant associated risk factors were being female, age > 50 years (odds ratio 2.5; 95% confidence interval 1.2–5.1) and the number of years on posting (odds ratio 1.3; 95% confidence interval 1.2–1.5).
Staphylococcal enterotoxin G and I: A novel cause of severe neonatal enteropathy?

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Introduction: Staphylococcal aureus is well known to produce a variety of toxins (A, B, C1-C3, D, E, G, H, I, l, and TSST1), associated with food poisoning and toxic shock syndrome. Enterotoxins G and I coexist in the same S aureus strains (SEG + SEI) and have been implicated in toxic shock and scarlet fever. We report SEG and SEI as causative agents of intractable diarrhoea with enteropathy in 2 neonates presenting to our unit.

Methods: Case note review and literature search.

Results: Infant 1 had diarrhoea from week 2 of life and was referred at 5 weeks with weight <-2 SD 4.4th centile. Infant 2 was referred at 7 weeks with one month’s history of diarrhoea and failure to thrive, and weight <-2 SD 4.4th centile. Both infants were severely malnourished. Elemental feeds were not tolerated and total parenteral nutrition (TPN) was required. S aureus producing SEG and SEI was isolated in stools in both infants. Intravenous flucloxacillin was commenced and there was marked clinical improvement. Follow up stool cultures were persistently negative. Histology showed subtotal villous atrophy (H and E) with abnormal brush border (PAS). Electron microscopy demonstrated severe destruction of microvilli, dilated mitochondria, and lysosomes with cellular debris. Repeat histology in infant 2, age 3 months, off TPN, showed a return to normal of microvilli architecture and brush border morphology.

Conclusion: Staphylococcal enterotoxin G and I induced enteropathy is a life threatening condition causing disruption of enteral mucosa, which responds well to supportive treatment with parenteral nutrition and flucloxacillin. In any neonate presenting in the first few weeks of life with severe failure to thrive and diarrhoea, S aureus isolation in stools has to be specifically requested and if present, toxin analysis by PCR should be performed.


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Introduction: Bradford has a population of around 480,000, of which 18% originate from the Indian subcontinent (ISC). We describe our experience of abdominal tuberculosis (ATB) over a 10 year period.

Methods: 59 cases of ATB were identified between 1992 to 2002 from the Tuberculosis Registry (TB), Bradford hospitals. 50 case records were available for retrospective review.

Results: Mean age of the patients was 41 years (range 14–81) and 29 (58%) were females. 46 (92%) patients originated from ISC, 3 (6%) were Caucasians, and 1 patient Arabic. Fever (90%), abdominal pain (88%), and weight loss (82%) were the commonest presenting features. Ascites in 22 (44%) and abdominal mass in 11 (22%) were common findings. At presentation, 25 (50%) patients had histology in 11 (22%) cases and 5 (10%) patients had past history of treated TB. Ileocaecal (IC) region in 20 (40%) patients and TB peritonitis in 16 (32%) cases were the commonest sites involved. Liver infiltration and colonic disease each, was seen in 6 (12%) cases and 8 (16%) patients had disseminated miliary TB. Simultaneous pulmonary involvement was present in 27 (54%) patients. Diagnosis of TB was confirmed by isolating acid fast bacilli (AFB) or by demonstrating caseating granulomas on biopsy in 36 (72%) cases. AFB isolated in all the 29 (58%) cases was Mycobacterium hominis and were sensitive to all standard anti-tubercular drugs (ATT) except in 1 case resistant to INH. All patients had ATT, which was well tolerated in 84%. Duration of ATT varied from 6–18 months.

Conclusion: Abdominal TB is a common problem in a multicultural community in the United Kingdom with a variety of presentations. High index of suspicion is required for early diagnosis. Multi drug resistant ATT has not been a significant problem in this series.

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Fatty liver in a female Bangladeshi population: A manifestation of insulin resistance?

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Introduction: Southeast Asians have increased insulin resistance manifest by a high prevalence of type II diabetes mellitus and prema-
ture ischaemic heart disease. Insulin resistance also plays a key role in the pathogenesis and progression of non-alcoholic fatty liver disease (NAFLD); the “two hit” theory proposes that there is accumulation of excessive hepatic fat due to insulin resistance and subsequently oxidative stress owing to reactive oxygen species.

Hypothesis: This background would suggest that Bangladeshi patients are at increased risk of NAFLD and possibly progressive liver disease.

Methods: 23 consecutive female Bangladeshi patients referred to the gastroenterology clinic with non-specific abdominal pain were investigated with abdominal ultrasound and liver echogenicity noted.
Body mass index (BMI) was calculated and risk factors for NAFLD were noted from the medical, alcohol, and drug history. Blood was taken for blood glucose, liver biochemistry, and lipids.

Results: The echogenicity of the liver was increased in 11/23 (48%) patients consistent with fatty liver. The mean age of these patients was 48 (+7) years. Only two of the patients with fatty liver had recognised risk factors (1 patient type II diabetes and 1 patient hypertriglyceridaemia). Three of the patients with fatty liver had a minor increase in serum transaminases (maximum ALT 68 U/l). BMI of the patients with fatty liver was increased (30.1 ± 2.3 kg/m²) compared with those without fatty liver (26.6 ± 3.2 kg/m², p = 0.02).

Conclusions: In this small but unselected series of patients attending a gastroenterology clinic serving a Bangladeshi community, there was a high prevalence of fatty liver on ultrasound. Population figures have estimated a prevalence of fatty liver of only 4–16% in patients without risk factors. The high prevalence of fatty liver in Bangladeshi women may be related to increased BMI but further studies are needed both to determine the natural history and the association with insulin resistance independent of obesity.

Introduction and Aims: Non-alcoholic steatohepatitis (NASH) has been associated with the insulin-resistant states. We aimed to investigate the prevalence of insulin resistant features in patients with both NASH and dyslipidaemia, to characterise changes over time in weight, liver biochemistry, serum lipids, and triglycerides, and to determine the effect of dietary advice.

Methods: Patients with both NASH and dyslipidaemia were identified from the Lipid and Gastroenterology Databases (1996–2001). Alcoholic, viral, autoimmune, or other metabolic diagnoses were excluded. Results: 21 patients were female. Mean age at fist visit was 52.3 years, weight 80.7 kg. BMi 29.03 kg/m². 48% were overweight and a further 40% obese. 67.7% were hypertensive and 30.8% were diabetic, of whom 50% were on diet alone. 20.5% were taking statins, 12.8% fibrates, and 7.7% omega-3 oils. Mean follow up was 583 days (median 400 days). Mean weight decreased from 80.7 to 78.25 kg (p = 0.053), triglycerides from 3.59 to 3.40 mmol/l (p = NS) and the ratio of total cholesterol to HDL decreased from 5.9 to 4.5 (p < 0.02) with a corresponding increase in median HDL from 1.08 to 1.35 mmol/l (p < 0.01). Mean ALT decreased from 57.1 to 55.7 IU/l (p = NS), with weight change significantly associated with ALT change (R² = 0.056, p < 0.04). Patients referred for weight and lipid lowering diets were significantly heavier at baseline (83.3 kg, n = 19, p < 0.01); neither group lost weight, but those referred lost weight significantly more (p < 0.04). Mean follow up was 583 days (median 400 days). Mean weight decreased from 80.7 to 78.25 kg (p = 0.053), triglycerides from 3.59 to 3.40 mmol/l (p = NS) and the ratio of total cholesterol to HDL decreased from 5.9 to 4.5 (p < 0.02) with a corresponding increase in median HDL from 1.08 to 1.35 mmol/l (p < 0.01). Mean ALT decreased from 57.1 to 55.7 IU/l (p = NS), with weight change significantly associated with ALT change (R² = 0.056, p < 0.04). Patients referred for weight and lipid lowering diets were significantly heavier at baseline (83.3 kg, n = 19) than those not referred (77.1 kg, n = 19, p < 0.01); neither group lost weight, but total cholesterol (by 0.31 mmol/l) and serum triglycerides (by 0.36 mmol/l) fell in the advice group only (excluding patients on lipid lowering agents) (p < 0.03).

Conclusions: These patients with both NASH and dyslipidaemia also had a strikingly high prevalence of hypertension, obesity, and diabetes mellitus. Dietary advice produced no overall weight loss in the group but appeared to improve lipid profile. ALT changed in association with weight. Hepatic tolerance of statins was good.

Non-alcoholic fatty liver disease—what is current UK practice?

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Background: Non-alcoholic fatty liver disease (NAFLD) encompasses steatosis and steatohepatitis. The prevalence of NAFLD is increasing but it is unclear how clinicians are managing this condition. This study aimed to establish how NAFLD is diagnosed and managed within the UK.

Methods: A postal questionnaire was sent to 200 members of the BSG. Number of NAFLD cases per month; parameters are used for diagnosis; indications for biopsy; treatment and follow up were requested.

Results: In total 117 questionnaires were returned (58%). 20 were hepatologists (17%), the remainder gastroenterologists. Alcohol (60%) was the commonest reason for outpatient referral, then NAFLD (26%). Hepatologists saw more NAFLD per month than gastroenterologists. Lipids, diabetic status, and body mass index were ranked as helpful in diagnosing NAFLD, but an echobright liver ultrasound was considered more informative. Waist:hip ratio and AST:ALT ratios were rarely used. Hepatologists biopsied significantly more suspected NAFLD than gastroenterologists (p < 0.05). Most gastroenterologists biopsy less than a quarter of suspected NAFLD cases. The strongest indications for biopsy were rising transaminases (53%), with transaminases twice normal the next commonest (29%). Age, AST:ALT ratio, diabetes status, and elevated triglycerides were not seen as indicators for biopsy. Hepatologists review more NAFLD cases yearly in outpatient clinics compared with gastroenterologists (p < 0.05), half of whom never follow up NAFLD cases. All advise weight loss and exercise. No drug therapy was common but statins, metformin, fibrates, and vitamin preparations were commonly used.

Conclusion: NAFLD is common but practice varies. biopsy is not common and therapy infrequent and variable. More evidence is needed before a consensus and guidelines can be formulated.

Frequency of heavy drinking and of liver disease in relatives of heavy drinkers with and without liver disease

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2Introduced by N.P. Thompson.

Background: Only a minority of heavy drinkers develop alcoholic liver disease (ALD): 13.5% in one large epidemiological study. The variable predisposition is thought to have a genetic component but this has not been quantified.

Aim: Comparison of family histories of heavy drinking and of liver disease between heavy drinkers with and without liver disease.

Methods: Questionnaire applied to two groups of heavy drinkers (> 60 U/wk (M) or 40 U/wk (F) for > 5 years), one with uncomplicated ALD (patients: n = 163, 114 M, age 48±50 years) and one with no clinical, laboratory or ultrasound evidence of serious liver disease (controls: n = 121, 92 M, age 49±9 years). We asked subjects to classify the drinking habits of their parents and siblings as abstinent, social, light, moderate or heavy; and also, whether any relatives had liver disease, available details of which were sought. ALD was defined as otherwise unexplained liver disease in a heavy drinker.

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<table>
<thead>
<tr>
<th>RELATIVES</th>
<th>Of Patients</th>
<th>Of Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>683</td>
<td>499</td>
<td>0.7</td>
</tr>
<tr>
<td>Informative</td>
<td>583</td>
<td>457</td>
<td>0.91</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>106 (16%)</td>
<td>84 (18%)</td>
<td>0.51 (0.71-1.03)</td>
</tr>
<tr>
<td>ALD (questionnaire)</td>
<td>13 (12%)</td>
<td>9 (11%)</td>
<td>1.43 (0.60-3.42)</td>
</tr>
<tr>
<td>All ALD</td>
<td>16 (15%)</td>
<td>9 (11%)</td>
<td>1.11 (0.52-2.36)</td>
</tr>
</tbody>
</table>

Includes 3 relatives independently known to have ALD not acknowledged in questionnaire.
* Includes 4 non-drinking relatives with other liver diseases (of patients: 1 "liver cysts"; of controls: 2 cryptogenic cirrhosis 1 primary biliary cirrhosis)".

Results: See Table. ALD expressed as percentage of heavy drinking relatives; all liver disease as % of all informative relatives. Conclusion: Although compatible with a genetic component to predisposition to ALD these data suggest that this component is modest.


Correlations with bone mineral density in male patients with chronic alcoholic liver disease

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Background: Men with alcohol dependence and related liver dysfunction have multiple risk factors for metabolic bone disease. In a
case controlled study we studied the prevalence of osteoporosis and we identified surrogate markers of low bone mass and risk factors for osteoporosis in these patients.

Method: We prospectively assessed 20 consecutive male inpatients with alcohol dependence syndrome who drank in excess of 40 units per week. They all had clinical evidence of cirrhosis (ascites) or deranged liver function tests [e.g. bilirubin, ALT, prothrombin, albumin, platelets, MCV, Chlůd-Pugh grading] and were free from any medication or alcohol for at least 6 months.

Results: Osteoporosis was defined as a T score of ≤-2.5 S.D. below the mean for age and sex-matched controls. T scores were recorded for all of the patients at the lumbar spine (L1-L4), non-dominant wrist, non-dominant elbow and non-dominant knee. Osteoporosis was defined as a T score of ≤-2.5 S.D. below the mean for age and sex-matched controls. Osteoporosis was identified in 11 patients (55%) and 9 patients (45%) had T scores of ≤-2.5 S.D. below the mean for age and sex-matched controls. Osteoporosis was identified in 11 patients (55%) and 9 patients (45%) had T scores of ≤-2.5 S.D. below the mean for age and sex-matched controls.

