Neurogastroenterology/
Motility free papers 001–011

001 DOES INFECTIOUS DIARRHOEA (ID) PREDISPOSE PEOPLE TO FUNCTIONAL GASTRO-INTESTINAL DISORDERS (FGIDs)? A PROSPECTIVE COMMUNITY CASE-CONTROL STUDY

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Introduction: Previous studies, many uncontrolled, suggest 4 to 32% of people develop irritable bowel syndrome (IBS) after ID. Little information is available on the development of other FGIDs after ID.

Aim: To determine if patients with stool culture confirmed bacterial diarrhoea were more likely to develop gut symptoms consistent with a diagnosis of IBS, functional dyspepsia or functional diarrhoea at 3 and 6 month follow up compared with community controls.

Methods: A prospective community-based case-control study over one year. Subjects with stool positive bacterial infectious diarrhoea and control subjects from the same primary care practice were invited to participate. The presence or not of IBS, functional dyspepsia or functional diarrhoea at the start and at follow up using self-complete Rome II modular questionnaires. The diagnosis of a baseline FGID excluded subjects from continuing. There were 128 cases and 219 control subjects eligible and who consented to participate.

Results: At follow up there was a higher incidence of FGIDs in the cases compared with controls, mainly due to a higher incidence of IBS (see table). There was no difference in the incidence of functional dyspepsia between cases and controls.

Conclusions: IBS and functional diarrhoea is diagnosed more frequently in people at three and six-month follow up after an episode of stool positive bacterial diarrhoea compared with community controls despite careful exclusion of people with pre-existing FGIDs and adds further support for the concept of post-infectious IBS.

002 GENETIC INFLUENCES IN IRITABLE BOWEL SYNDROME: A TWIN STUDY

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Background: Aggregation of irritable bowel syndrome (IBS) in families of patients with IBS has recently been described. This may be due to learned responses to abdominal symptoms or a significant genetic contribution to the visceral hypersensitivity of patients with IBS. We have therefore studied IBS symptoms in monozygotic (MZ) (100% of genes shared) and dizygotic (DZ) (approximately 50% of genes shared) twins to assess the contribution of genetic factors to IBS.

Methods: 4480 unselected twin pairs from a national volunteer twin register were asked to complete a validated questionnaire. IBS was defined on the basis of the Rome II criteria as abdominal pain for at least 12 weeks in the last year with two of: relief with defaecation/change in bowel frequency with pain/change in bowel consistency with pain.

Results: 5032 respondents (56% response rate), including 1878 evaluable twin pairs. 892 MZ pairs (82 male, 810 female, median age 53 [range 19–81] years) and 986 DZ pairs (69 male, 917 female, age 54 [20–82] years). The prevalence of IBS among the twin pairs was 638/3756 (17%). There was no significant difference in casewise concordance rates in the MZ and DZ twins (see table).

Conclusion: This study suggests that genetic factors do not contribute substantially to the aetiology of IBS.

Abstract 003

ENDOGENOUS CHOLECYSTOKININ MODULATES TOLERANCE TO AN INTRAGASTRIC LIQUID LOAD BY AN EFFECT ON GASTRIC EMPTYING IN HUMANS

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The role of CCK in human eating behaviour is unclear. Exogenous CCK reduces food intake, but a similar role for endogenous CCK is not established. Fatty acid release of CCK is chain length sensitive: dodecanoic acid (C12) releases CCK but decanoic acid (C10) does not. We have shown previously that C12 reduces tolerance to an intragastric liquid load to a greater degree than C10 (Lal 2001 Gastroenterology 120: A710).

Aim: To determine whether the effect of C12 on tolerance to an intragastric liquid load is (a) mediated by an effect on gastric emptying, and (b) is blocked by Dexloxiglumide, a CCK-1 receptor antagonist.

Methods: (a) Vehicle (250 ml PBS/Tween-80) alone or with 0.1M C10 or C12 was infused into the stomach of 8 healthy volunteers in a randomised manner after an overnight fast. 20 minutes later, water was infused into the stomach at 200 ml/min to maximum volume tolerated. Gastric contents were then aspirated. (b) 8 subjects were randomised in a double-blind, Latin square design to receive either i.v. dexloxiglumide (Dex; 5–15 mg/kg/h) or saline (Sal) and either intragastric vehicle (Veh) or C12 followed by water infusion. Data are mean±SEM (ml) compared by ANOVA followed by post hoc multiple comparison tests as appropriate.

Results: (a) Subjects tolerated more water following vehicle (1481±220) than with 0.1M C10 or C12 was infused into the stomach of 8 healthy volunteers in a randomised manner after an overnight fast. 20 minutes later, water was infused into the stomach at 200 ml/min to maximum volume tolerated. Gastric contents were then aspirated. (b) 8 subjects were randomised in a double-blind, Latin square design to receive either i.v. dexloxiglumide (Dex; 5–15 mg/kg/h) or saline (Sal) and either intragastric vehicle (Veh) or C12 followed by water infusion. Data are mean±SEM (ml) compared by ANOVA followed by post hoc multiple comparison tests as appropriate.

Results: Subjects tolerated more water following vehicle (1481±220) than with 0.1M C10 (1400±227) than C12 (925±173; p<0.05 vs. C10 & veh), confirming previous results. There was no difference in...
the volume of gastric contents aspirated at the end of the infusion period following any of the test meals (veh: 1045 ± 162; C10:1071 ± 153; C12:1065 ± 147), indicating that tolerance was limited by intragastric capacity, which in turn is determined by gastric emptying. b) Dex abolished the reduction in water tolerance induced by C12 [Dex/Veh: 1763 ± 176; Sal/Veh: 1581 ± 58; Dex/C12: 1625 ± 204; Sal/C12: 1211 ± 210 (C12 vs. other conditions), indicating a CCK-1 receptor mediated effect.

Conclusion: CCK-releasing fatty acids reduce tolerance to an intragastric liquid load in humans (a) by delaying gastric emptying and (b) via a CCK-1 receptor mediated effect.

004 GASTRIC MUCOSA IS INNERVATED BY HIGH THRESHOLD ACID SENSING NON-CAPSACIN SENSITIVE SPINAL AFFERENTS

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Introduction: Many patients suffer from acid sensitive dyspepsia yet the gastric mucosa is normally anaesthetic to luminal acid. We have previously reported that only a small proportion of mucosal spinal afferents are sensitive to protons at pH 6.1 and hypothesised that this was an adaptation to the presence of luminal acid.

Aims: To determine whether gastric mucosal nerves have a higher threshold for activation by acid than non-gastric nerves.

Methods: To study the effects of pH on the cell bodies of gastric mucosal nerves, we injected a neuronal tracer, Texas Red, into the dorsal root ganglia (DRG). Cultured DRG cells were placed in a perfusion chamber mounted on a fluorescence microscope where those of gastric origin were identified by excitation of the Texas Red within them. The cells were loaded with the calcium sensitive ionophore, FURA 2-AM to detect the rise in calcium concentration accompanying cell activation and perfused with a Hepes based buffers from pH 7.4 to pH 6.1 to establish thresholds for cell activation. Following this, cells insensitive to pH 6.1 but sensitive to pH 5 were identified and the threshold for activation by acid than non-gastric nerves.

Results: Preliminary dose ranging experiments suggested 2 populations of acid sensitive gastric cells based on threshold for activation (pH 6.7 or pH 5). Following this, pH 6.1 and pH 5 were chosen as thresholds for cell activation and perfused with a Hepes based buffers from pH 7.4 to pH 6.1 to establish thresholds for cell activation. Following this, cells insensitive to pH 6.1 but sensitive to pH 5 were identified and the effects of exposure to the vanillin receptor antagonist Capsazepine (5μM) and capsaicin (5μM) were studied.