Conclusion: Osteoporosis is a significant problem in patients with advanced alcoholic liver disease and may be an important factor in the pathogenesis of osteoporosis in this patient group and may be the dominant factor in the aetiology of low bone density in these patients.
DOES uPA ACTIVITY INCREASE AFTER PARTIAL HEPATECTOMY IN HUMANS?

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Introduction: An increase in the activity of the urokinase like plasminogen activator (uPA) has been recorded almost immediately after partial hepatectomy in rats but not confirmed in humans.

Aims: To determine whether changes in uPA activity occur in humans immediately after hepatectomy.

Methods: Samples of liver tissue were taken from the liver before resection was commenced (Sample 1). Further samples were taken from the resected and remnant liver tissue at completion of resection (Samples 2 and 3) and finally just before wound closure (Samples 4 and 5). These were homogenised in MCPBS buffer sucrose containing appropriate proteases inhibitors. uPA activity was determined fluorometrically by the hydrolysis of Z-gly-gly-arg-AMC substrate in washed membrane fractions prepared from the homogenate. Zymography was performed using standard techniques. The surgeon estimated percentage hepatic parenchyma resected.

Results: 18 patients undergoing hepatectomy were studied. Median (range) age was 67.5 (24–78) years. Percentage liver parenchyma resected (median, range) was 35% (10–80%). Mean (SD) uPA activity in the samples were calculated and compared between patients having < 50% hepatectomy (n = 11) with those having > 50% hepatectomy (n = 7) as shown in the table.

Abstract 383

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
<th>Sample 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>10.1</td>
<td>10.3</td>
<td>9.9</td>
<td>10.6</td>
<td>17.1</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>9.1</td>
<td>9.9</td>
<td>8.3</td>
<td>9.4</td>
<td>24.8*</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>10.9</td>
<td>10.7</td>
<td>11.0</td>
<td>11.5</td>
<td>10.9</td>
</tr>
</tbody>
</table>

*p < 0.005 vs sample 1.

Conclusion: Increases in uPA activity occur in the remnant liver in humans after major (>50% or more) hepatectomy and may represent the first stage in the degradation of extracellular matrix as a prelude to regeneration.

MITOGENIC THERAPY ADMINISTERED AFTER THE INDUCTION OF LIVER FAILURE ENHANCES THE PROLIFERATIVE RESPONSE OF HEPATOCYTES WITHIN THE FAILING ORGAN

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Background: We characterised the clinical, biochemical, metabolic, and histological pattern of thioacetamide induced (TAA) hepatic failure in the rat, to create a model of substantial severity (60% mortality), which fulfils the criteria of reproducibility, reversibility, and the provision of a therapeutic window. The animals (n = 20) received two intra-peritoneal injections of TAA 8 hours apart and developed Grade I/11 encephalopathy by 24 hours, followed by grade I11I/V encephalopathy at 48 hours. Overall the mortality over 96 hours was 60%. There was a persistent elevation in serum ALT levels from 24 hours (> 2000 iu/ml cf ≤ 100 iu/ml in normal rats). There was a peak in serum ammonia levels seen at 48 hours (196 ± 33 iu/ml cf 54 ± 9 in normal rats). The histological sections at postmortem showed evidence of cirrhotic hepato- cellular necrosis. Previous studies administered primary mitogens prior to or at the time of necrogenic liver injury and have therefore not provided appropriate models of clinical scenarios.

Aim: To characterise the effects of the primary mitogen, triiodothyronine (T3) on cell proliferation within the liver, when administered following thioacetamide induced liver injury.

Methods: 6 pairs of rats received two intra-peritoneal (IP) injections of thioacetamide (500 mg/kg) 8 hours apart. The first group received a subcutaneous injection of T3 (4 mg/kg) 12 hours after the second thioacetamide injection and the second group received vehicle only. The animals were sacrificed 24 hours after the T3, or vehicle was administered. An IP injection (50 mg/kg) of 5-bromo-2-deoxyuridine (bromdU) was given to all rats one hour prior to sacrifice.

Results: Both groups followed a similar clinical, biochemical course with no difference in ALT between groups at sacrifice (> 2000 iu/ml). H & E staining: there was an equivalent degree of centrilobular necrosis in both groups. Cell proliferation index: the BrdU index was greater in the T3, group at 27 ± 3.5% compared with 20 ± 2.5% in the vehicle only group (t test, p < 0.05). Distribution of BrdU staining: in both groups there was equivalent 6 BrdU staining in the necrotic centrilobular region reflecting BrdU incorporation in the context of both cell proliferation and as part of a DNA repair mechanism. However, there was an increase in the number of BrdU labelled cells in the midzonal region of the liver in the T3 group as compared with the vehicle only group. The liver architecture in the midzonal region was normal and the BrdU incorporation was within an intact nucleus and cell, thus occurring within the context of cell proliferation.

Discussion: A mitogenic dose of thyroid hormone enhances cell proliferation during fulminant hepatic failure in rats. If applicable to humans, primary mitogens that enhance liver cell proliferation might be valuable adjuncts therapeutically.

HEPATIC GRANULOMAS: A 10 YEAR SINGLE CENTRE EXPERIENCE


Introduction: Epithelioid granulomas have been reported in 2–15% of unselected liver biopsies with numerous underlying aetiologies described. However, most series were reported prior to the identification of hepatitis C and the improvement in laboratory markers of other causes of liver dysfunction. This study was performed to evaluate the current aetiologies of hepatic granulomas and in particular to assess the prognosis for the “idiopathic” group in whom no underlying cause was identified.

Methods: A retrospective study of the pathology department records at Glasgow Royal Infirmary was undertaken over the 10 year period 1991–2001. All patients who had a liver biopsy revealing epitheloid granulomas had their case notes reviewed and a standard proforma completed.

Results: Over the 10 year period, of 1662 liver biopsies performed, 63 were identified with hepatic granulomas (4.2% of biopsies). Of those identified, 47 (75%) were female with a mean age of 42 years (range 17–81). Underlying aetiologies were as follows: PBC (23.8%), sarcoidosis (11.1%), idiopathic (11.1%), drug induced (9.5%), HCV (9.5%), PBC/AIH overlap (6.3%), Hodgkin’s disease (6.3%), AIH (4.8%), TB (4.8%), resolving biliary obstruction (3.2%), and other single miscellaneous causes (9.5%). With respect to the 7 patients with idiopathic hepatic granulomas, one was lost to follow up, one died of a stroke, and the remaining 5 were all well with no liver related morbidity at a mean follow up of 6.2 years.

Conclusions: The aetiologies of granulomas on liver biopsy are confirmed to be broad ranging with HCV a significant cause in our population. Despite extensive investigations, there remain a significant minority who have “idiopathic” hepatic granulomas. The prognosis in this latter group appears to be excellent.

INFLAMMATION SIGNIFICANTLY EXACERBATES THE EFFECT OF HYPERAMMONEMIA ON NEUROLOGICAL FUNCTION IN CIRRHOSIS

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Background: The neuropsychological effects of hyperammonemia in cirrhosis is well described. However, the amount of ammonia (NH3) generated bears little relation to the manifest symptoms. It is probable that other factors in addition to hyperammonemia are required to cause the observed mental deterioration. We hypothesise that inflammatory mediators, such as nitric oxide (NO) and proinflammatory cytokines, exacerbate the response to NH3. To test this, we compared patients with cirrhosis during and after recovery from infection.

Methods: 10 patients with cirrhosis of varying aetiology (6 male, mean age 52 [43–61]) were studied within 24 hours of admission for infection, and postantibiotic therapy, mean 9 [7–12] days, afterwards. Hyperammonemia was induced via a simulated upper gastrointestinal bleed by the administration of a haemoglobin mimic,
alpha-1-acid glycoprotein. Blood sampling and a battery of neuropsychological tests were undertaken.

**Results:** The NH₄⁺ generated in response to the simulated bleed did not differ on admission and following antibiotic therapy (p = 0.6). No differences were found in indices of liver function. Inflammatory markers were reduced with resolution of the infection (White cell count (WCC) p < 0.001, C reactive protein (CRP) p < 0.001), as were measured inflammatory mediators (NO, p < 0.001, Interleukin 6 (IL 6) p < 0.001). The deterioration in neuropsychological function brought about by induced hyperammonemia and assessed by digital symbol substitution test, randt memory and choice reaction time were significantly greater when the patients showed evidence of on going inflammation.

**Conclusion:** Our results support a critical role for NH₄⁺ in the pathogenesis of hepatic encephalopathy. We show for the first time that the acute neuropsychological effects of hyperammonemia in cirrhosis may be modulated by the inflammatory state of the patient.

**387** THE GLYCOSYLATION PATTERN OF ALPHA-1-ACID GLYCOPROTEIN (AGP) COULD INDICATE PROGRESSION FROM HEPATITIS TO CIRRHOSIS

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**Aims and Hypothesis:** The acute phase response to injury or infection results in both qualitative and quantitative alterations in the expression of plasma proteins of hepatic origin. Many of these molecules are glycosylated with oligosaccharide chains that become structurally modified in certain diseases. The acute phase glycoprotein, AGP undergoes increased production and altered glycosylation of its five oligosaccharide chains in several physiological and pathological conditions. We hypothesise that subtle alterations in AGP glycosylation could be diagnostic for distinguishing individual liver diseases (LD) specifically hepatitis and its progression from/to other conditions.

**Methods:** The glycosylation of AGP from the plasma of patients with viral hepatitis (VHD), alcoholic liver disease (ALD), primary biliary cirrhosis (PBC), and viral hepatitis was determined by high pH anion exchange chromatography. Lectin (concanavalin A) affinity chromatography was used to analyse the branching pattern of the oligosaccharide chains. Fucosyltransferase (FT) and fucosidase (FD) activities were determined by EUSA.

**Results:** The hepatitis samples were clearly distinguishable from the other LD in terms of branching (con A ratio) and fucosylation of AGP oligosaccharide chains together with the appearance of the unusual monosaccharide N-acetylgalactosamine (GalNAc) on the oligosaccharide chains. Additionally lower than normal levels of fucosidase were detected in the plasma of hepatitis C patients.

**Conclusions:** Variations in AGP glycosylation can be used to detect and distinguish between specific LD particularly hepatitis C and viral hepatitis. The hepatitis C patients showed features of severe cholestasis without accompanying inflammation or bile duct damage. Immunostaining for the canalicular transporter, MRPs2 responsible for biliary secretion of several organic anions including bilirubin glucuronides showed canalicular expression, as seen in the normal liver. There was also aberrant expression of MRPs2 on the basolateral membrane of hepatocytes, a pattern that has not been reported previously.

**Conclusions:** We postulate that intracellular redistribution of MRPs2 may reflect an adaptive, compensatory mechanism that helps in elimination of the drug or its cholestatic metabolites from the hepatocyte back to the sinusoidal space and subsequent excretion in urine. These findings may have implications for elucidating the hepatic response in other cholestatic conditions.

**389** LOW UPTAKE OF TESTING FOR HEREDITARY HAEMOCHROMATOSIS IN FIRST DEGREE RELATIVES OF C282Y HOMOZYGOTES: THE IMPLICATIONS FOR POPULATION SCREENING

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**Background and Aims:** The clinical significance of HFE mutations in hereditary haemochromatosis (HH) remains uncertain. Long term follow up studies of homozygotes identified by genetic screening are not available and the natural history associated with this genotype remains only partially understood. The penetrance of the HFE (C282Y) mutation may be considerably lower than previously thought. For this reason population screening by genotyping is no longer advocated. Screening by phenotype (iron assays) may be feasible. Studies have shown that screening costs are substantially reduced if first degree relatives are identified, but none address the likely uptake of testing. This 4 year follow up study reports on the uptake of testing for HH in first degree relatives of index cases identified by screening 10 500 blood donors (all received verbal and written information offering family testing) and compares uptake after a further proactive approach.

**Methods:** Consenting first degree relatives were interviewed (mainly at home) and counselled by a physician. Blood samples were obtained for transferrin saturation, serum ferritin and HFE genotyping.

**Results:** 56 of 72 index C282Y homozygotes were available for further study. 164 (91%) of available relatives were interviewed. Only 25% had previously been tested for HH. After counselling, 99% elected to have testing. 23 C282Y +/+ were identified. 17 (74%) were previously unaware of the diagnosis.

**Conclusions:** The uptake of testing for HH in these first degree relatives reveals a poor uptake among relatives of cases picked up by population screening, which throws considerable doubt on the overall efficacy of population screening for HH, as currently advocated. By contrast, a focused proactive approach towards the families of index cases yields a greatly increased uptake of testing. Such rates are unlikely to be currently achievable in primary care. The use of centralised resources is recommended, but likely to be time consuming and costly.

**390** DEVELOPMENT OF A NEW NON-INVASIVE SCAN FOR APOTOPSIS IN THE LIVER EMPLOYING POSITRON EMISSION TOMOGRAPHY

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**Aim and Background:** We are developing molecular imaging techniques to study apoptosis (programmed cell death) in vivo directly without the need for biopsy. During apoptosis phosphatidylserine (PS) translocates from the inner to the outer leaflet of the plasma membrane. Annexin V, a protein that binds with high affinity to PS, has been shown to bind specifically to apoptotic cells in vitro and in vivo. We are investigating the use of annexin V, radiolabelled with iodine-124, as a probe for the measurement of apoptosis in vivo using PET.