Results: Low grade inflammation occurs with irritable bowel syndrome (IBS), which is also associated with an increase in enteroendocrine cells. IBS peaks in the early 20s, when exposure and responsiveness to intestinal infections is maximal.

Aims: To determine the relationship between enteroendocrine (E) cell to inflammatory cell numbers in young and older healthy controls.

Methods: Twenty young (median 27 yrs [21–33]) and twenty older healthy volunteers (median 59 [59–70]) underwent colonic transit measurement and rectal biopsy. These were immunostained using antibodies to the following markers: synaptophysin, 5HT & PYY (enteroendocrine cells), CD3 (lymphocytes) and mast cell tryptase (mast cells).

005 5-HT, RECEPTOR AGONISM SUPPRESSES POST-PRANDIAL ANTRAL-PYLORO-DUODENAL MOTILITY IN MAN

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5-HT, receptor agonism delays gastric emptying. This is associated with prolongation of the lag phase and relaxation of the gastric fundus. The aim of this study was to assess the effect of 5-HT1 receptor agonism on post-prandial antro-pyloro-duodenal motility.

Methods: Antral (3 sites, 1.5 cm apart), pyloric (sleeve sensor position) and duodenal (4 sites, 3 cm apart) motility was recorded for 3 hours after ingestion of a solid meal and subsequent administration of either sumatriptan (50 μg, s.c.) or saline control (s.c.) in 8 healthy volunteers (aged 18–37, 1 female). Treatment order was randomised and double blind.

Results: During the first post-prandial hour S significantly decreased antral (activity index: 5.27 mmHg [8, 109]; mmHg·median (IQR) v placebo 105 mmHg [67, 320] mmHg; p < 0.05), pyloric (13 mmHg [5, 25] mmHg v 63 mmHg [40, 82] mmHg; p < 0.02) and duodenal (78 mmHg [40, 203] mmHg v 291 mmHg [143, 458] mmHg; p < 0.05) motility. During the 2nd post-prandial hour, only pyloric motility remained significantly reduced (21 mmHg [8, 38] mmHg v 38 mmHg [21, 62] mmHg; p < 0.02), with neither antral (30 mmHg [15, 199] mmHg v 238 mmHg [231, 365] mmHg) nor duodenal (92 mmHg [55, 207] mmHg v 251 mmHg [120, 355] mmHg) motility being significantly affected. By the 3rd hour there were no significant differences in either antral (56 mmHg [11, 230] mmHg v 143 mmHg [11, 338] mmHg), pyloric (18 mmHg [7, 42] mmHg v 12 mmHg [5, 24] mmHg) or duodenal (70 mmHg [57, 101] mmHg v 85 mmHg [46, 138] mmHg) motility between S and placebo groups. Finally the number of isolated pyloric pressure waves were not affected by S 1st hour: 77 [40, 90] v 68 [50, 94], 2nd hour: 53 [18, 168] v 40 [27, 163], 3rd hour: 36 [8, 64] v 18 [3, 50].

Conclusion: S-5-HT receptor agonism with S suppresses antro-pyloro-duodenal motility immediately after meal ingestion, which may contribute to the increase in lag phase seen during gastric emptying. GlaxoWellcome, UK, kindly supplied the sumatriptan for this study.

006 A ROLE FOR 5-HYDROXYTRYPTAMINE (5-HT) IN THE POSTPRANDIAL EXACERBATION OF SYMPTOMS IN FEMALE PATIENTS WITH DIARRHOEA PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)

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Meal ingestion is often associated with an exacerbation of gastrointestinal symptoms in patients with IBS. Furthermore, plasma 5-HT concentrations appear to increase more after a meal in patients with diarrhoea predominant IBS than healthy volunteers, suggesting that abnormalities in 5-HT release may be responsible for the postprandial symptoms associated with IBS. We have assessed platelet depleted plasma 5-HT concentration for 2 hours (60 minute intervals) under fasting conditions, and then for a further 4 hours (at 30 minute intervals) after a standard carbohydrate meal (457 kcal) in 21 female patients with diarrhoea predominant IBS (aged 19–50 yrs). IBS symptomatology, in particular abdominal pain and urgency, was assessed throughout the study, and platelet depleted plasma 5-HT concentration compared in patients “with” and “without” a postprandial exacerbation of their IBS symptomatology. 5-HT concentration was measured by a reverse-phase high performance liquid chromatography with fluorometric detection.

Results: Thirteen patients experienced abdominal pain and/or urgency with meal ingestion. These patients exhibited significantly higher postprandial levels of platelet depleted 5-HT concentration than patients without any symptoms (postprandial area under the curve [AUC] fasting AUC) with:without symptoms, 1.34; ratio with:without symptoms (95% CI), 1.66 (1.05, 2.62); p = 0.033). Furthermore, the peak postprandial concentration of 5-HT was significantly higher in patients “with” compared to patients “without” a postprandial exacerbation of their IBS symptomatology (peak: with symptoms, 18.53 ng/ml v without symptoms, 8.71 ng/ml; ratio with:without symptoms, 2.13 (1.09, 4.15); p = 0.029).

Conclusions: These data support a role for 5-HT in the postprandial exacerbation of symptoms seen in female patients with diarrhoea predominant IBS.

Recent studies have suggested that low grade inflammation occurs with irritable bowel syndrome (IBS), which is also associated with an increase in enteroendocrine cells. IBS peaks in the early 20s, when exposure and responsiveness to intestinal infections is maximal.

Aims: To determine the relationship between enteroendocrine (E) cell to inflammatory cell numbers in young and older healthy controls.

Methods: Twenty young (median 27 yrs [21–33]) and twenty older healthy volunteers (median 59 [59–70]) underwent colonic transit measurement and rectal biopsy. These were immunostained using antibodies to the following markers: synaptophysin, 5HT & PYY (enteroendocrine cells), CD3 (lymphocytes) and mast cell tryptase (mast cells).

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007 CORRELATION OF 5-HT-CONTAINING ENTEROENDOCRINE CELL NUMBERS WITH MUCOSAL LYMPHOCYTES IN NORMAL RECTAL MUCOSA

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Recent studies have suggested that low grade inflammation occurs with irritable bowel syndrome (IBS), which is also associated with an increase in enteroendocrine cells. IBS peaks in the early 20s, when exposure and responsiveness to intestinal infections is maximal.

Aims: To determine the relationship between enteroendocrine (E) cell to inflammatory cell numbers in young and older healthy controls.

Methods: Twenty young (median 27 yrs [21–33]) and twenty older healthy volunteers (median 59 [59–70]) underwent colonic transit measurement and rectal biopsy. These were immunostained using antibodies to the following markers: synaptophysin, 5HT & PYY (enteroendocrine cells), CD3 (lymphocytes) and mast cell tryptase (mast cells).
THE ROLE OF ANTICIPATION IN THE BRAIN PROCESSING OF HUMAN VISCERAL PAIN

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Introduction: Psychophysiologicals have demonstrated that learned autonomic responses can be produced in the gastrointestinal (GI) tract external stimuli. By employing classical conditioning techniques, the formation of a learned association between a previously unrelated stimulus (conditioned stimulus, CS) and a biologically relevant stimulus (unconditioned stimulus, UCS) can be maximised in order to interpret the effect that anticipation has on the cortical processing of oesophageal pain.

Methods: Six healthy volunteers (5 male) with a mean age of 22 years (age range 20–26 years) participated in the study.

Oesophageal stimulation: a standard manometry catheter with a silicon rubber balloon attached was passed trans-nasally into the distal oesophagus.