**Methods:** The probes developed in this investigation were evaluated in an in vitro Jurkat cells were treated with camptothecin (2
Heme oxygenase (HO) is the rate limiting enzyme in the catabolism of heme to biliverdin, iron and carbon monoxide. Two isoforms of HO have been characterised: the constitutive isoform (HO-2), the major isoform present under physiological conditions, and the stress induced isoform (HO-1), which is also known as heat shock protein 32k. In this study 15 liver biopsies from patients with cirrhosis secondary to hepatitis B and C and three biopsies from healthy controls were investigated for the expression of HO-1 and HO-2 protein using a standard immunohistochemical method. In normal liver, HO-1 immunoreactivity was seen in Kupffer cells. In cirrhotic liver, increased HO-1 immunoreactivity was seen in Kupffer cells, the endothelial lining of portal vein and hepatic sinuoids, and to a lesser extent, in hepatocytes. In Kupffer cells, dense perinuclear HO-1 reactivity was seen, whereas in hepatocytes HO-1 reactivity was weak and diffuse throughout the cytoplasm. HO-2 immunoreactivity was seen only in hepatocytes in both control and cirrhotic livers. By comparison with control tissues, HO-1 but not HO-2 reactivity of cirrhotic liver showed increased levels (p < 0.04). This result shows that in human liver cirrhosis, HO-1 expression is increased significantly and is seen preferentially in Kupffer cells. This suggests that Kupffer cells may act as sensory cells that detect the elevation of intrasinusoidal pressure accompanying hyperdynamic states secondary to portal hypertension, implicating an increase in regional wall stress in sinusoids and thereby alter the ability of Kupffer cells to degrade heme through HO-1 induction. Another mechanism by which HO-1 could be upregulated in liver cirrhosis is via nitric oxide, and we have previously shown high expression of NOS in liver cirrhosis. This study suggests a role for HO-1 in the development of cirrhosis in viral hepatitis and points out the need for additional work in this area.

related CLD suffer from impaired HRQOL compared with patients undergoing LT for indications not associated with early disease recurrence.

Methods: A prospective longitudinal study of HRQOL utility measures was performed in patients undergoing LT for CLD. All patients underwent the following utility measurement techniques: feeling thermometer (FT), time-trade off (TTO) and standard gamble (SG). pre-LT, and post-LT. Mean utility scores, where “0” represents death and “1” perfect health, were compared using the student t-test.

Results: The Child-Pugh class (CPC) distribution pre-LT was comparable between the 2 groups. A significant improvement in all three parameters was observed in both groups post-LT compared with pre-LT measures (all p < 0.004) [see Table].

Conclusions: On longitudinal study, patients with CLD undergoing LT experience a dramatic and significant improvement in HRQOL at 1 year, which is comparable in patients undergoing LT for HCV related CLD.

395 A PROSPECTIVE STUDY TO ASSESS RESPONSE TO 3 MONTHS OF COMBINATION TREATMENT IN CHRONIC HEPATITIS C INFECTION


Current recommendations, including NICE guidance, suggest treating genotype 1 hepatitis C with combination treatment for 12 months and genotype II/III for 6 months. However, this prolonged course of treatment has numerous associated disadvantages such as cost and lack of suitably trained staff, and fear of needles. There are two alternatives to venous samples, however, namely a capillary blood sample in the form of a dried blood spot (DBS) or saliva. These can be administered on-site immediately after patient consent has been obtained and have none of the disadvantages associated with standard venepuncture. We have assessed the diagnostic utility of such samples among patients of known HCV status attending hepatology clinics at St George’s. To perform testing we modified the standard protocol of the Ortho third generation EIA and employed an in-house nested HCV RTPCR on DBS samples. A total of 65 patients provided both DBS and saliva samples. All of the 24 HCV antibody negative patients by conventional venous blood testing were antibody negative in DBS and saliva. Of the 41 HCV antibody positive patients, 39/41 (95%) and 25/41 (61%) were antibody positive by dried blood spot and saliva, respectively. Of the two false negative patients on DBS one was only weakly antibody positive with standard methodology, the other had recovered infection. Additionally we tested DBS samples from 24 HCV antibody positive patients by RTPCR; 20/24 (83%) were viraemic, thus establishing chronic infection. This pilot study has shown that dried blood spot samples are easy to administer, have high sensitivity, and specificity and should be offered where venous testing has previously had a poor uptake.

397 THE TREATMENT RESPONSE OF HEPATITIS C INFECTED PATIENTS AND ITS ASSOCIATION WITH MUTATIONS IN THE VIRAL PROTEINS E2 AND NS5A

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Background: Interferon resistance in hepatitis C is a major problem. Double-stranded RNA dependent protein kinase (PKR) is a key mediator of the anti-viral effects of IFN. The viral proteins E2 and NS5A bind to and inhibit PKR function in vitro. Mutations in key regions of E2 (PKR-eIF2 phosphorylation homology domain-PePHD) and NS5A (PKR binding domain, including the “interferon sensitivity determining region”, ISDR) prevent this binding. It is not known whether mutations in PePHD are associated with treatment response and there is conflicting data for ISDR from different geographical areas.

Aim: We wanted to determine whether there was a correlation between the number of mutations in PePHD and the PKR binding domain (including ISDR) and interferon resistance.

Methods: Pre-treatment serum samples from 27 treatment naive patients infected with genotype 3 were analysed by direct sequencing of PePHD and the PKR binding domain. All had received between 3 and 12 months of alpha-interferon at a dose of at least 3 MU 3 times per week. There were 9 sustained responders (SR), 13 transient responders (TR), and 5 non-responders (NR).

Results: For PePHD the mean number of mutations was SR = 0.8 (range 0–2), TR = 0.2 (range 0–1) and NR = 0.2 (range 0–1). There was no significant difference in the frequency of mutations, SR vs NR p = 0.31 and SR vs (TR+NR) p = 0.15. For the PKR binding domain, including ISDR the mean number of mutations was SR = 1.0 (range 0–2), TR = 1.0 (range 0–4), and NR = 0.2 (range 0–2). There was no significant difference in the frequency of mutations, SR vs NR p = 1.0 and SR vs (TR+NR) p = 0.66. There was no significant difference for ISDR alone.

Conclusion: The results are consistent with European studies and differ from Japanese studies. The intrinsically higher frequency of mutant strains in Japanese populations may account for this difference.
alleles on the classical autoimmune haplotype including the TNF promoter polymorphism TNF-308A. This study was designed to examine the association of PSC with 5 other polymorphic sites in the TNF promoter region.

Methods: 100 patients with accurately characterised PSC, and 357 healthy controls were studied. Genotyping of 6 TNF promoter polymorphisms and high resolution class I and class II HLA typing was carried out using PCR-SSP. SNPs within the TNF gene were constructed into gene haplotypes using the statistical computer software, PHASE. Analysis was carried out using a Chi-squared test with a Bonferroni correction factor of 7.

Results: See Table.

Conclusion: PSC is associated with TNF haplotype 2. This contains the variant allele –308A, which has previously been described in association with PSC. This allele is found on the highly conserved autoimmune haplotype A1 B8 DR3. An association between TNF –308A and PSC independent of other alleles on this haplotype was not found. Dissecting out the primary associated allele requires the study of a greater number of informative recombinant haplotypes which can only be achieved by much larger international collaborative studies.

THE NATURAL HISTORY OF LIVER INVOLVEMENT IN PATIENTS WITH PULMONARY SARCOID


Background and Aims: Sarcoidosis is a chronic multi-system disease in which the liver can be affected with or without pulmonary involvement. The severity of liver sarcoid can vary from asymptomatic biochemical changes through to liver failure. Corticosteroids may normalise liver enzymes, but may not reverse histological changes. Guidelines how best to manage liver sarcoid are lacking. We reviewed the prevalence and extent of liver disease in a series of patients with pulmonary sarcoid between 1986–2002.

Patients and Methods: 131 consecutive patients (69M:62F) who fulfilled diagnostic criteria for pulmonary sarcoid. Median age was 37 years. Hepatic involvement was defined as: serum alkaline phosphatase greater than 1.5 the upper limit of normal and GGT more than twice normal for > 3 months.

Results: 41 patients (31%) had liver involvement. Liver involvement was not associated with a greater incidence of hyper-calcaemia (22% vs 21%), neurosarcoid (10% vs 8%), skin sarcoid (39% vs 27%, p > 0.5) or more severe pulmonary disease. 5 patients had alcohol alco- hol and 1 had a high titre ANA antibody detected, but none underwent liver biopsy. Liver biopsy was performed in 2 patients with suspected liver sarcoid, 1 was diagnosed with hepatitis C. In those patients without liver involvement 79/90 (88%) required treatment for their lung disease compared with 39/41 (95%) patients with liver involvement. There was no difference between the age distribution of the 2 groups or immunosuppressants.13 patients with liver sarcoid eventually required either azathioprine (n = 6) or methotrexate (n = 7) for their chest. Liver function subsequently normalised in 5 (methotrexate 3, azathioprine 2). Liver histology was not obtained in any of these patients.

Conclusion: Liver involvement is a common finding in patients with sarcoidosis and is said to signify more severe disease. Our data do not support this but do demonstrate the need for a more complete assessment of liver disease in sarcoidosis and for a multicentre collaborative database to be developed to gather data on these rare patients.

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A SINGLE CENTRE EXPERIENCE OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPSS) INSERTION FOR REFRACTORY ASCITES IN CIRRHOSIS

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Ascites is a common and serious complication of cirrhosis with a 2 year mortality of approximately 50%. The treatment options are limited with only 2 RCTs comparing TIPSS to paracentesis. As a tertiary referral centre we have performed over 350 TIPSS procedures and have audited TIPSS insertion for refractory ascites.

Methods: 563 TIPSS were performed between July 1991 and June 2002. The primary indication for 61 of these was refractory ascites and complete follow up was available in 35 cases. These patients were assessed at 3, 6 months and at 1 year. Survival was calculated using Kaplan Meier analysis on all 61 patients. Absence of response was defined as the persistence of ascites requiring paracentesis.

Results: Of the 35 patients 20 had alcoholic liver disease, 7 viral hepatitis, 2 PBC, and 6 other aetiologies. Mean age at insertion was 55.9±11 years. 57.6% were Childs C and 42.4% were Childs B. TIPSS was successfully positioned in 32 of the 35 patients. Response rates were 36% at 3 months and 37% at 6 months (these percentages do not include patients who did not attend follow up but do include deaths). The estimated probability of survival without transplantation was 46.1% at 1 year. Of the 6 patients with encephalopathy prior to the procedure 3 (50%) developed worsening of their condition and 7 (27%) of the remaining patients developed encephalopathy.

Conclusion: Response rates in our experience are relatively poor in comparison with other studies, however, mortality and post procedural encephalopathy rates are similar. Refractory ascites is associated with a poor prognosis in most patients and TIPSS helps in a minority. Better selection criteria are needed to select those who will benefit.

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TRENDS IN MORTALITY FROM LIVER DISEASE IN WALES

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Aims: To assess changes in mortality from liver disease across the Principality of Wales over the past decade, and to relate these changes to published figures on alcohol consumption by region.

Methods: Deaths from liver disease were identified from public health mortality files supplied by the Office for National Statistics, searching ICD9 reference codes 570–573 for regions throughout Wales between 1991–2000. Population data for the corresponding regions during this time period were also provided. Data on alcohol consumption by region were obtained from the Welsh Health Survey (1995 and 1998). Data are presented for the quinquennia, 1991–5 and 1996–2000.

Results: In all regions mortality from liver disease has increased in the second quinquennium (see Table). There is a significant correlation between liver mortality rates and published data on the proportion of the respective populations consuming alcohol above recommended levels (Spearman’s test, r = 0.484, p = 0.022).

Conclusions: All regions of Wales have seen a modest increase in mortality from liver disease over the past 5 years—not to the extent of that reported from the West Midlands (threelfold increase). Increased mortality rates were seen in areas of high alcohol consumption. Anecdotally alcoholic liver disease remains the major cause of death from liver disease in Wales, the contribution of genetic and racial background and chronic HCV infection require further examination.

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Abstract 398

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IS PHYSICAL ACTIVITY PROTECTIVE AGAINST GALLSTONES—A PROSPECTIVE COHORT STUDY

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Background: The aetiology of gall stones is unknown, although it is plausible that increased physical activity may protect against stone formation by reducing bile stasis. No prospective studies have investigated this hypothesis using a physical activity questionnaire which has been validated against physiological measurements.

Methods: 25233 men and women aged 45–79 years were recruited into EPIC-Norfolk (European Prospective Investigation Into Cancer). Participants completed a short questionnaire at recruitment assessing their fitness, assessed by sub-maximal oxygen uptake. Based on their responses to the questionnaire, subjects’ physical activity was classed into one of four categories, namely: inactive, moderately inactive, moderately active, or active. Participants were followed up for the development of symptomatic gall stones. Each case was matched with four controls for age and sex.

Results: 175 persons (67% women) developed symptomatic gall stones at a median age of 65.8 years. Increased physical activity was inversely associated with the development of symptomatic stones in a linear manner across the four categories of physical activity (OR across categories = 0.78, 95% CI = 0.66 to 0.92, p = 0.003). The odds ratio for an active vs inactive level of physical activity was 0.38 (95% CI = 0.21 to 0.71). The trends of the protective effect of physical activity were similar in both men and women when they were adjusted for possible confounding factors, including BMI, alcohol, parity, and HRT.

Conclusions: Increased physical activity was associated with a decreased risk of gall stones. Encouraging the inactive and moderately inactive groups to participate in between half to one hour of recreational activity per day might potentially reduce the number of cholelithectomies in this group by 23%.


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Background: The frequency of admissions and operations for gall stones increased in Western countries from the 1950s to the early 1990s. Since 1990, ERCP and laparoscopic cholecystectomy have been increasingly used, and recent trends of frequency of admission to hospital and in-hospital case fatality for cholelithiasis in England 1989/1990–1999/2000, and to determine population mortality rates for the period 1979–1999.


Methods: Hospital Episode Statistics for admissions were obtained from the Department of Health and mortality data from the Office for National Statistics. Age standardised hospital admission rates (ASAR) were calculated using the European standard population. For operation rates, the age distribution of hospital admissions for cholelithiasis was used as the standard population.

Results: See Table.

Conclusion: There has been a steady increase in admission rates for cholelithiasis. Male rates increased by 30.3%, female rates by 64.3%. Female age specific admission rates were generally higher than those for males until age 75, after which rates were similar in men and women. While the frequency of operations among patients admitted with gallstone disease declined, the proportion of patients undergoing ERCP increased. During the same period, there has also been a decline in the in-hospital case fatality rate and the population mortality rates. Cholelithiasis continues to be an important part of the workload of both the medical and surgical gastroenterologist.

ENDOSCOPY POSTERS 404–430

A PROSPECTIVE AUDIT OF FAST TRACK NURSE LED EVALUATION OF THE GASTROINTESTINAL TRACT IN PATIENTS WITH IRON DEFICIENCY ANAEMIA

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Introduction: Iron deficiency anaemia (IDA) is often not appropriately investigated. Incomplete work up and unacceptable delay in its investigation may lead to poor outcome.

Methods: General practitioners and consultants were offered a nurse led, fast track service for gastrointestinal investigation of IDA. The nurse specialist completed a proforma based on a telephone call and/or a clinic consultation. IDA was defined as haemoglobin < 13 gm/dl for men and < 12 gm/dl for women, with at least one of the following: ferritin < 20 ug/l; MCV < 76fl; transferrin saturation index <10%. In asymptomatic patients aged over 45, the initial investigation was colonoscopy. Oesophagogastroduodenoscopy (OGD) was the first investigation in younger subjects. In symptomatic patients, the nature of symptoms determined the sequence of investigation. If the initial endoscopic investigation failed to reveal an acceptable cause of IDA (cancer, coeliac disease, and inflammatory bowel disease), the patient went on to have endoscopy of the other end of the digestive tract.

Results: 90 patients were referred during first 9 months. 72 were eligible for analysis (inappropriate referral = 9, defaults = 9). 67 had investigations as per protocol and 5 attended for part of the investigative process. The median age was 68 years (range 22 to 91). There were 22 men and 40 women. 47 patients had colonoscopy as first investigation, 1 had barium enema. 38 of 40 without serious colonic disease then had OGD. 24 had OGD first. 19 of 23 without serious upper GI disease then had colonoscopy. The median interval from initial referral was 6 weeks to the first endoscopic procedure and 9 weeks to the end of the diagnostic process. 21 patients had 22 serious pathologies (colorectal cancer = 8, upper GI cancer = 4, advanced colonic adenoma = 4, coeliac disease = 3, IBD = 2, caecal ulcer = 1). 12 had 13 less serious diagnoses (oesophagitis = 5, oesophageal stricture = 2, Barrett’s metaplasia = 2, small colon adenomas = 2, solitary rectal ulcer = 1, gastric ulcer = 1). 3 had dual pathology.

Conclusion: Over 29% of patients with IDA had serious and a further 17% had less serious but still significant gastrointestinal pathology. Introduction of a nurse led direct access diagnostic service has led to rapid processing of these patients and may result in a better outcome.

Gut: first published as 10.1136/gut.52.suppl_1.a1 on 1 April 2003. Downloaded from http://gut.bmj.com/ on November 14, 2021 by guest. Protected by copyright.
ARGON PLASMA COAGULATION AND ADRENALINE INJECTION FOLLOWED BY INTRAVENOUS PANTOPROZOLE INFUSION FOR ACUTE BLEEDING PEPTIC ULCER DISEASE—A PRELIMINARY STUDY

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(introduced by D.P. Jewell). Departments of Gastroenterology, Repatriation General Hospital and Flinders Medical Centre, Adelaide, South Australia

Dual therapy with injection and thermal treatment is regarded as gold standard management of high risk bleeding PUD. Recent work has suggested that high dose IV omeprazole can further reduce rebleeding rate. Argon plasma coagulation (APC) has been suggested as modality for applying thermal treatment. Prior to 2001, due to a lack of a heater probe, high risk PUD were managed at FMC and RGH via adrenaline injection alone.

Aim: To examine the safety and efficacy of combination treatment with adrenaline injection, argon plasma coagulation (thermal modality), and 48 hours of high dose pantoprazole.

Methods: 33 patients enrolled over 15 months were given quadruple injections of adrenaline and APC applied to the visible vessel followed by IV pantoprazole for 48 hours. Rebleeding, mortality, and surgery rates, transfusion requirements, and length of stay were compared with 33 patients who were treated prior to this trial with adrenaline alone.

Results: No complications occurred from the APC. Rebleeding rates were significantly decreased in the combination group (4/3 –12.1% vs 9/33–27.3%, p = 0.025). Transfusion requirements was not significantly reduced but there was a trend for reduction of length (10 to 6 days) of hospital stay.

Conclusions: Combination treatment with adrenaline and APC and IV pantoprazole infusion is safe. The results are sufficiently encouraging to warrant a larger trial.

COLONOSCOPY IS SAFE WITH HIGH PROCEDURAL SUCCESS RATE AND DIAGNOSTIC YIELD IN PATIENTS AGED 80 YEARS AND OVER

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Introduction: Clinicians are reluctant to refer elderly patients for colonoscopy because of a perception of significant risk of complications and procedural failure in this age group.

Methods: Data were collected prospectively over a 2 year period on indications, sedation, crude and adjusted total colonoscopy rates (CTCR and ATCR), ileoscopy rate (IR), anus to caecum time (ACT), and complications and procedural failure in this age group.

Results: Of 329 traceable patients, 276 questionnaires were returned (84%). Median responder age was 55 (range 26–84, 59% male). Median number of previous colonoscopies was 6 (range 1–15, total 1777), 75% were not frightened at the prospect of colonoscopy. 60% described their most recent colonoscopy as comfortable or very comfortable. Median dose of midazolam was 1.25 mg, and pethidine 25 mg. 38 patients (14%) chose to have no sedation. 81% felt their medication dose was about right, 16% too little and 4% too much. 85% felt fully awake or slightly drowsy during the procedure. 81% had no change in colitic symptoms following colonoscopy, 12% felt their colitis had improved, whereas 7% felt it had worsened. 17% experienced some pain attributable to colonoscopy in the week following the procedure. In 4% the pain was significant enough to disrupt everyday activities. 4 patients had previously experienced rectal bleeding following a colonoscopy (2 needing repeat colonoscopy), equating to a post-colonoscopic bleed rate of 0.23%. There were no perforations and no patient required surgery.

Conclusion: Colonoscopy rarely worsens colitic symptoms. A conscious sedation policy is well tolerated. Most patients do not find the procedure uncomfortable. Post-colonoscopy, 4% experienced abdominal pain significant enough to interfere with everyday activities. Complications following surveillance colonoscopy were rare. The bleeding rate was 0.23%, the perforation rate was 0% and no patients required surgery.

SYNERGISTIC USE OF ARGON PLASMA COAGULATION (APC) AND SELF-EXPANDING METALLIC STENTS (SEMS) FOR THE PALLIATION OF MALIGNANT DYSPHAGIA

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Introduction: Malignancies of the oesophagus or cardia are usually inoperable at presentation and the resulting dysphagia often requires endoscopic palliation.

Aims: We describe a single centre experience in the synergistic use of APC and SEMS for the palliation of malignant dysphagia.

Patients and Methods: Between Jan 2000 and Sept 2002, 51 consecutive patients with inoperable malignant dysphagia (31 adenocarcinoma, 19 squamous, 1 small cell) were referred for palliation.

Dependent on patient frailty and tumour characteristics, patients either had SEMS insertion (group 1: frail patient, long/schirrous tumour) or were entered into an APC programme (group 2: less frail, short/exophytic tumour) in a non-randomised fashion. In group 1, Fla- minga stents or Oesophageal Wallstents II (Boston Scientific) were used. In group 2, APC (70W, Erbe) was repeated every 2–6 weeks.

Results: Group 1: N = 19 (12M:7F, mean age 75.7 year). All patients were stented successfully. Improvement in dysphagia occurred in 88% (mean reduction of dysphagia score = 1.5). Complications: bleeding 1, perforation 0, death 0. One patient developed dysphagia due to tumour overgrowth requiring secondary APC. Group 2: N = 32 (16M:16F, mean age 82.2 year). 20/32 were successfully palliated with repeated APC sessions (mean reduction of dysphagia score = 1.5, mean number of sessions per patient = 2.4, range 1–5). The remaining 12 either became too frail to continue with APC or dysphagia progressed despite APC— in these patients, SEMS
were inserted after 1–4 sessions of APC. In 2/12 stented patients, tumour overgrowth occurred requiring further APC. There was no complication from APC. Overall, 45/51 have died (overall survival: mean 161 days, median 111, range 6–977; survival not significantly different in the two groups (p = 0.1)).

**Conclusion:** With careful patient selection, APC and SEMS can be used in co-operation to provide effective palliation of malignant dysphagia.

### Abstract 410 Table 1

<table>
<thead>
<tr>
<th>Procedure name</th>
<th>Number undergoing procedure</th>
<th>Number taking herbal products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>167</td>
<td>20 (12%)</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy (FS)</td>
<td>106</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>OGD</td>
<td>48</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>OGD plus FS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>OGD plus Colonoscopy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ERCP</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>326</td>
<td>26 (8%)</td>
</tr>
</tbody>
</table>

This study confirms the regular use of herbal products (notably St Johns Wort), in this group, which should be part of the patient’s documented history and management plan prior to sedation and invasive endoscopy.

### Abstract 411

**Endoscopist** | **A** | **B** | **C** | **D** | **Mean**
--- | --- | --- | --- | --- | ---
**Sensitivity** | 95 | 100 | 95 | 80 | 92.5
**Specificity** | 87.7 | 63.9 | 91.6 | 97.4 | 85.1

**Conclusion:** Zoom endoscopy is likely to be an effective method for detecting coeliac disease. These figures show that even with minimal training, and under adverse conditions (ie single image), recognition of villous atrophy on zoom endoscopy is an easily transferrable skill. A large scale study is under way to assess the efficacy of zoom endoscopy in screening for coeliac disease in patients attending for direct access endoscopy.

### Abstract 412

**Objectives:** To determine the impact of increasing the age cut off for endoscopy in uncomplicated dyspepsia from 45 to 55 years of age; would we miss early upper GI cancer?

**Background:** BSG guidelines [1996] suggest open access endoscopy for all patients with uncomplicated dyspepsia above the age of 45 and for younger patients with alarm symptoms. The incidence of upper GI cancer increases dramatically with age—information from
the Welsh Cancer Intelligence Surveillance Unit for the year 2000 shows 51 out of 453 oesophageal cancers were under 55 (11%), for gastric cancer the figure is just 5% (31 of 610). To try and reduce the pressure on the open access service, it has recently been suggested that we can safely increase the age to 55 (BSG web site April 2002).

Methods: All patients who received a gastroscopy and had a diagnosis of upper GI malignancy were included from the endoscopy and pathology records of Llandough hospital, over five years (April 1997 to April 2002); presenting symptom and outcome were determined.

Results: Of 1145 gastroscopies were performed and a total of 228 upper GI malignancies were detected: 199 oesophageal, 109 gastric. Twenty-five patients (14 oesophageal, 11 gastric) were under 55 years old (11% of total cancers); two of these were less than 45 years. Most presented with alarm symptoms (22 / 25 – 88%), including both < 45 years. Of the remaining three patients, two men aged 54 had abdominal pain only but advanced oesophageal or gastric cancer. The other man, aged 52, had no upper GI symptoms but was found incidentally to have early gastric cancer while being investigated for possible coeliac disease.

Conclusions: Upper GI malignancy is uncommon under the age of 55. Most of these young patients present with alarm symptoms. Our data also suggest that it is safe to increase the age for the investigation of uncomplicated dyspepsia from 45 to 55 years; it would not miss any curable malignancy in this age group.

413 UPPER GI TRACT DISEASE IN FAECAL OCCULT BLOOD POSITIVE, COLONOSCOPY NEGATIVE PATIENTS


Introduction: The presence of occult blood in the faeces is generally assumed to indicate lower GI tract pathology. It is not clear what is the best management of patients who are faecal occult blood (FOB) positive but have no abnormality detected at colonoscopy. Some studies have suggested that these ‘FOB-positive, colonoscopy-negative’ patients should all undergo endoscopy, as a significant number will have pathology in the upper GI tract. The aim of this study was to determine the prevalence of upper GI tract disease in FOB positive patients undergoing colonoscopy.

Methods: A retrospective audit was performed of all patients who underwent a complete colonoscopy and endoscopy on the same day between January 2000 and December 2001. Patients were identified from the endoscopy record books and data were collected from the retrieved case notes.