Protocol: Comprised of three contiguous phases. (1) Learning phase: Presentation of 20 trials of a blue coloured circle (CS) paired with a phase 1 painful oesophageal distension (UCS). (2) Anticipation: Randomised presentation 10 trials of CS alone, and 10 trials of CS + UCS. (3) Extinction: Presentation of 20 trials of CS alone. Behavioural data measuring subjective perception of stimulus was acquired pre and post acquisition using visual analogue scales.

Magnetic Resonance Imaging: Non-contiguous axial slices were acquired using a 1.5 Tesla system and an event related design.

Results: During the learning phase anterior cingulate cortex, bilateral insula, thalamus, left cerebellum, anterior frontal cortex, periaque- ductal grey and secondary sensory cortex were activated. These regions were also activated in the anticipation and the extinction phases with the exception of the periaqueductal grey matter and with additional activation in the right dorsolateral prefrontal cortex (DLPFC).

Conclusions: Anticipation of painful visceral stimuli results in activation of cerebral regions normally associated with processing painful sensory information. We therefore demonstrate that the cognitive-evaluative component of the pain matrix significantly contributes to the central processing of visceral pain.

VALUE OF A DIETITIAN-LED CLINIC IN THE MANAGEMENT OF YOUNG PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS)

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Introduction: Irritable bowel syndrome (IBS) entails a heavy clinical load for gastroenterologists. It may often successfully be treated by diet. In order to reduce medical outpatient attendances we have established a dietitian-led IBS clinic (DLC).

Methods: Patients aged 16–45 were selected by review of GP referral letters by consultants, and randomised to DLC or standard medical appointments (MOPD). Those fulfilling the Rome criteria, with no history of rectal bleeding, chronic medication, or psychiatric illness, were eligible for DLC if screening before their clinic visit revealed there was no evidence of an anxiety state using a validated questionnaire, stool culture was negative and haematological and biochemical markers including C reactive protein and gliadin antibodies normal. Physicians who saw the patients randomised to MOPD were allowed to investigate them as appeared clinically indicated.

Results: Of 58 patients randomised to DLC, 15 were excluded (11 because of an anxiety state), but 43 fulfilled admission criteria. 7 failed to keep the first appointment, so that 36 followed a standardised dietary protocol. In 22, [61%] symptoms were successfully relieved. 47 patients were randomised to MOPD. Only 1 received a full IBS screen, and 23 unnecessary investigations were performed, including colonoscopies and barium x-rays. 17 were referred for dietary treatment and 12 accepted, of which 42% obtained symptomatic relief.

Conclusions: DLC provides an effective way of screening and treating young patients with IBS whose results compare favourably with those obtained when these patients are referred to MOPD.
Oesophageal free papers

012 OESOPHAGEAL CANCER AND CACHEXIA: THE EFFECTS OF THALIDOMIDE ON WEIGHT LOSS AND LEAN BODY MASS IN A SEQUENTIAL (METABOLIC) STUDY

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Aim: To investigate the potential for using thalidomide as an anti-cachectic agent in patients with advanced oesophageal cancer by studying its effect on body composition and weight.

Methods: 11 patients with non-obstructing and inoperable oesophageal cancer were included in the study.

Study protocol: Patients were established on an isocaloric diet over a 10-day period. Body weight, body composition studies with DEXA scanning, REE (resting energy expenditure) and serum levels of insulin, thyroxine, catecholamines and cortisol were measured at the entry and then after two weeks on diet alone. Patients were then started on thalidomide for 2 weeks and the measurements were repeated. Quality of life (QOL) was similarly measured as a secondary end point.

Results: Ten patients completed the study protocol. The average caloric intake remained the same throughout the study period in all these patients. 9/10 (95% CI 0.60, 0.98) lost weight on diet alone. The mean gain on thalidomide in the following two weeks was 1.75 kg (median 1.33 kg). A similar trend was shown in lean body mass. There were missing data for one patient, so nine were analysed. 8/9 (95% CI 0.57, 0.98) initially lost mass on diet alone. The mean gain in thalidomide in the following two weeks was 1.29 kg (median 1.25kg). A similar trend was shown in lean body mass.

Conclusions: In this sequential study of patients with progressive inoperable cancer, thalidomide treatment appeared to reverse loss of weight and lean body mass over the two week trial period. However to establish its role as an anti-cachectic treatment a full placebo-controlled trial is warranted.

013 A 5-YEAR, DOUBLE-BLIND, RANDOMISED COMPARISON OF RABEPRAZOLE AND OMEPRAZOLE IN GORD MAINTENANCE TREATMENT: EFFICACY RESULTS

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Background: Many studies have found proton-pump inhibitors to be effective and safe in preventing relapse of gastro-oesophageal reflux disease (GORD) over a period of several months to a year. There is, however, little evidence from randomised trials about their long-term safety and efficacy.

Objectives: To compare the efficacy and safety of rabeprazole and omeprazole in the prevention of relapse in patients with healed gastro-oesophageal reflux disease during 5 years of treatment.

Methods: Patients were eligible for the study if they had previously been diagnosed with GORD, which had healed as shown by endoscopy. Patients received randomised, double-blind treatment with rabeprazole (10 mg or 20 mg) or omeprazole (20 mg) once daily for up to 5 years. The main outcome measure was endoscopically confirmed GORD relapse (Heitel-Dent score = 2). Endoscopy was done after 13, 26, and 52 weeks, and yearly thereafter, or if symptoms suggested GORD relapse.

Results: 243 patients entered the study, of whom 123 completed all 5 years of treatment. Relapse rates were 9/78 (11.5%) in the 20 mg rabeprazole group, 8/82 (9.9%) in the 10 mg rabeprazole group, and 11/83 (13.3%) in the 20mg omeprazole group. The differences in relapse rates were not statistically significant. All three treatments were safe and well tolerated.

Conclusions: Rabeprazole at a daily dose of 10 mg is as effective as omeprazole 20 mg or omeprazole 20 mg in preventing relapse of GORD over 5 years of treatment.

014 OESOPHAGEAL MANOMETRY AND PH STUDIES CHANGE THE MANAGEMENT AND OUTCOME OF PATIENTS WITH NON-CARDIAC CHEST PAIN

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Background: Oesophageal disease is a well-recognized cause of non-cardiac chest pain (NCCP). The role of Oesophageal Manometry (OM) and pH studies remain unclear, particularly in changing outcome.

Aim: To assess whether Oesophageal Manometry and pH studies affect the management and outcome of NCCP patients in a district hospital.

Methods: Retrospective study of patients with NCCP with repeated admissions to hospital (Negative ETT, normal Coronary Angiogram or normal Thallium scan) who were further investigated with OM and pH studies between November 1998 and May 2001 (2.5 years/60 patients). Diffuse Oesophageal Spasm (DOS), Nutcracker oesophagus and Achalasia, as defined by Spechler and Castell (Gut 2001;49:145–51), were the only motility disorders recognized as causes of NCCP in this study.

Results: All patients had normal endoscopy or barium swallows. 17 (28%) patients had significant reflux disease, 14 (23%) had DOS and 6 (10%) had nutcracker oesophagus (of whom 50% also had reflux). Normal studies were found in 25%. 5 patients had non-specific oesophageal dysmotility and 2 patients had hypomotility. All patients with significant reflux disease were treated with PPI and 3 patients had anti-reflux surgery. 90% of patients with nutcracker Oesophagus and DOS were treated with Nitrates or calcium blockers with/without PPI. 37% of patients had reflux symptoms and predictive values for significant reflux were 64% (positive), and 92% (negative). 22% of patients had dysphagia. Predictive values for significant dysmotility were 69% (positive) and 72% (negative). Management was changed in 67% (40 patients) who had OM and pH studies. The nature of the diagnosis was carefully explained in all patients with positive studies. Only one (1.6%) had been readmitted and one (1.6%) had further cardiac investigations (mean follow-up 1.5years).

Conclusions: A positive diagnosis of oesophageal dysmotility or reflux changed the management, reduced readmission rates and the need for further cardiac investigations. The presence or absence of GI symptoms has a high predictive value for OM and pH abnormalities in NCCP.

015 OESOPHAGEAL MOTOR FUNCTION AND GASTRO-OESOPHAGEAL REFLUX IN VENTILATED NEONATES

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Introduction: Sick neonates often require ventilation for prolonged periods of time. Gastro-oesophageal reflux (GOR) is very common in newborn infants, particularly those who are preterm. This can lead to significant morbidity and in extreme cases the neonate can only be successfully weaned off the ventilator after anti-reflux surgery.

Aim: To evaluate oesophageal motor function and acid clearance mechanisms in ventilated neonates.

Methods: Combined pressure and pH monitoring was undertaken in 10 neonates requiring assisted ventilation using Dentsleeve...
Results:

- As expected, oesophageal acid exposure (% time pH<4) was greater in patients with reflux disease and variably exposed to acid. Transient buffering is seen following meal ingestion. Acid exposure is greater in patients with reflux disease and the proximal stomach that fails to be buffered by food. The location of this acid in relation to the cardia and distal oesophagus was unclear.

Aims: To establish the relationship between the unbuffered proximal acid pocket and the squamo-columnar junction (Z-line).

Methods: Ten healthy subjects were studied using a dual channel pH electrode with a 1 cm distance markings. The squamocolumnar junction (Z-line) was marked by attaching metal clips at endoscopy. The pH electrodes were withdrawn by 1 cm increments from the stomach into the oesophagus. The minimum pH at each electrode position, the distance from the nostril to the pH step-up and from the nostril to metal clip (Z-line) were shown on X-ray was measured in each subject under fasting conditions after a meal of fish and chips.

Results: The pull through studies revealed a pocket of acid in the region of the gastro-oesophageal junction which escaped the buffering effect of meals, remaining highly acidic (pH 1.6) compared to the cardia and body of the stomach. The pocket of acid was greater in patients with reflux disease (p<0.002) defined as pH<2 compared to controls (p<0.01). The pocket of acid, which extended over 2 cm (range 1–4 cm). The pH step-up distance moved after the meal (46.0 cm fasting vs 44.4 cm postprandial p<0.05). In contrast the distance to the Z line did not change significantly (46.3 cm fasting vs 46.2 cm postprandial).

Conclusions: This study shows that after a meal unbuffered gastric acid traverses the Z-line and extends from the cardia to the distal oesophagus. This observation is likely to be relevant to the high prevalence of mucosal pathology recognised to occur at the Z-line and just below the squamo-columnar junction.

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**INTRAGASTRIC PH IN AMBULANT SUBJECTS AND ITS RELATIONS TO PHYSIOLOGICAL AND PATHOLOGICAL REFLUX**

**Abstract 016**

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**Background and Aims:** Episodes of gastro-oesophageal reflux (GOR) are usually associated with a loss of lower oesophageal sphincter (LOS) pressure. However, on many occasions barrier pressure is lost yet reflux does not occur. This suggests that other factors also influence the occurrence of reflux. The aim of this study was to measure pH at the gastric cardia in ambulant subjects and determine its relations to physiological and pathological reflux.

**Methods:** 17 asymptomatic volunteers (9 males, aged 21–33 years) and 17 patients (11 males, aged 33–53 years) with non-erosive reflux disease were studied. Standard station pull-through manometry was employed to measure pH at the gastric cardia in ambulant subjects and volunteers. Significant buffering was not seen. Significant buffering was not seen.

**Results:**

<table>
<thead>
<tr>
<th>% time (pH)</th>
<th>Pre-prandial</th>
<th>Meal</th>
<th>Post-prandial</th>
<th>Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>37.0 (5.5)</td>
<td>21.7 (5.5)</td>
<td>35.8 (5.0)</td>
<td>38.3 (5.5)</td>
</tr>
<tr>
<td>GORD</td>
<td>80.5 (1.5)</td>
<td>47.3 (2.5)</td>
<td>68.2 (1.5)</td>
<td>57.4 (1.5)</td>
</tr>
<tr>
<td>P&lt;0.0018</td>
<td>P=0.005</td>
<td>P=0.0034</td>
<td>P=0.006</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Under ambulatory conditions, the gastric cardia is variably exposed to acid. Transient buffering is seen following meal ingestion. Acid exposure is greater in patients with reflux disease and this is likely to influence the occurrence of reflux when barrier pressure is lost.

**UNBUFFERED HIGHLY ACIDIC GASTRIC JUICE EXTENDS FROM THE CARDIA ACROSS THE SQUAMO-COLUMNAR JUNCTION AND INTO THE DISTAL OESOPHAGUS AFTER MEALS**

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**Background:** The gastric cardia and distal oesophagus are common sites of upper GI disease and deserve further study. We have shown that after a meal there exists a pocket of highly acidic gastric juice in the proximal stomach that fails to be buffered by food. The location of this acid in relation to the cardia and distal oesophagus was unclear.

**Aims:** To establish the relationship between the unbuffered proximal acid pocket and the squamo-columnar junction (Z-line).

**Methods:** Ten healthy subjects were studied using a dual channel pH electrode with a 1 cm distance markings. The squamocolumnar junction (Z-line) was marked by attaching metal clips at endoscopy. The pH electrodes were withdrawn by 1 cm increments from the stomach into the oesophagus. The minimum pH at each electrode position, the distance from the nostril to the pH step-up and from the nostril to metal clip (Z-line) were measured in each subject under fasting conditions after a meal of fish and chips.

**Results:** The pull through studies revealed a pocket of acid in the region of the gastro-oesophageal junction which escaped the buffering effect of meals, remaining highly acidic (pH 1.6) compared to the cardia and body of the stomach. The pocket of acid was greater in patients with reflux disease (p<0.002) defined as pH<2 compared to controls (p<0.01). The pocket of acid, which extended over 2 cm (range 1–4 cm). The pH step-up distance moved after the meal (46.0 cm fasting vs 44.4 cm postprandial p<0.05). In contrast the distance to the Z line did not change significantly (46.3 cm fasting vs 46.2 cm postprandial).

**Conclusions:** This study shows that after a meal unbuffered gastric acid traverses the Z-line and extends from the cardia to the distal oesophagus. This observation is likely to be relevant to the high prevalence of mucosal pathology recognised to occur at the Z-line and just below the squamo-columnar junction.

**METHYLENE BLUE CHROMOENDOSCOPY IN BARRETT’S (COLUMNAR LINED) OESOPHAGUS**

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**Background:** The value of methylene blue directed biopsies (MBDB) to detect specialised intestinal metaplasia (SIM) and dysplasia in Barrett’s oesophagus remains unclear.

**Aim:** To compare the accuracy of MBDB technique against random biopsy (RB) to detect intestinal metaplasia and dysplasia in patients with Barrett’s oesophagus.

**Methods:** A prospective randomised cross over trial was undertaken comparing MBDB and RB in patients with =3 cm Barrett’s oesophagus without macroscopic evidence of dysplasia or cancer. Biopsies were taken from the stained and unstained mucosa in focal staining Barrett’s segment and random four quadrant in the case of diffuse and heterogeneous staining Barrett’s segment. RB was done using standard endoscopic biopsy forceps from the four quadrants at 2 cm intervals. Dysplasia was defined as: indeterminate dysplasia (ID), low grade dysplasia (LGD), high grade dysplasia (HGD) and carcinoma (Ca). The histopathologist was blinded (unaware of which samples were methylene blue stained).