Results: Of the 292 patients who underwent both colonoscopy and endoscopy, 139 had a positive FOB recorded. Forty of these patients were excluded from further analysis [28 patients had an incomplete colonoscopy and 12 patients had either acute GI bleeding or known GI tract pathology]. Of the remaining 99 patients, 56 were females and the mean age was 60 years (range 18-83 years). Fifty-three of the 99 patients comprised the negative colonoscopy group. Significant upper GI tract disease was noted in 27 (39%) of the colonoscopy negative group compared to 9 of the 30 (30%) colonoscopy positive group (p<0.5). Within the colonoscopy negative group, neither the presence of anaemia or dyspeptic symptoms predicted positive upper GI tract disease.

Conclusions: A high proportion of FOB positive patients have upper GI tract disease; however, the prevalence of such findings is similar in colonoscopy negative and colonoscopy positive patients. The performance of an endoscopy in FOB positive patients should not be dependent on the presence or absence of lower GI tract disease.

414 THE RELATIVE WORKLOADS OF UK ENDOSCOPY UNITS

A. Douglas1, M.G. Bramble1, J.G. Barrison1. 'James Cook University Hospital Middlesbrough, 2St Albans City Hospital, St Albans, UK

Introduction: The BSG working party report 2001 serves as a guide to the facilities and workload that trusts are expected to provide and serves as a benchmark to enable units to plan service and equipment improvements in order to sustain an increasing demand for GI services.

Aims and Objectives: To ascertain the workload intensities of JAG registered units in the UK.

Methods: All endoscopy units registered with JAG were asked to complete a questionnaire detailing the level of endoscopy activity, endoscopy staffing, and unit size. Units that did not reply were sent two further reminders. Number of endoscopy rooms was used as a surrogate marker of unit size. The results of the 150 (76.5%) units that responded are presented.

Results: There were 19, 90, 27, and 14 units with 1, 2, 3 and 4+ endoscopy rooms, respectively. The workload for upper GI endoscopy (per 1000 population, per year) can be seen in Table 1.

<table>
<thead>
<tr>
<th>Unit Size</th>
<th>OGD</th>
<th>Colon</th>
<th>FS</th>
<th>ERCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1777.3</td>
<td>506.1</td>
<td>429.9</td>
<td>137.7</td>
</tr>
<tr>
<td>2</td>
<td>1375.4*</td>
<td>431.6</td>
<td>444.1</td>
<td>103.5</td>
</tr>
<tr>
<td>3</td>
<td>1182.3*</td>
<td>448.2**</td>
<td>291.1</td>
<td>111.8**</td>
</tr>
<tr>
<td>4</td>
<td>1031.0*</td>
<td>355.9**</td>
<td>282.8</td>
<td>92.7*</td>
</tr>
</tbody>
</table>

*p < 0.005 w.r.t. 1 endoscopy room. **p = 0.07.

Abstract 414 Table 1

Abstract 414 Table 2

<table>
<thead>
<tr>
<th>Unit Size</th>
<th>OGD</th>
<th>Colon</th>
<th>FS</th>
<th>ERCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.8</td>
<td>2.4</td>
<td>2.7</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>10.4</td>
<td>3.9¶</td>
<td>3.7</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>11.1</td>
<td>3.9¶</td>
<td>2.7</td>
<td>1.0¶</td>
</tr>
<tr>
<td>4</td>
<td>12.2</td>
<td>4.1¶</td>
<td>3.3¶</td>
<td>1.1¶</td>
</tr>
</tbody>
</table>

¶p<0.05 for single room vs 4+ rooms centres.

Smaller units performed significantly more procedures per room, per year, as outlined in Table 2.

Conclusions: Units were working at intensities comparable to those estimated in the BSG report. Larger units perform more sigmoidoscopies and ERCP per population. Smaller units have rooms that perform a greater number of procedures. This intensity of work may impinge on teaching time without adequate safeguards.

415 IMPACT OF OPEN ACCESS ENDOSCOPY ON STAGE OF UPPER GI CANCER: A DISTRICT GENERAL HOSPITAL EXPERIENCE 1994–2001

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Aim: To assess the impact of an open access endoscopy service on stage of oesophageal and gastric malignancy 1994–2001.

Methods: BSG guidelines were issued to GPs at the start of the study and a further dyspepsia guideline package re-issued in 1998. Data were retrieved from a prospectively collected registry of upper GI cancers and correlated with a prospectively compiled endoscopy database. Patients diagnosed in 1994–1997 were compared with those diagnosed in 1998–2001 with regard to presenting symptoms and stage of disease.

Abstract 415

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not staged</td>
<td>28 (20%)</td>
<td>25 (15%)</td>
</tr>
<tr>
<td>Stage I</td>
<td>10 (7%)</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>20 (14%)</td>
<td>39 (22%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>42 (30%)</td>
<td>48 (28%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>40 (29%)</td>
<td>47 (27%)</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>172</td>
</tr>
</tbody>
</table>

Results: There were 140 upper GI cancers in the period 1994–97 (median age 71) and 172 in 1998–2001 (median age 73). Site of tumour and mode of referral were similar in each time period. There was a small increase in patients with benign symptoms in the second period (12.8% vs 19.9%) associated with a similar increase in stage II disease (see Table) though these did not reach statistical
significance. There was a lower rate of resection in the second period (35% vs 28%) and no difference in stage of disease in those patients undergoing resection.

**Conclusions:** Despite a steady increase in open access endoscopy (3037 examinations in 1994–97 and 5383 in 1998–2001), we found no evidence for detection of upper GI cancer at an earlier stage in this series.

### 416 DIAGNOSTIC YIELD OF COLONOSCOPY FOLLOWING FLEXIBLE SIGMOIDOSCOPY IN PATIENTS REFERRED TO RECTAL BLEEDING CLINIC

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**Introduction:** Patients referred to the rectal bleeding clinic (RBC) for open access flexible sigmoidoscopy (FS) may require further investigations.

**Aims:** To look at the diagnostic yield of colonoscopy following FS.

**Results:** Between 1/12/99 to 30/11/2001, 318 patients attending the RBC had further investigations requested (268 colonoscopies, 44 barium studies, 5 repeat F/S, 1 abdominal USS). Of the 268 colonoscopies requested 211 were performed. In those patients who had colonoscopy the indications for the FS referral were: rectal bleeding (n = 168), altered bowel habits (n = 36), abdominal pain (n = 7). The indications for performing colonoscopy in these patients were: further evaluation of rectal bleeding (n = 41), change in bowel habit (n = 64), abdominal pain (n = 9), polyps on FS (n = 84), weight loss (n = 2), colorectal cancer found at FS (n = 2), inflammatory bowel disease found at FS (n = 8) and anaemia (n = 1). Additional findings at colonoscopy were divided into those that were within the limits of the previous FS examination as stated on the FS report, and those beyond the reach of the previous examination, ie if the FS report stated that the instrument had been passed to the descending colon then a lesion found subsequently in the sigmoid at colonoscopy would be counted as a "left-sided lesion".

**Conclusions:** A substantial number of patients attending for open access FS warranted full colonoscopy as the initial investigation of choice, suggesting a need to improve the screening of referrals. The diagnostic yield of additional significant lesions found at colonoscopy was high. However, almost all of these lesions were found within the reach of FS.

### 417 A REVIEW OF HOW WELL ENDOSCOPY UNITS ARE EQUIPPED

A. Douglass1, M.G. Bramble1, I.G. Barrison1. James Cook University Hospital Middlesbrough; St Albans City Hospital, St Albans, UK

**Introduction:** The National Audit of Emergency Endoscopy Provision (NAEEP) (1994–1997 and 1998–2001) commented that many endoscopy units were under-equipped, and there was a need to utilise open access flexible sigmoidoscopy (FS) in these centres. We aimed to assess the present level of provision of endoscopy services in JAG training units from the first phase of the NAEEP.

**Methods:** The BSG working party report of 2001 was used to construct a questionnaire about the provision of endoscopic equipment/services each unit is required.

**Results:** Of 196 JAG units, 150 (76.5%) units returned a completed questionnaire. The majority of units (85%) owned their scopes less than 10 years. Of the equipment provided, there was at least one Achalasia balloon (67% units had more than one) and 91% units had oesophageal dilators (39% Bougie and 70% celesten/savary-millar type). 83% units had a mechanical lithotriptor. Diagnostics: the availability of radiological modalities was: therapeutic USS – 97%, Spiral CT – 89%, MRI – 79%, Radiolabelled WCC scan 68%, SeChat scanning 48%. 56% had pH testing and 48% had manometric facilities. Meetings: meeting did not take place at least a monthly in 14% centres for x ray/pathology, 27% for audit and 65% for evidence based practice.

**Conclusions:** Most units have adequate levels of endoscopic equipment but many at least one endoscope short of recommended levels. The majority of units have good radiological support but only half offer manometry. Training units must also address the lack of joint x ray and pathology meetings reported by 1 in 7 units.

### 418 THE ROLE OF NURSE ENDOSCOPIST IN THE UK: A NATIONAL AUDIT

A. Douglass1, M.G. Bramble1, I.G. Barrison1. James Cook University Hospital Middlesbrough; St Albans City Hospital, St Albans, UK

**Introduction:** The increasing demand for all endoscopic procedures means that a consultant based service is impossible. Many units have looked to the "nurse endoscopist" (NE) to potentially ease this problem.

**Aims and Objectives:** To determine the prevalence of NE in JAG registered training units, to assess their workload and additional clinical commitments.

**Methods:** All JAG registered units in 2001 were circulated a questionnaire regarding the role of their nurse practitioners, as defined in the BSG working party document 2001. Units failing to respond were sent further reminders in early 2002. 196 units were contacted; the results of the 150 (76.5%) respondents are presented.

**Results:** 64% of units employed nurse endoscopists and performed gastroscopies (OGD) in 43.2% of units (5.3% had > 1 upper GI NE) flexible sigmoidoscopies (FS) in 62.1% and colonoscopies in 11.6% of centres (14.7% had > 1 lower GI NE). Of those that did no, 66.7% had been in post for less than 1 year. The average duration in post for all NE was 19.6 ± 2.0 months. Nurse endoscopist performed a mean of 15.3 ± 1.5 OGDs, 12.4 ± 1.0 FSs and 5.6 ± 1.7 colonoscopies per week. The number of dedicated sessions was 2.56 ± 0.2. 23.9% of Upper GI NE were experienced in PEG tube placement. Centres who employed NE, listed their additional duties in 81% of respondents: colorectal nurse specialist 21%, managerial 18%, multiple duties, 36%, general clinics 15%, MDT and patient care pathways 12.6%, manometry and "normal" nursing duties both in 6%, and miscellaneous, 21%.

**Conclusions:** Nurse endoscopists are becoming an integral part of the endoscopy workforce and the vast majority have their own dedicated lists as well as other roles. Units without a NE will need to consider whether they sustain this policy and still have time to train SPRs.

### 419 A NATIONAL AUDIT OF EMERGENCY ENDOSCOPY PRACTICES WITHIN JAG REGISTERED UNITS

A. Douglass1, M.G. Bramble1, I.G. Barrison1. James Cook University Hospital Middlesbrough; St Albans City Hospital, St Albans, UK

**Introduction:** Upper gastrointestinal bleeding (UGIB) carries a significant mortality. Emergency endoscopy, with the potential for therapeutic gain should be available in all large hospitals for such patients. Staff and facilities are important aspects in the management of GI haemorrhage but there is no national data on how such services are planned and funded. Clinical governance should ensure that all hospital admitting patients with GI bleeding have adequate systems in place to offer an effective emergency endoscopy service.

**Aims and Objectives:** To assess nationally the current level of emergency endoscopy provision in JAG registered training units.

**Methods:** An audit based on the BSG working party report (2001) on the provision of emergency related procedures, was distributed to all JAG registered units between 2001 and 2002. Data were entered into a standard statistical package for analysis.

**Results:** 150 (76.5%) units returned a completed questionnaire. 111 units performed an average of 91.2 ± 8.1 per 1000 population emergency endoscopies per year. 29.6% were performed out of
421 BOWEL PREPARATION FOR INPATIENT COLONOSCOPY

J.C. Brooker, H. Francis, P.D. Fairclough. Endoscopy Unit, Barts and the London NHS Trust, Royal London Hospital, London, E1 1BB, UK

Introduction: Good quality bowel preparation is a prerequisite for accurate colonoscopy. We perceived bowel preparation to be less effective in hospital inpatients (i-p), and tested whether more effective communication with ward staff would lead to better compliance and a cleaner colon.

Methods: Compliance with pre-colonoscopy instructions was surveyed in consecutive i-p and out-patients (o-p). Exclusions were: combined OGD/colonoscopy, acromegaly, and inability to complete the questionnaire. Preparation was: day 1, restricted diet; day 2, clear liquids, 5 mg bisacodyl and Picolax (2); day 3, colonoscopy. Endoscopists scored preparation quality on visual analogue scales (perfect = 100, no prep = 0), blinded to a separately administered questionnaire assessing compliance. In phase 1, preparation instructions were telephoned to the ward 2 days before the scheduled procedure. In phase 2, additional printed instructions were stuck prominently in both the medical and nursing notes.

Results: See Table.

Conclusions: Compliance and preparation were better in o-p than in i-p. Extra written instructions failed to improve compliance or bowel preparation in i-p. Improved compliance as well as a more effective preparation regime may be needed to improve bowel preparation in hospital i-p, who tend to be older and generally less mobile.