**Results:** Fifty-seven subjects were recruited, of whom 44 were male. The mean age was 60 years range (31–85). The mean length of Barrett’s was 5.4 cm, range (1–12 cm). Using MBDB technique 651 biopsies were obtained (mean 11.42, range 5–23). SIM was present in 491 biopsies (75.42%). Dysplasia and carcinoma were diagnosed in 26 patients: ID1, LGD21, HGD2, Ca2. Using RB technique 618 biopsies were obtained. SIM was present in 421 biopsies (68.12%). Dysplasia and carcinoma were diagnosed in 23 patients: ID3, LGD16, HGD2, and Ca2.

**Conclusion:** The diagnostic accuracy of MBDB technique was similar to RB technique in identifying HGD and Ca. However, there was a trend towards increased detection of SIM and LGD using MBDB technique. MBDB did not reduce the number of biopsies taken. Further studies involving larger number of patients are needed to detect a significant difference between the two techniques. Until then there is no role for MBDB in the routine use for Barrett’s surveillance.

**INTERPHASE FLUORESCENCE IN SITU HYBRIDISATION (FISH) ON BARRETT’S COLUMNAR LINED PROGRESSES TO OESOPHAGEAL ADENOCARCINOMA**

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**Introduction:** Barrett’s oesophagus is a pre-malignant condition characterised by the conversion of the normal squamous cell oesophageal
epithelium to a mucosa comprised of columnar cells as a result of chronic gastro-oesophageal reflux. This lesion progresses in a step-wise fashion through histologically identifiable stages and ultimately develops into oesophageal adenocarcinoma in approximately 10% of patients. To determine when specific genetic alterations arise during this neoplastic progression, FISH was employed.

Methods: Gastroscopic cytology brushes were used to exfoliate epithelial cells from patients at each stage of progression (Barrett’s metaplasia to oesophageal adenocarcinoma). Interphase cell preparations were generated and subsequently analysed by application of fluorescently labelled centromeric probes for chromosomes 4, 8, 9, 20 & Y and locus specific probes for the p53, p16 & Rb genes.

Results: Increased copy numbers of chromosomes 4 & 8 occurred in 13/15 & 10/15 Barrett’s metaplastic samples respectively, thus representing the most prominent and earliest alteration arising during neoplastic progression. Loss of the p16 tumour suppressor gene also arises during metaplasia (4/15) and was found to precede chromosome 9 amplifications, but in contrast, p53 loss is a later event first appearing in HGD. Increasing loss of chromosome Y occurs with progression.

Discussion: Aneuploidy is an early occurrence during the progression of Barrett’s oesophagus with copy number increases of chromosomes 4 & 8 present in the majority of metaplastic samples. However, it appears to be the stage at which most aberrations accumulate, thus this genetic instability may possibly account for the high proportion of these patients that progress to cancer.

020 CYTOKINES INDUCE PREFERENTIAL SQUAMOUS EPITHELIAL CELL REPAIR FOLLOWING PHOTODYNAMIC THERAPY FOR PATIENTS WITH BARRETT’S OESOPHAGUS: AN IN VITRO MODEL

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Background: Photodynamic therapy (PDT) is an emerging endo-scopic treatment for patients with Barrett’s oesophagus. Application of PDT to Barrett’s oesophagus ideally leads to regeneration of non-dysplastic, stable squamous mucosa. A limitation of this technique is the persistence of Barrett’s epithelium, including buried glands, which may still have dysplastic potential. Since the cellular microenvironment is crucial to epithelial repair it might be possible to manipulate this to promote squamous epithelial re-growth.

Aims: (a) to investigate [a] differences in early repair (restoration) of an oesophageal cell monolayer following mechanical or PDT injury; (b) whether restitution can be altered by adding growth factors/cytokines.

Methods: Cells line; Squamous (OE21), Barrett’s (OE33) and co-cultures were injured mechanically or with PDT (5-amino laevulinic acid and blue light) using a novel applicator. Wounds were measured over 24 hours and immunofluorescence for cytokeratins identified squamous versus columnar cells. Transforming Growth Factor beta (TGF-β1), Hepatocyte Growth Factor (HGF), Interleukin 8 (IL-8) and Keratinocyte Growth Factor (KGF) were added individually to assess their effect on restitution compared with serum free media.

Results: In co-culture, squamous cells (OE21) underwent greater restitution than columnar cells (OE33). In both mechanical wound and PDT assays of co-cultures, TGF-β1 increased cell repair by restitution compared with controls (p<0.05). This effect was not seen in individually cultured cell lines. KGF and HGF stimulated restitution of squamous and co-culture cells after mechanical injury and also inhibited columnar cells significantly (p<0.05). IL-8 had no effect on cell restitution.

Conclusions: Restitution, in the first 24 hours after PDT and mechanical injury in vitro, can be influenced by growth factors. It may be possible to manipulate the microenvironment to favour squamous re-epithelialisation after PDT.

021 BARRETT’S SURVEILLANCE IS WORTHWHILE AND DETECTS CURABLE CANCERS


Aim: To establish whether Barrett’s surveillance is worthwhile in terms of incident cancers and whether outcomes are favourable.

Method: A prospective non-randomised single centre Barrett’s surveillance program commencing 1/1/1992 through 1/4/2001 (100 months). Oesophagectomy recommended for high grade dysplasia or carcinoma.

Results: Of 23,725 endoscopies, 506 patients were diagnosed as Barrett’s oesophagus and 24 (5%) had carcinoma at diagnosis (prevalence cancers). 126 patients had at least one surveillance endoscopy, 248 surveillance endoscopies were performed spanning 338 patient years. 13 surveillance (incidence) cancers were detected. The surveillance cancers were all detected after 1 year of surveillance and no patient had dysphagia at diagnosis. In the prevalence cancer group 12 of the 24 patients underwent oesophagectomy. Lymph nodes showed evidence of metastases in 10 of the 12 resections. In the surveillance group 10 patients underwent oesophagectomy. All had carcinoma in the resection specimen. Lymph nodes showed evidence of metastases in 1 of the 10 resections. 3 patients in the surveillance cancer group did not have an oesophagectomy. 1 of these patients died. 1 patient in the prevalence cancer group had an oesophagectomy. 5% of these operated patients remain disease-free more than 2 years post-oesophagectomy. Assuming the 7 patients in the surveillance cancer group are cured and that the cost of endoscopy is £120, the cost per cancer cured is £4250. One curable cancer was detected per 48 patient years of surveillance (338/7).

Conclusion: 5% of Barrett’s patients undergoing endoscopy have prevalent cancers. If surveillance is performed, 4% per year (13/338 %) develop cancer and 2 % per year are cured of their cancers. Most surveillance cancers are operable and of those undergoing surgery 70% are cured. Barrett’s surveillance is cost-effective compared with other cancer screening or surveillance initiatives.

022 SURVEILLANCE FOR BARRETT’S OESOPHAGUS: EXPERIENCE FROM A DISTRICT GENERAL HOSPITAL

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Background: The incidence of adenocarcinoma of the oesophago-gastric junction is rising. Barrett’s oesophagus (BO) is considered a premalignant condition for this cancer. The effectiveness of endoscopic cancer surveillance programmes is unproven and controversial.

Aims: To measure the incidence and outcome of adenocarcinoma in a BO surveillance population over a 3 year period and to evaluate the effectiveness of endoscopic screening in a DGH.

Methods: All patients with BO attending Royal Bournemouth Hospital Endoscopy Unit between 1998–2001 were included. Cases were identified from the pathology computer database.

Results: We identified 299 patients with known BO in a biannual surveillance programme, with a mean age of 65 years. In the 3 year study period there were 34 BO-associated adenocarcinomas detected. 7 (19%) were identified as a result of a surveillance endoscopy. There were no interval cancers in the surveillance group. 27 (81%) were diagnosed de novo at index endoscopy. The mean age of patients with BO-adenocarcinomas was 69 years; 29/34 (85%) were male. Cancer incidence per patient year of follow-up was 1.79. All of the 7 BO-adenocarcinomas detected during endoscopy were early stage (<T2, N0) and had a resection (70%) or conservative mucosal resection (2/7). All have survived to date (range 9–28 months). De novo BO-adenocarcinomas were generally more advanced at presentation. 17/27 were suitable only for palliative therapy; 16/17 have died.

Conclusions: New oesophageal cancers were found during surveillance endoscopy at a higher rate compared with most published studies. The reason for the high detection rate in this study may be due to the advanced age of this surveillance population. Nevertheless, most adenocarcinomas occurred in patients without a previous diagnosis of BO. There was a bias towards early stage cancers in patients with BO under surveillance. The outcome in these patients has been favourable compared with BO-related cancers diagnosed de novo at index endoscopy. Our experiences support endoscopic surveillance in selected patients with BO.

023 PHOTODYNAMIC THERAPY TO ERADICATE DYSPLASIA AND EARLY CARCINOMA IN BARRETT’S OESOPHAGUS

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Background: Photodynamic therapy (PDT) is a minimally-invasive alternative to oesophagectomy for high-grade dysplasia (HGD) or intramucosal adenocarcinoma (T1 AdCa) arising in Barrett’s columnar lined oesophagus. Initial reports using 5-amino laevulinic acid...
(ALA) suggest that HGD can be eradicated in 80% of patients. Our aim is to identify parameters associated with successful eradication of disease.

Methods: 15 previously untreated patients (13 M, 2 F) with HGD (11) or T1m AdCa (4) were treated over a 3-year period. Ethical approval was obtained. Patients were photosensitised with ALA 60mg/kg (light activation 635 nm) and received 30 PDT sessions: median of 2 per patient (range 1–3). ALA light doses were 500–1000J/cm2 diffuser fibre and treatments took approximately 40 minutes per 4cm length of columnar mucosa. Two delivery devices were tested (16 and 25mm diameter). 3 patients were treated additionally with the photosensitiser meso-tetrahydroxyphenylchlorin (mTHPC, 0.15mg/kg).

Results: Disease (HGD 5, AdCa 3) was eradicated in 8 patients (53%): 6 patients (40%) with ALA alone, 2 with additional mTHPC. Median follow-up is 10 months (range 2–29) with no deaths and no oesophageal strictures. One patient developed new HGD 2 years after successful treatment and is being re-treated. Benign glands "burned" under neo-squamous epithelium were seen in 7/15 cases. Failure of treatment was associated with the length of Barrett's segment (median in responders 89.7, non-responders 20.8, p=0.02) and with the presence of multi-focal disease (success in only 2/8 versus 6/7 for unifocal disease, p=0.04). Age, sex, presence of hiatus hernia, and size of delivery device did not appear to influence outcome.

Discussion: Using current treatment parameters, PDT with ALA for dysplasia and T1m carcinoma in Barrett's oesophagus is effective in less than half of one patient's. A long Barrett's segment and multi-focal disease are associated with a poor outcome. Techniques to achieve a deeper effect (such as adding an iron chelator to ALA or using a different photosensitiser) may give better results.

USE OF ENDOCINCH® FOR THE MANAGEMENT OF GASTRO-ESOPHAGEAL REFUX DISEASE

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A method has been developed whereby sutures can be placed via an endoscope just below the oesophagogastric junction (OGJ) whose purpose is to improve the function of the OGJ and thereby prevent oesophageal reflux. The aim of this work is to assess the safety and efficiency of the BARD Endocinch© for the treatment of GORD. 20 patients with symptoms of GORD were recruited; all were followed for 6 months and 14 for 1 year. The inclusion criteria included a dependence on proton pump inhibitor (PPI) drugs to control their reflux symptoms, and a documented oesophageal acid reflux. Exclusion criteria were age less than 18 years, pregnancy, dysphagia, BMI > 40, previous upper gastrointestinal surgery and an hiatus hernia > 2 cms. Pre-procedure assessment included symptom scoring, oesophageal endoscopy, manometry and 24 hour oesophageal pH, and completed questionnaire. Post-procedure assessment was performed at 1, 3, 6 and 12 months. A method has been developed whereby sutures can be placed via an endoscope just below the oesophagogastric junction (OGJ) whose purpose is to improve the function of the OGJ and thereby prevent oesophageal reflux. The aim of this work is to assess the safety and efficiency of the BARD Endocinch© for the treatment of GORD. 20 patients with symptoms of GORD were recruited; all were followed for 6 months and 14 for 1 year. The inclusion criteria included a dependence on proton pump inhibitor (PPI) drugs to control their reflux symptoms, and a documented oesophageal acid reflux. Exclusion criteria were age less than 18 years, pregnancy, dysphagia, BMI > 40, previous upper gastrointestinal surgery and an hiatus hernia > 2 cms. Pre-procedure assessment included symptom scoring, oesophageal endoscopy, manometry and 24 hour oesophageal pH, and completed questionnaire. Post-procedure assessment was performed at 1, 3, 6 and 12 months. The median duration of the procedure was 50 minutes. The mean heartburn symptom score (heartburn frequency x severity) was 19 pre-procedure and 3 at six months (p = 0.0004). Moderate to severe regurgitation symptoms improved from 76% to 12% at 6/12 (p=0.004). Overall the mean pH DeMeester score reduced from 39.7 to 30.8 (p = 0.03), uprights 13.3 to 6.2 to 9.4 to 6.0 (p = 0.008), number of reflux episodes 168 ± 68 to 117.4 ± 67.7 (p = 0.015). 12/20 patients had a normal pH profile at 3 months follow up. Use of PPI reduced from 100% to 38%.

No significant adverse events occurred. QOL assessment showed significant improvement in all modalities (p = 0.001). Endocinch is a safe and effective method of managing GORD. Three months post procedure demonstrated improved symptoms, reduced acid reflux and reduced requirement for PPI drugs. The degree of improvement in symptoms and PPI requirement remained constant for up to 1 year post procedure.

COMPARISON OF SURGICAL PERFORMANCE IN UPPER GASTROINTESTINAL SURGERY USING HIERARCHICAL LOGISTIC REGRESSION

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Introduction: Predictive models are increasingly being applied to evaluate surgical performance in upper GI surgery. We describe the use and limitations of hierarchical models in making quantitative comparisons between teaching and non-teaching institutions. Methods: A longitudinal study of 981 patients undergoing major oesophagogastrectomy resections from 31 UK hospitals from 1995 to 2000. Primary outcome was in-hospital mortality and risk-adjusted mortality. A two-level random effect logistic regression model was developed using age, pre-operative POSSUM and staging as "level 1" patient risk factors and teaching unit status as "level 2" risk factors.

Results: Mortality in the study was 11.3%. On univariate analysis crude operative mortality was significantly different between units (range 0% to 26.8%, p=0.001) and between teaching (8.8%, n=374) and non-teaching (13.3%, n=607) hospitals (p=0.032). Following risk-adjustment for patient related covariates, the teaching hospital status was not an independent predictor of outcome in the hierarchical model (Odds ratio 0.87, CI=0.63–1.21) despite a significant variation in inter-hospital operative mortality.

Conclusions: Although the divergence in performance may relate to bias in data collection, the study suggests that the 'institution or surgeon effect' plays a determining role in the quality of healthcare provision in Upper GI surgery.

Funding: The Royal College of Surgeons of England.