<p>| Abstract 421 |</p>
<table>
<thead>
<tr>
<th>In-patients n=100</th>
<th>Out-patients n=184</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (sd)</td>
<td>67.0 (16.0)</td>
<td>54.0 (15.8)</td>
</tr>
<tr>
<td>Ambulant</td>
<td>41/68</td>
<td>18/32</td>
</tr>
<tr>
<td>Compliance:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>51/93</td>
<td>173/184</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>43/76</td>
<td>177/184</td>
</tr>
<tr>
<td>Picolax</td>
<td>76/78</td>
<td>176/184</td>
</tr>
<tr>
<td>Preparation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score left colon</td>
<td>53 (35)</td>
<td>68 (28)</td>
</tr>
<tr>
<td>Mean score right colon</td>
<td>50 (35)</td>
<td>62 (30)</td>
</tr>
</tbody>
</table>

420 VALIDITY AND RELIABILITY OF A VIRTUAL REALITY UPPER GASTROINTESTINAL (GI) SIMULATOR

K. Moorthy, Y. Munz, M. Jiwanji, S. Bann, A. Darzi (T. Orchard). Department of Surgical Oncology and Technology, 10th Floor, QEQM Building, St Mary's Hospital, Praed Street, London, W2 1NY

Background: This study aims to establish the validity and reliability of an upper GI simulator as a tool for the assessment of endoscopic skills.

Methods: Subjects with varying levels of experience undertook 4 cases on the upper GI simulator. Data on the time taken for the procedure, percentage of mucosa and pathologies visualised and the number of inappropriate retroflexions were retrieved from the simulator’s database. We calculated the efficiency of performance as the percentage of mucosa visualised divided by the total time taken for the procedure. We analysed the data for all 4 cases to calculate the reliability of the simulator’s assessment. Statistical analysis was done using non-parametric tests and Cronbach’s alpha coefficient for reliability.

Results: There were 11 novices (group 1), 11 trainees with intermediate experience (10–50 procedures, group 2) and 10 experienced endoscopists (≥ 200 procedures, group 3). There was a significant difference in the total time taken to perform the procedure (p < 0.001), percentage of mucosa visualised (p < 0.001), efficiency of performance (p < 0.001), percentage of pathologies visualised (p = 0.002) and the number of inappropriate retroflexions (p = 0.016) across the groups. Inter-group analyses were significant between groups 1 and 3 for all parameters and in between 2 and 3 for four of the parameters. There was a significant difference in the percentage of mucosa visualised between groups 1 and 2. The reliability of performance assessment was 0.90 for time taken, 0.89 for mucosa visualised, 0.86 for efficiency and 0.80 for pathologies visualised.

Conclusion: This study has established the construct validity and the reliability of the simulator which can strongly discriminate between groups with varying experience.

422 CLINICAL EFFECTIVENESS OF IV OMEPRAZOLE IN ENDOSCOPICALLY TREATED PEPTIC ULCERS

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Introduction: Airedale Hospital is a DGH serving a population of 200,000 in North and West Yorkshire. Publication of RCT data has recently demonstrated significant benefits of a 72 hour IV omeprazole infusion, for patients with peptic ulcers who undergo endoscopic haemostasis. This therapy was therefore incorporated into clinical practice in November 2001.

Aims and Methods: To assess the effectiveness of IV omeprazole on outcomes, a retrospective audit of all patients receiving this therapy was undertaken. This group was compared to all those who had previously received endoscopic therapy alone in the same unit. Patients were identified by their endoscopy reports, held on computer database. Case notes were then examined to assess age, Rockall score, time to endoscopy, transfusion requirements, rebleeding, surgery rate, and 30 day mortality. Groups were compared using the Mann-Whitney U and Chi-squared tests as appropriate.

Results: There was 100% case note retrieval. Over 11 months, 26 patients (14 DUs, 12 GUs) received IV omeprazole after endoscopic therapy for peptic ulcers. 27 controls (16 DUs, 11 GUs) were identified over the previous 2 years. Mean age (65.3 vs 64.9), Rockall score (5.2 vs 5.3), and time to endoscopy (79.3% vs 81.5%) within 24 hours were not significantly different between the 2 groups. The rebleed rate (19.2% vs 29.6%), surgery rate (11.5% vs 25.9%) and 30 day mortality (3.8% vs 11.1%) were all improved in the group receiving IV omeprazole, but did not reach statistical significance. Blood transfusion requirements were significantly lower (3.1 vs 6.6 units, p < 0.005).

Conclusions: Patients receiving IV omeprazole had lower rates of rebleeding, surgical intervention and mortality, as well as lower transfusion requirements. Only the number of units transfused reached statistical significance, but all other outcome measures improved in the IV omeprazole group. Historical controls were used and there was no difference in age or risk stratification between the 2 groups, suggesting the improvement was due to a real effect. Use of IV omeprazole following endoscopic haemostasis is effective in a DGH setting.
**423** COMPLICATIONS ARISING FROM SELF-EXPANDING METAL BILE DUCT STENT INSERTION BEFORE DEFINITIVE HISTOLOGICAL DIAGNOSIS


**Background:** Self-expanding metal bile duct stents are excellent palliation for inoperable malignant disease. Problems may arise if metal bile duct stents are inserted before definitive histological diagnosis and staging. We aimed to determine the outcome of such patients.

**Methods:** Retrospective case note review of patients referred to a tertiary pancreato-biliary centre between 1994 and 2002, in whom a metal bile duct stent had been inserted endoscopically (n = 11) or percutaneously (n = 1) before definitive histological diagnosis.

**Results:** 12 patients (5 female, 7 male; mean age 64 years, range 31–88 years) were identified in whom a metal bile duct stent had been inserted for presumed non-resectable malignant disease: (i) later found to be due to benign disease (n = 3), (ii) later found to be resectable (n = 2), (iii) before an eventual delayed confirmed malignant diagnosis (n = 4), and (iv) where the diagnosis still remains uncertain (n = 3). In group one, the median number of cholangitis episodes and plastic stent insertions were 2 (range 0–5 episodes) and 2 (range 0–4 changes), respectively, during a median follow up of 24 mo (range 12–96 mo). Tissue ingrowth into the stents was common and histologic confirmation of benign disease technically difficult. One of the patients underwent surgical bypass for recurrent cholangitis, while two patients’ stents remain in situ. In group two, both patients underwent percutaneous-ducodenectomy for operable ampullary carcinoma, following a delay of 4–6 mo. In group three, the median delay to diagnosis was 3 mo (range 1–24 mo). In group four, a median of 3 (range 1–5) percutaneous biopsies have been negative for malignancy, during a median follow up of 24 mo (range 6–48 mo).

**Conclusion:** These cases indicate that metal bile duct stent insertion before definitive histological diagnosis and staging should be avoided. A small proportion of such patients will be found to have benign strictures or resectable malignant disease, and in others the histological diagnosis of malignancy may be delayed.

**424** A PROSPECTIVE ENDOSCOPIC STUDY IN CHEST PAIN PATIENTS


Among the indications for endoscopy referral are patients with chest pain. A proportion of these are referred from cardiology when exercise stress testing or coronary angiography fail to elucidate a cause. The aim of the study was to examine consecutive patients who attended for endoscopy when chest pain was one of the indications, and to assess the usefulness of this examination in such patients. Consecutive patients with chest pain were prospectively recruited at the time of endoscopy. Other symptoms and endoscopy findings were recorded. Thirty-five patients with chest pain were recruited. 37% had concomitant reflux symptoms, 11.4% had concomitant abdominal pain and 11.4% had dysphagia, 46% of patients were found to have a hiatus hernia, 40% had oesophagitis, 3% had Barrett’s oesophagus, 6% had duodenitis, 3% had duodenal ulceration, 20% had gastritis, and 26% had no abnormal findings. In conclusion, upper gastrointestinal endoscopy is a useful examination in patients presenting with chest pain. A positive finding was present in approximately three quarters of patients.

**425** CAPSULE ENDOSCOPY: INDICATIONS, EFFECTIVENESS AND INFLUENCE ON CLINICAL OUTCOME

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**Background:** Capsule endoscopy is a novel endoscopic technology allowing complete wireless examination of bowel previously beyond visualisation of push enteroscopy or enteroclysis.

**Aims and Methods:** This study examined the indications for capsule endoscopy in an initial cohort from our practice and its effect on subsequent patient management of small bowel pathology and obscure or occult gastrointestinal bleeding. All patients had prior endoscopic evaluation of the upper and lower gastrointestinal tract without diagnosis. Patients swallowed a disposable M2A imaging capsule (Given Imaging Ltd) that transmitted signals to an attached recorder. A total of 14 patients (9 female, 5 male, age range 30–69 years) were investigated. 10 patients (71%) were referred for investigation of obscure GI bleed and 4 for investigation of malabsorption in coeliac disease (1), persistent nausea and vomiting (1), persistent diarrhoea (1), and to identify a possible gastrointestinal source for Streptococcus bovis infection (1).

**Results:** All the patients were able to swallow the capsule without any difficulty and tolerated the procedure well. The capsule was retrieved in all patients and the average transit time was 5 hours. Of the 14 procedures carried out 5 were abnormal (36%). 4 (40%) patients referred with obscure GI bleeding had a source of bleeding identified. 2 received definitive treatment involving surgical resection of small bowel haemangiomas, and resection of a small bowel melanoma. 

**Conclusion:** Capsule endoscopy is safe and well tolerated by patients. It altered subsequent management in 40% of patients referred. We would recommend its use in selected patients after negative upper and lower gastrointestinal endoscopy where occult or obscure small intestinal bleeding is suspected.

**426** DAY CASE LAPAROSCOPIC CHOLECYSTECTOMY

P.C. Leeder, T. Matthews, T.C.B. Dehn. Royal Berkshire Hospital, Reading, Berkshire, UK

**Aim:** A prospective study was carried out to assess the feasibility of performing true day case laparoscopic surgery in a district general hospital setting.

**Methods:** All patients admitted consecutively under the care of one surgeon for laparoscopic cholecystectomy were included in the study. Laparoscopic cholecystectomy has been performed as a day case at the study hospital since July 2000. Selection criteria for day case procedure included an American Society of Anaesthesiologists score of I to III and the availability of a responsible carer at home. Patients were discharged four to six hours after surgery with a standard analgesia pack and a contact number for advice. All patients were contacted by telephone on the day following discharge. In addition, a postal questionnaire was sent to the first 80 patients to assess satisfaction with the day case process.

**Conclusion:** With appropriate patient selection and staff education, routine day case laparoscopic cholecystectomy is a practical option. The above study demonstrates a low admission rate and a high degree of patient satisfaction.

**427** THE SHEFFIELD COLONOSCOPY COURSE IMPROVES KNOWLEDGE AND PERFORMANCE OF CANDIDATES

M.E. McAlindon, M.T. Donnelly, J.M. Hebdon, S.A. Riley. Sheffield Teaching Hospital Trust

**Background:** JAG guidelines recommend that all trainees attend a course in basic colonoscopy skills. The Sheffield course is an intensive 3 day course featuring lectures, seminars, mannequin training and hands on colonoscopy training.

**Aims:** To provide subjective and objective assessments of the learning experience of course delegates.

**Methods:** Trainees were studied immediately before and on completion of the course. We assessed: 1) the trainees’ perception of their knowledge in 14 key areas using visual analogue scales, 2) 50 true/false questions (with negative marking), 3) the trainees practical, observational and reporting skills using an observer-blinded assessment of colonoscopy performance on a mannequin. Statistics were analysed using a paired t test.

**Results:** Following the course, trainees’ perception of their knowledge and understanding increased with respect to informed consent, indications/contraindications, sedation/monitoring, landmark recognition, loops and resolution, diathermy, hot biopsy and polypectomy, dye spraying and endoscopic mucosal resection (p < 0.05). A less clear improvement was seen in knowledge of bowel preparation (p = 0.08) and endoscopic dissection (p = 0.06). There
was no change in scores in 3 interventional techniques not taught on the course. True/false test scores improved from 22 (14–35) to 36 (23–42), p < 0.05. In addition, the quality of the withdrawal technique improved in all trainees and withdrawal time more than doubled (4m 16s (1m59s–1m19s) to 8m 58s (6m36s–11m28s), p < 0.05). All significant pathology, missed by some before the course, was detected on retesting.

Conclusions: Basic skills colonoscopy courses provide measurable improvements in perception and knowledge and practical colonoscopy skills. The results of these assessments may be usefully fed back to the trainees.

428 AN AUDIT OF EARLY REFERRAL FOR SUSPECTED UPPER GI CANCER

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In January 2001 the NHS Executive published the guidelines on improving the outcomes in upper GI cancers. These recommended that patients suspected of having upper GI cancer should be seen within 2 weeks. Referral criteria were agreed by a working group of GI physicians, surgeons and GPs as follows; unexplained iron deficiency anaemia in patients over 40; progressive dysphagia; jaundice; upper abdominal mass. We report on an audit of all patients referred from August 2000 to July 2001 with respect to 1) compliance with the 2 week rule; 2) clinical outcomes.

Method: All patients referred urgently with suspected UGI cancer were included in the audit. The sample was collected via the 2 week wait office, outpatient administration departments and endoscopy databases. 81 patients were identified, 2 were excluded due to their failure to attend initial appointment.