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A COMPARISON OF SYSTEMATIC REVIEWS OF HELICOBACTER PYLORI ERADICATION FOR NON-ULCER DYSEPSIA

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Objectives: We have published a Cochrane systematic review on the efficacy of H. pylori eradication therapy in non-ulcer dyspepsia (NUD). We reported that this intervention had a statistically significant effect in curing dyspepsia symptoms. A US systematic review suggested there was no significant effect of H. pylori eradication therapy on NUD symptoms. We explored reasons for these discrepant results.

Results: We identified six differences in methodology. The US review included all dual, triple and quadruple H. pylori eradication therapies, searched until December 1999, did not contact authors, included abstracts, assumed drops outs were treatment failures and...
analysed results as odds ratio for cure. The Cochrane review included all therapies proven to successfully eradicate *H. pylori*, searched until May 2000, contacted authors, only included abstracts if further information was available, excluded drop-outs from the analysis and analysed results as relative risk of remaining dyspeptic. The influences these factors had on the conclusion of the review are outlined in Table. Excluding trials published in 2000 had a major impact on the results. This study aimed to determine whether *H. pylori* inhibited these two processes in vitro.

Methods: Extracts of three *H. pylori* strains were tested on human umbilical vein ECs: a cagA+ vacA s1/m1 (toxigenic) strain, its VacA-isogenic mutant (non-toxigenic) and a cagA+ vacA s2/m2 (non-toxigenic) strain. Campylobacter jejuni and Escherichia coli were also tested. To determine proliferation, ECs were exposed to extracts for 24, 48, 72 and 96 hrs. An MTT proliferation assay quantified EC proliferation over 4.5 hrs using a microchemotaxis chamber following a 24 hr pre-incubation period. Relevant controls were performed in all cases.

Results: Control ECs significantly proliferated at 72, and 96 hrs (P<0.01). No proliferation was observed with the *H. pylori* strains or *C. jejuni*. ECs treated with *E. coli* showed similar proliferation to controls. No significant increase in apoptotic or necrotic cell number (P<0.01). No proliferation was observed with the *C. jejuni* or *E. coli*. VEGF significantly increased control migration in vitro and serum gastrin measured basally (BAO) and in response to infusion of Gastrin 17 at 7, 20, 60, 180 and 800 pmol/Kg/h. This allowed one to calculate their sensitivity to gastrin ie gastrin concentration achieving 50% maximal acid output (MAO).

Discussion: The higher gastrin and lower sensitivity to gastrin in *Cag+ve* are likely to be explained respectively by more severe antral gastritis and more severe body gastritis.

Conclusion: Any protective effect of Cag+ve infection in reflux disease cannot be explained by effects on acid secretion but might be explained by effects of hypergastrinaemia.

### Abstract 028

**STUDIES OF THE EFFECT OF H. PYLORI CAGA +VE VERSUS CAGA –VE H. PYLORI INFECTION ON ACID SECRETION IN HEALTHY VOLUNTEERS**

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**Introduction:** The presence of a Cag+ve strain of *H. pylori* is protective against oesophagitis and GO junction cancer. Some have suggested that this effect may be due to acid hyposecretion in Cag+ve. However, we have previously reported that Cag+ve subjects have a higher degree of hypergastrinaemia than Cag–ve, yet a similar level of acid secretion basally and in response to gastrin stimulation. It remained unclear why the higher plasma gastrin was not leading to an increased acid secretion in Cag+ve infection.

**Aims:** To determine the effect of Cag status on gastric physiology.

**Methods:** 15 Cag+ve and 11 Cag–ve *H. pylori* positive healthy subjects and 27 *H. pylori* negative healthy subjects had their acid output and serum gastrin measured basally (BAO) and in response to infusion of Gastrin 17 at 7, 20, 60, 180 and 800 pmol/Kg/h. This allowed one to calculate their sensitivity to gastrin ie gastrin concentration achieving 50% maximal acid output (MAO).

**Results:** The Cag+ve had a reduced sensitivity to gastrin compared with both Cag–ve and *H. pylori* negatives. However, the Cag+ve also have a higher gastrin level resulting in a similar acid output to both Cag+ve and *H. pylori* –ve [see table].

**Conclusion:** Laparoscopy improved the perceived preoperative computed tomographic stage of gastric cancer.

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**Background:** The recent audit of oesophagogastric cancer in Wales demonstrated that many surgeons continue to undertake small case loads and revealed an open and close laparotomy rate of 23%. Wider use of laparoscopy was advocated strongly.

**Aims:** The aim of this study was to examine the benefit of universal staging laparoscopy in the preoperative staging of gastric cancer and to determine the strength of agreement with the true histopathological stage.

**Methods:** One hundred consecutive patients (median age 71 years [35–86], 59 male) were studied prospectively. All patients underwent staging computed tomography (Siemens somatom +4) prior to laparoscopy. The strength of agreement between the perceived preoperative radiological stage, the laparoscopic stage and the histopathological stage was determined by means of the weighted Kappa statistic (Kw).

**Results:** See table.

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### Table: BAO 3.2 (2.6–9.6) 2.4 (3.0–3.8) 2.3 (0.9–5.4) 7pmol/Kg/h 7.8 (3.3–14.3) 7.7 (2.7–14.2) 8.6 (5.6–15.2) 20pmol/Kg/h 15.0 (11.5–23.5) 17.2 (11.2–23.2) Sensitivity (%)* 67 92 98 98 Kw 0.35* 0.30** 0.49* 0.70* Kw 95% C.I. 0.18–0.53 0.11–0.49 0.35–0.64 0.57–0.85

**Conclusion:** Laparoscopy improved the perceived preoperative stage from fair to moderate for T stages and there was a significant twofold improvement from fair to good for M stages. This resulted in an open and close laparotomy rate of 12% rather than the 33% (Chi² 12.65, P<0.0001) that would have resulted without laparoscopy.
THE EFFECT OF REDUCED QUALITY OF LIFE ON THE SUBSEQUENT DEVELOPMENT OF DYSPEPSIA AND IRритABLE BOWEL SYNDROME: A PROSPECTIVE COHORT STUDY

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Introduction: Dyspepsia and irritable bowel syndrome (IBS) are associated with reduced quality of life (QoL). The temporal relationship between these events is unclear. We evaluated this in a cohort study.

Methods: This cohort study was nested in a randomised controlled trial that evaluated the clinical benefit of H pylori screening and treatment in the community. Subjects between the ages of 40–49 years were randomly selected to attend their local general practice. H pylori status was assessed by 13Curea breath test and infected individuals were randomised to eradication therapy or placebo and followed up for two years. QoL was assessed by the Psychological General Well Being Index (PGWBI, equivalent to the Gough Disability Scale), Dyspepsia Severity Score, ++ve subjects who have a deficient dietary intake and low plasma vitamin C concentration pre-treatment. The further reduction in systemic vitamin C in H pylori +ve subjects during proton pump inhibitor therapy may contribute to their propensity to develop atrophic gastritis during such therapy.

THE WORK PATTERNS OF GASTROENTEROLOGY SPECIALTY TRAINERS IN THE UK - A Prospective Audit

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PROTON PUMP INHIBITOR THERAPY REDUCES BIOAVAILABILITY OF DIETARY VITAMIN C

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Background and Aims: Vitamin C is denaturated in gastric juice of high pH being converted irreversibly to diketogulonic acid. We have examined the effect of the elevation of intragastric pH which occurs during proton pump inhibitor therapy on the bioavailability of dietary vitamin C.