Results: The compliance with the 2 week standard was 78% (range 1–60 days). Of the patients diagnosed with cancer 8 were referred on the 2 week proforma, 18 via GP letter, 3 via open access clinics. 51% of all referrals did not have cancer; dysphagia and weight loss were the commonest presentations (59% of cancer diagnosis). Dysphagia was a significant predictor of a malignancy finding (OR 14.3). Age (OR 0.05), dyspepsia and sinister symptoms were unhelpful predictors for benign pathology. Multivariate analysis for oesophageal disease found dysphagia (OR 3.86) dyspepsia (OR 1.97) significantly associated with outcome (p < 0.0001). Similarly haematemesis had increased odds of a benign endoscopic finding with haematemesis (OR 0.55) and dysphagia (OR 0.31) were negative predictors. For benign gastric findings dysphagia was a negative predictive outcome.

Conclusion: Although this data support the concept of increasing age for endoscopy in patients with benign symptoms to exclude cancer, the predictability of benign pathology, including premalignant conditions is difficult to determine from age, sex, and presentation.

429 A PROSPECTIVE STUDY TO REDEFINE REFERRAL GUIDELINES FOR OPEN ACCESS ENDOSCOPY

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Aim: To relate characteristics at presentation (symptoms, age and sex) to endoscopic findings to redefine referral guidelines.

Methods: From a prospective database of > 9000 patients > 45 years (1994–2001), age, sex, and presentation (benign/pain/dyspepsia and sinister-dysphagia, anaemia, vomiting, anorexia/weight loss) and final endoscopic diagnoses were analysed. The odds ratio (OR) for presentation of benign findings and upper GI malignancy were determined by univariate and multivariate logistic regressions.

Results: Overall 57% presented with benign symptoms (dyspepsia 41%, pain 16%) and 43% with sinister symptoms (eg anaemia 16%, dysphagia 12%). Benign disease occurred in 71% with malignancy in 3%. Out of 256 cancer patients, the risk for males with benign symptoms increased with age from 0.7% < 55 years to 3.3% ≥ 75 years. With sinister symptoms this ranged from 3.4% to 10% over the same age span. The findings were less marked in women. Using gender, incremental age and symptoms in a multivariate model OR varied from 0.96 for dyspepsia to 1.43 for dysphagia with the area under ROC curve 84%. 6201 patients had benign findings (oesophageal 41%, 42% gastric, 16% duodenal). Although statistically significant benign and sinister symptoms were unhelpful predictors for benign pathology. Multivariate analysis for oesophageal disease found dysphagia (OR 3.86) dyspepsia (OR 1.97) significantly associated with outcome (p < 0.001). Similarly haematemesis had increased odds of a benign endoscopic finding with haematemesis (OR 0.55) and dysphagia (OR 0.31) were negative predictors. For benign gastric findings dysphagia was a negative predictive outcome.

Conclusion: Although this data support the concept of increasing age for endoscopy in patients with benign symptoms to exclude cancer, the predictability of benign pathology, including premalignant conditions is difficult to determine from age, sex, and presentation.
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The editors will decide as before whether to also publish it in a future paper issue.

To perform or not to perform liver biopsy: an alternative view

I would like to thank Joy and Scott for their comments in their letter in response to my review (Gut 2002;51:9–10).1 I entirely agree with their view that ultrasound is highly specific and sensitive for the diagnosis of fatty liver, but to see whether or not to perform liver biopsy needs to be completed by considering the anatomical factor in the study of gastrointestinal reflux disease (GORD) before advocating any non-medical appropriate treatment (fundoplicator, Stratten procedure, Gastropexie, etc.).

The multiple controversies arising from all non-medical proposed treatments, with contradictory results, are due to the complete neglect of delimitating the cardio-oesophageal junction (CEJ) and the shape of the angle of HIS, and the role of the anatomical factor in selecting the correct candidate for successful non-medical treatment.

The new generation of gastrointestinal specialists, who come after the endoscopy era, are not aware of the radiology of the gastro-intestinal tract, particularly when we need to have the anatomical configuration of the CEJ.

Physiological and junction motility are the next step in evaluating any case of GORD.

Imposing the study of the anatomical feature of the junction, which is very variable from person to person, is the first step in evaluating any proposed treatment of GORD, medically or surgically.

Applying the devices (Plicator, Stratten procedure, etc) without studying the anatomy of the junction is behind the side effects of these proposed procedures.

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Association between K469E allele of intercellular adhesion molecule 1 gene and inflammatory bowel disease in different populations

We read with interest the article by Matsuzawa et al showing an association between the K469E allele of intercellular adhesion molecule (ICAM-1) gene and inflammatory bowel disease (IBD) in a Japanese population (Gut 2003;52:75–8).

The ICAM-1 gene lies on chromosome 19p13, previously implicated in determining susceptibility to IBD, and codes for a surface glycoprotein that belongs to the immunoglobulin superfamily. ICAM-1 plays an important role in the trafficking and activation of leucocytes and is upregulated in the inflamed mucosa of IBD patients. Matsuzawa et al found that the allelic frequency of K469 was significantly higher in both Crohn’s disease (CD) and ulcerative colitis (UC) patients than in healthy controls. The G241R polymorphism of the ICAM-1 gene was also investigated in these studies, and IBD patients were stratified by antineutrophil cytoplasmic antibody (ANCA) status. In particular, Yang et al found a significantly increased frequency of the G241R polymorphism both in ANCA negative UC and ANCA positive CD patients while Braun et al showed an association between R241 and UC, independently of ANCA status.

We also searched for the K469E mutation in 42 consecutive Italian IBD patients (31 males, mean age 36 (14) years, 17 with CD and 25 with UC, and 227 ethnically matched controls. Our preliminary results (see table 1), although obtained in a limited number of patients, are in contrast with the findings of Matsuzawa et al (Gut 2003;52:75–8) and confirm those obtained in Caucasians patients.

The possible explanation for such a discrepancy in results is the influence of the different geographic distribution of the genetic mutation. Japanese patients with IBD have a genetic background that differs from Western patients, as also demonstrated recently for the NO2/CARD15 mutations in Caucasians but not in Japanese cohorts.

These data indicate that there may be significant genetic heterogeneity between different ethnic and racial IBD populations and environmental factors may play a leading role in the pathogenesis of IBD. Thus gene-environment interactions represent a crucial event in the pathogenesis of IBD and they cannot be considered as distinct entities.

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Table 1: Allelic frequencies of the E/K469 ICAM-1 polymorphism in Italian patients affected by IBD, and in controls

<table>
<thead>
<tr>
<th>Allelic frequency (%)</th>
<th>Controls (n=22)</th>
<th>IBD (n=42)</th>
<th>UC (n=25)</th>
<th>CD (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E469</td>
<td>45</td>
<td>46</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>K469</td>
<td>55</td>
<td>54</td>
<td>56</td>
<td>56</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; ICAM, intercellular adhesion molecule.
Authors’ reply

We would like to address the possible cause of the inconsistency of the ICAM-1 alleles, which associated with inflammatory bowel disease (IBD), between Japanese (K469) (Gut 2003;52:75–8) and German White populations. Increases in the associated alleles of the certain complex genetic disease among ethnic groups has been repeatedly described in the literature for the association study between inflammatory bowel disease (IBD) and HLA alleles. For example, the positive association between ulcerative colitis and DRB1*0103 in a Caucasian population but DRB1*1502 in the Japanese has been reported in many studies. Such allelic inconsistency in the ethnic group would be required to detect the increase in the predisposing haplotype.

In conclusion, this inconsistency of the associated ICAM-1 allele is most likely due to the difference in linkage disequilibrium of the ICAM-1 allele to the DPM in 19p13 among ethnic groups. Hoffmann et al. (2003) found the positive associations between the ICAM1 polymorphism and IBD in these ethnic groups highlights the potential importance of this region in the search for the predisposing gene(s) to IBD.

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Eosinophilic oesophagitis: treatment using Montelukast

I read with interest the paper by Attwood and colleagues (Gut 2003;52:181–5) on eosinophilic oesophagitis (EO). According to the authors, the distinct clinical syndrome of EO is not usually seen either as a component of gastro-oesophageal reflux disease or as a variant of eosinophilic gastroenteritis (EG).

The diagnostic hallmark of EO is oedynaphagia and the diagnosis is always histologically dependent (>20 eosinophils/high power field) (Gut 2003;52:181–5). In the paediatric setting, the condition is widely recognised but the adult EO may escape diagnosis due to general lack of awareness of the condition. In this respect, the paper by Attwood and colleagues (Gut 2003;52:181–5) is a valuable contribution towards understanding the complex pathological condition.

The pathophysiology of EG or EO may be similar to that of asthma. Asthmatic patients demonstrate increased production of cytokine leukotrienes during acute asthma attacks. Cysteinyl leukotrienes have potent chemotactic properties for eosinophils and play an important role in the pathophysiology of asthma.

In EG, accumulated eosinophils cause severe tissue damage characteristic of EG. Cysteinyl leukotrienes, along with cytokines interleukin 5 and 3, and growth factors play a role in the recruitment of eosinophils into the tissue causing the damage.

No controlled treatment trial for EG or EO exist. Limited results have been achieved with oral cromolyn, ketotifen, and other antihistamines. Oral corticosteroids are effective but long term use is complicated by side effects.

Montelukast is a leukotriene receptor antagonist (LTRA) which actively and selectively blocks the leukotriene D4 (LTD4) receptor. Because LTD4 is both a bronchoconstrictor and a chemotactic factor for eosinophils, this may provide the rationale for treating a patient with EG or EO with a LTRA. The first reported case of successful Montelukast treatment for an young EG patient was published in 1999. Montelukast was originally licensed in the UK for use in asthma. There has been some concern regarding association between the use of LTRA and Churg-Strauss syndrome (CSS) in asthma. This syndrome has previously been associated with the use of Zafirlukast. The Committee on Safety of Medicines has received 12 reports of CSS and pulmonary eosinophilia possibly associated with Montelukast. There are other reports of Montelukast induced CSS in asthma patients in the literature.

Attwood and colleagues (Gut 2003;52:181–5) observed nausea in four patients and anorexia in one in the Montelukast group but there was no mention of CSS. In the previous report of Montelukast therapy in EG, it was shown that Montelukast did not decrease the number of eosinophils (TE) or symptoms in a patient with severe EG complicated by oesophageal stricture. In another report, Montelukast reduced tissue eosinophilia in peripheral eosinophilic disease but there was no mention of whether TE was reduced. In Attwood et al’s paper (Gut 2003;52:181–5), treatment with Montelukast for a median
period of 14 months in eight patients out of a cohort of 12 patients with EO did not change the density of TE. However, subjective improvement did not occur in seven patients with swallowing difficulties in Attwood's series, one of eight patients on Montelukast.

LTRA s are a useful therapy for EO. While anti-leukotriene drugs are generally safe and effective for most patients, from the asthma experience I conclude that clinicians need to be vigilant of any development of CSS in all patients with eosinophilic oesophagitis undergoing treatment with Montelukast. I agree with the authors that further randomised control trials are required to assess the full benefits of Montelukast therapy in EO.

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Effect of a rapid access flexible sigmoidoscopy clinic on the yield of early stage rectal cancer

We read with interest the debate on population based endoscopic screening for colorectal cancer (Gut 2003; 52:323–6). While we agree that the case for population screening is compelling, we believe that Macadam and Scholefield's statement that “earlier diagnosis is unlikely to occur through increased awareness or patient education alone” is unnecessarily pessimistic.

We have recently had the opportunity to audit the impact of a dedicated rapid access flexible sigmoidoscopy clinic established in the endoscopy department of Dewsbury and District Hospital in January 1997. General practitioners were invited to use a proforma to refer patients to the clinic who were over 40 years old and had presented with a history of a recent change in bowel habit, rectal bleeding, or iron deficiency anaemia. Following initial consultation using a structured history form and clinical examination, flexible sigmoidoscopy was carried out by a consultant surgeon or a nurse endoscopist. If significant pathology was encountered, biopsy material was obtained and further investigations and management were planned as appropriate.

During the period January 1993 to December 1999, 167 patients underwent surgery for histologically confirmed adenocarcinoma of the rectum. Introduction of the dedicated rapid access flexible sigmoidoscopy clinic occurred 48 months into this audit period, with 87 patients treated before the introduction (clinic period 1) and 80 patients after (clinic period 2). Comparison of the groups of patients treated before and after reorganisation of the colorectal service demonstrated significant differences in several important clinical variables, with early stage tumour regression, complete circumferential margin clearance, and absence of visible residual tumour following excision all commoner in the later period (table 1).

<table>
<thead>
<tr>
<th>Clinic period 1 (n=87)</th>
<th>Clinic period 2 (n=80)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>ASA</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Admission Emergency</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Elective</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>Treatment Curative</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Palliative</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>CRM</td>
<td>Clear</td>
<td>56</td>
</tr>
<tr>
<td>Positive</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Dukes’</td>
<td>A</td>
<td>10</td>
</tr>
<tr>
<td>B-D</td>
<td>77</td>
<td>59</td>
</tr>
</tbody>
</table>

Table 1 Association between treatment before [clinic period 1; 1993–96] and after [clinic period 2; 1997–99] the introduction of a dedicated rapid access flexible sigmoidoscopy clinic and the clinicopathological characteristics of resected rectal adenocarcinomas.

detect a significant increase in fractures experienced by treated coeliacs might reassure many patients and physicians. However, this study, and the accompanying commentary by Compston (Gut 2001; 52:459), need full and critical assessment before changes in practice are adopted and coeliaccs are no longer targeted to be screened for osteoporosis.

It not surprising that no significant increase in fracture could be detected in this population of well treated coeliaccs, given previous findings. The American Gastroenterol- ogy Association recently reviewed studies of osteoporosis in gastrointestinal diseases, in- cluding coeliac disease, according to standard levels of evidence. 1 All such studies have shown low mean bone mineral density (BMD) around the time of diagnosis of untreated coeliac disease, with a pooled analysis showing very low bone mass (age and sex adjusted z scores below –2) in 40% in the spine and 15% at the hip. However, many reports, including our own, 2 have shown nor- mal or near normal mean values after treatment. This reflects the great improve- ment in BMD and calcium absorption 3 which occurs when enteropathy is reversed with a gluten free diet. The real issues are how to recognise previously undiagnosed cases, and how to identify potential patient subgroups who might still be at risk due to suboptimal treat- ment. 4

The study also did not have sufficient power to detect any increase in those fractures most typical of osteoporosis which have a high prevalence late in life. 5 Such fractures typi- cally include vertebral collapse and deformity, causing significant morbidity, but which commonly are undiagnosed unless looked for radiologically. In a 50 year old woman, there is a 32% life time risk of subsequent vertebral fractures. 6 However, these were not recorded in either coeliacs or controls in this study, indicating that the questionnaire method employed led to marked underreporting. Femoral neck (hip) fractures, the most serious complication of osteoporosis, have a popula- tion incidence of less than 1% by the age of 65 years but approaching 20% by the age of 90 years. In this study, only about one third of coeliacs were aged over 65 years and only
one-tenth (n=20) over 75 years. Approximately 400 cases and controls would be needed in a prospective study to detect a 50% increase in risk from 20% to 30% with 80% power. Hence the ability of this study to detect a significant lifetime increase in fracture risk in the minority of coeliac patients is very limited. Much larger groups are needed in a prospective study which includes radiological ascertainment of vertebral fractures.

A relevant comparison can be made with the large US Study of Osteoporotic Fractures Research Group where over 9000 women older than 65 years of age were studied. In 1814 subjects with a daily calcium intake less than 400 mg, those below the median for fractional calcium absorption (so resembling untreated coeliac) experienced an incidence of hip fractures of about 9 per 1000 person-years—2.5-fold greater than those with absorption above the median.2

The absolute lifetime risk of osteoporotic fractures is reasonably large in the ageing population, even if the relative risk in coeliac is not that great. Patients will be reassured by the knowledge that BMD has improved with dietary treatment and that individual risk has decreased. We hold that as the true risk of fracture in treated and untreated elderly coeliac is unknown at present, judicious use of DXA measurements following appropriate guidelines to monitor calcium homeostasis and the benefits of treatment should continue.

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References
1 Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastroenterological practice. Gastroenterology 2003;124:795–841

Collagenous colitis: constipation or diarrhoea?

As an axiom, collagenous colitis is characterised by diarrhoea, lymphocytic inflammation, and a thickened subepithelial collagen layer in the colonic mucosa.3 Various case presentations in the literature have reported that those patients with diarrhoea introduces the clinical picture of collagenous colitis and intermittent or continuous diarrhoea can remain.4 On the other hand, numerous cases never suffer from episodes of watery diarrhoea but suffer from chronic constipation. Can we call into question the “incontestable” definition? Bondereg et al investigated the clinical and histological effect of oral budesonide in the treatment of collagenous colitis in 20 patients and concluded that budesonide is a highly effective and well tolerated treatment. The histological inflammation grade in the sigmoid mucosa and the thickness of the collagen layer were significantly reduced. A correlation between the grade of inflammation as well as collagen layer thickness and stool weight was found (Gut 2003;52:248–51).

In our recent study, we investigated 32 patients with histologically identified collagenous colitis. In contrast with the literature, 18 had chronic constipation and only 14 had the well known diarrhoea. We also treated all of them with budesonide (Budenofalk; Dr Falk Pharma) and constipated patients receiving budesonide had a clinical response: stool frequency and weight. These conflicting results suggest a role for additional factors other than the thickened collagen layer of collagenous colitis. For example, allergy (food allergy), a great mimic, can cause both diarrhoea and constipation. Diseases or symptoms (that is, food protein induced enterocolitis, diarrhoea, or constipation) involving the gastrointestinal system have been attributed to hypersensitivity reactions to food.5 Many of these symptoms reflect the concept of “delayed” reactions. This notion presumes that certain clinical symptoms reflect allergies to food which develop over a period of hours or days (or longer) and are caused by immunological mechanisms other than immediate type hypersensitivity. For example, cow’s milk protein allergy should be considered as a cause of chronic refractory constipation in children although the underlying mechanisms still require further investigation. Albeit the aetiology of collagenous colitis is still unknown, the subepithelial band-like collagenous deposit may be produced by histiocytes after immune stimulation. Our hypothesis was to test whether collagenous colitis might be related to food allergy. Patient sera were analysed for common food antigens. Our data support the hypothesis that patients with collagenous colitis have laboratory and/or clinical evidence of food allergy: the high frequency of specific antibody bodies to food antigens and the increased total IgE levels imply a possible connection between collagenous colitis and food allergy and suggest a possible reason for the paradox of diarrhoea-constipation. Corticosteroids are the most effective drugs available for the treatment of allergic diseases and are very useful in treatment because they have potent anti-inflammatory effects.6 Topical corticosteroids work by reducing the effects of histamine and other inflammatory mediators involved in the allergic response and repeated dosing inhibits both the early and late phase allergic reactions, including priming and hyper responsiveness. These observations suggest that patients with collagenous colitis are needed to prove this hypothesis.

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References
the fact that many acute liver diseases have an immunological basis, it might have been appropriate to highlight immunology in volume 3 where it fit very well with the excellent chapters on hepatic regeneration and fibrosis. Section 3 contains an informative chapter on laparoscopy but only a four page section on hepatic imaging. Imaging is subsequently covered in the individual chapters in section 4 but given the major advances in interventional radiology and imaging it would have been appropriate to give this subject a chapter of its own. For example, there are only two brief references to positive emission tomography in the whole book.

Individual chapters are extremely well referenced although it might help to highlight the most significant references or those that provide an in depth review. One minor criticism is the quality of some of the figures. The chapters are richly illustrated but there is an irritating variation in the quality and style of the line drawings. It would have improved the overall appearance of the book if figures had been redrawn in a uniform style, and for some of the figures this would also have improved their clarity. The reluctance to use colour is presumably based on cost considerations. However, the recently published Comprehensive Clinical Hepatology edited by O’Grady, Lake, and Howdell (Mosby), provides an example of how the use of modern technology can provide outstanding illustrations that enhance the readability of the book.

How does Zakim and Boyer compare with other similar volumes? The two main rivals are the Oxford Textbook of Clinical Hepatology and Schiff’s Diseases of the Liver, both of which were last revised in 1999. All three works are excellent. There are some differences in emphasis and presentation between them but all three are highly readable and cover the field comprehensively. I have greatly enjoyed having access to Zakim and Boyer over the last few weeks and would recommend the fourth edition unreservedly to anyone with an interest in liver disease, whether research scientists, specialist hepatologists, or gastroenterologists. The editors are to be congratulated for managing to improve an already outstanding reference work.

D H Adams

Genetic Disorders of the Exocrine Pancreas


This multi-authored work, derived from a symposium held in April 2001, summarises our current knowledge of the genetics of exocrine pancreatic cancer. As is usual with such publications, the individual chapters have been written as free standing presentations which results in a degree of repetition. The editors have attempted to combine the chapters into sections: a “consensus conference” dealing with ethical issues and with guidelines for prevention, screening, and treatment is followed by sections on hereditary pancreatitis (HP), pancreatic cancer, and cystic fibrosis. Finally, there is a conference report and a monograph celebrating the work of Henry Lynch of the Mayo Clinic.

The first section will be of the most practical interest to general gastroenterologists. Gastrointestinal physicians and surgeons should already be aware of the ethics of screening from more common conditions such as colon cancer. A brief overview of these issues is followed by advice on whom to test, appropriate pre-test information, post-test information, and acting on the results. The algorithm looks forbidding but is straightforward and logical. Both service and research testing are covered. Screening for cancer in HP is a more difficult issue. The advantage that patients over 40 years should have annual screening at a specialist centre however may build a knowledge base for future patients but will not necessarily help our current population.

The HP section suffers from its symposium origins. In the six years since David Whitcombe and his colleagues identified a mutation in the PRSS1 (cationic trypsinogen) gene in a kindred with HP a new understanding of the relationship between the three entities of acute and chronic pancreatitis and pancreatic cancer has developed. It is a pity that the format of this book has not allowed this to be made explicit. It starts well with a two page overview neatly logging the known PRSS1 and SPINK mutations. Unfortunately, the chapters dealing with the mechanisms by which these mutations might translate into clinical disease, which logically should follow, are instead towards the end of the section (although an earlier chapter on gene mutations in children does cover some of this ground). The general reader might well find the intervening chapters on national experiences superficial. The review of inborn errors of metabolism is useful but surely belongs at the end of the section rather than in the middle.

The pancreatic cancer section is better organised and provides a comprehensive review of the contribution of genes to disease. In contrast with HP there are no defined single gene mutations identified for pancreatic cancer. Families with two or more affected members have been reported: whether this simply represents random clustering is discussed. The risk of pancreatic cancer in accepted cancer syndromes such as FAMMM, Lynch syndrome II, BRCA2 mutation, and Peutz-Jehgers syndrome is also considered. The chapters on surveillance and molecular diagnosis will be of particular interest as they offer the first glimpse of hope for early detection and treatment. Non-pancreatologists may not be aware that premalignant duodenal lesions termed PanINs have now been described and classified. Ways in which this discovery and molecular markers such as K-ras mutations may be exploited in screening strategies are reviewed, as are the practical difficulties of assessing the pancreas even with the benefit of EUS and CT. Ultimately however, all strategies being considered or tried will lead to a prophylactic pancreatectomy: the practicalities of the timing and extent of pancreatectomy are covered in the final chapter.

The final section covering cystic fibrosis and the Shwachman-Diamond syndrome is limited in its scope and appears to reflect one centre’s interests and research. Currently, pancreatic disease is either self limiting or incurable. Effective treatments for pancreatitis and pancreatic cancer will come from molecular and genetic research of the type described here. The presentation of this book is not perfect but the information it contains should be available to anyone dealing with pancreatic disease. Ask your library to buy it.

D Fine

In the BSG Abstracts supplement, there was an error in abstract 179 by Li et al (Gut 2003;52 Suppl I:A48). In their results section the sentence after the table should read “1 year survival for all patients with and without pre-existing Barrett’s was 51.5% and 31% respectively, and for those undergoing potential curative resection, was 72.6% and 52.7% respectively”. The authors apologise for the error.

In the author index of the BSG Abstracts supplement, J E Crabtree should have been listed as an author on abstract 126 by Jeremy et al (Gut 2003;52 Suppl I:A34). This was due to a technical error for which the journal apologises.

NOTICES

British Society of Gastroenterology Sir Francis Avery Jones Research Award 2004

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TWENTY COPIES) should include:

• A manuscript (2 A4 pages ONLY) describing the work conducted
• A bibliography of relevant personal publications
• An outline of the proposed content of the lecture, including title
• A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years old or less on 31 December 2004 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

British Society of Gastroenterology Hopkins Endoscopy Prize 2004

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TEN COPIES) should include:

• A manuscript (2 A4 pages ONLY) describing the work conducted
• A bibliography of relevant personal publications
• An outline of the proposed content of the lecture, including title
• A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TEN COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.
European Helicobacter Study Group (EHSG)
This meeting, on Helicobacter infections and gastroduodenal pathology, will be held on 3–6 September 2003 in Stockholm, Sweden. Further details: Professor Torkel Wadstrom, President-EHSG, Lund University, Department of Infectious Diseases & Medical Microbiology, Division of Bacteriology, Solvegatan 23, SE-223 62 Lund, Sweden. Tel: +46 46 173 241; fax: +46 46 152 564; email: Torkel.Wadstrom@mmb.lu.se; website: www.helicobacter.org

Falk Symposium
135—Immunological Diseases of Liver and Gut
This symposium will be held on 12–13 September 2003 in Prague, Czech Republic. Further details: Falk Foundation e.V., Congress Division, PO Box 6529, Leinenweberstr. 5, 79041 Freiburg/Jr, Germany. Tel: +49 761 15 140; fax: +49 761 15 14 359; email: sympoisa@falkfoundation.de; website: www.falkfoundation.de

The European Society of Parenteral and Enteral Nutrition (ESPEN)
ESPEN will celebrate its silver anniversary at the time of the annual congress, which is to be held on 20–23 September 2003 in Cannes, France. Further details: www.espen.org

XII Falk Liver Week
The XII Falk Liver Week, in honour of Hans Popper's 100th birthday, will be held on 15–22 October 2003 in Freiburg, Germany. Further details - see Falk Symposium above.

European Course on Laparoscopic Endoscopy
This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Haute 322, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straelb.asmb@proximedia.be; website: www.straelb-asmb.com

4th Nutrition and Health Conference
A multidisciplinary event will be held on 21–22 November 2003 in London, UK. This year's topics include cancer, obesity, exercise on prescription, menopause, ageing, motivation skills, and coronary heart disease. Further details: Tanya Carr, 16 Brownlow Court, Lyttelton Road, London N2 0EA. Tel/fax: +44 (0)208 455 2126 or 6570; website: www.nutritionandhealth.co.uk

Hong Kong-Shanghai International Liver Congress 2004
This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is “Liver Diseases in the Post-Genomic Era”. Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org