Methods: 29 healthy volunteers (13 female, 15 H. pylori positive) had their fasting plasma vitamin C measured on 4 occasions before and again on four occasions during the last week of a one month course of omeprazole 40mg/day. Vitamin C was measured by HPLC using a reverse-phase column, and a mean value calculated for each patient for before treatment and during the fourth week of treatment. 24h intragastric pH was also monitored in each patient before and during the last week of treatment. Dietary intake of vitamin C was measured over the week pre-treatment and last week of treatment using daily food diaries and the Diet 5 dietary analysis programme.

Results: Prior to commencing omeprazole, the mean plasma vitamin C concentration (µg/ml) in the H. pylori –ve subject was 25.1 (range 16.1–33) and substantially lower at 17.4 (6.7–29) in the H. pylori +ve subject (p=0.001). Mean daily dietary intake of vitamin C (mg/day) was also markedly lower in the H. pylori +ve group compared to the H. pylori –ve group (141, 23–282) (p<0.001) and the fall was similar in the H. pylori +ve and –ve subjects. Dietary intake of Vitamin C (mg/day) was the same before (94.7) and during omeprazole treatment (93.3).

Conclusion: Proton pump inhibitor therapy lowers the bioavailability of dietary Vitamin C. This is likely to be of clinical significance in H. pylori +ve subjects who have a deficient dietary intake and low plasma vitamin C concentration pre-treatment. The further reduction in systemic vitamin C in H. pylori +ve subjects during proton pump inhibitor therapy may contribute to their propensity to develop atrophic gastritis during such therapy.

GASTROINTESTINAL HAEOMORRHAGE AND OVER THE COUNTER IBUPROFEN USE

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Introduction: Ibuprofen, a frequently used analgesic, is available without prescription (over the counter, OTC). Upper gastrointestinal complications (UGIC) ranging from minor dyspeptic symptoms to life threatening events such as haemorrhage and perforation may occur. Risks of UGIC depend on factors such as age, previous history of GI and other comorbid diseases, and the dose of ibuprofen used. We have calculated the excess number of UGIC requiring hospitalisation that may be expected from the amount of ibuprofen sold for OTC use in 2000 in the United Kingdom (UK) for a low risk population.

Methods: The risk for UGIC was calculated from the population in Tayside, Scotland who had redeemed a prescription for ibuprofen (>200mg/day, equivalent to the maximum daily dose (MDD) available OTC) between Jan 1989 and Dec 1995, and were at risk for GI events. We linked exposure to hospitalisation for UGIC in these patients exposed and not exposed to ibuprofen. IMS Health (UK) supplied data on the total weight of ibuprofen sold in the UK in 2000. Assuming the UGIC risk in Tayside was the same as the UK, the excess number of UGIC for the estimated OTC use in 2000 was calculated.

Results: The risk of UGIC whilst exposed to OTC MDD ibuprofen was 1.62 events/thousand patient years (TPY) and unexposed was 0.85 events/TPY. Thus, the excess risk was 0.75 events/TPY: 46,000 kg of ibuprofen was sold OTC in 2000. Assuming all usage at the MDD, 81 UGIC would be attributable to OTC ibuprofen exposure. An equivalent of 1.3 events per million population.

Conclusion: There is a small estimated excess risk of serious GI events associated with ibuprofen at doses available OTC. Ibuprofen when used at recommended OTC dosages in a low risk population must be considered very safe.

WORKLOAD AND TRAINING: AN AUDIT COMPARING THE WORK PATTERNS OF GASTROENTEROLOGY TRAINEES WITH OTHER MEDICAL SPECIALTIES

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Background: Most consultant gastroenterologists provide a service in both acute medicine and gastroenterology and most trainees seek dual accreditation. Reports confirm a growing workload for consultants and the need for workforce expansion. One of the aims of the “Calman” specialist registrar programme was to provide higher quality training in a shorter time period. A recent survey in our region suggested that changes arising from the “New Deal” would lead to reductions in clinic and endoscopy experience amounting to a loss of about 30 weeks of training. The aim of this study was to compare the workload and training patterns of gastroenterology trainees with those of other medical specialties.

Methods: All trainees in our region were asked to complete a survey documenting their typical weekly timetable and an identical survey was completed by a sample of trainees from other medical specialties.

Results: 25 gastroenterology trainees from 14 hospitals (5 teaching, 9 DGH) completed questionnaires. 23 trainees from other
WHAT DOES OPEN ACCESS ENDOSCOPY ACHIEVE?

Aims: To determine whether open access endoscopy identifies significant numbers of patients with malignant upper GI disease. To determine whether we could identify low risk groups that could be managed without endoscopy.

Methods: Data on all open access endoscopies was collected over a 2 year period. A retrospective analysis was undertaken to identify patients with a diagnosis of gastric and oesophageal cancer. All patients in the group were compared with 50 who attended over the same time period. Both groups completed three questionnaires, namely: (1) Demographic and lifestyle details, including alcohol and cigarette consumption, employment and home circumstances. (2) The modified Glasgow Dyspepsia Scoring Questionnaire, as an index of their dyspepsia. (3) Fear of the endoscopy (where 0 = no fear and 10 = terrified). The DNA group was asked to select an appropriate reason for failure to attend from a list of prepared options.

Results: There was no significant difference between the mean ages of the DNA group (48.0 yrs) and those attending (54.8 yrs, p>0.05). The DNA group were more likely to be male (p<0.05), smokers (p<0.05), to live alone (p<0.05) and had a significantly higher fear score (6.9 vs 3.9, p<0.05) but a lower dyspepsia score (7.4 vs 8.9, p>0.05) than those attending. The most frequently stated reason for non-attendance was fear of the test (44%), and 46% of those stated they would have attended had the test been better explained to them.

Conclusion: Those who fail to attend for OAE tend to be male, are smokers, live alone and have a high fear of the test. The DNA rate could be reduced if GPs were advised of the characteristics of those likely to fail to attend and a better explanation of the procedure was given to patients, especially those with a high fear score.

THE IMPACT OF PATIENT CHOICE ON GASTROENTEROLOGY (GI) CLINIC AND ENDOSCOPY SERVICE EFFICIENCY

Aims: To redesign GI clinic and endoscopy booking systems to allow patients a choice of hospital appointments. To assess the effect on cancellation, rearrangement and attendance rates.

Methods: Initially, all patients being referred from GPs to our open access colonoscopy service and to one of our GI clinics were involved. Upon receipt of the referral, patients were contacted immediately by return of post, inviting them to telephone the unit to negotiate a convenient date. Two call centres were established—for clinic and open access colonoscopy referrals.

Results: Clinic: In the preceding 6 months, 259 were seen, the “Did Not Attend” (DNA) rate was 9 % and the cancellation & rearrangement rate was 15 %. In the first 2 months of the new system, 119 patients were seen. The DNA rate and patient cancellation & rearrangement rate had fallen to 2.5 % (p < 0.05) and 2 % (p < 0.05) respectively.
A041 EMPIRICAL ACID-SUPPRESSING DRUG THERAPY (AST) IS ASSOCIATED WITH DELAYED DIAGNOSIS OF OESOPHAGO-GASTRIC CANCER

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Background: The detection of Early Gastric Cancer (EGG) in the UK remains low despite the widespread availability of gastroscopy. It has been suggested that acid-suppressing therapy (AST) given prior to gastroscopy can delay diagnosis.

Aims: This large retrospective study aimed to examine the history prior to the diagnosis of oesophago-gastric adenocarcinoma and identify the potential for making the diagnosis earlier.

Methods: All upper GI adenocarcinomas diagnosed in South Tees Health District (population ~350,000) were identified from the pathology and NYCRIS databases. The GP records were reviewed and the data correlated with the pathology and hospital records.

Results: 747 patients were identified (April 1991 to April 2001). 92% had primary adenocarcinomas (29% oesophageal, 71% gastric). 6% were excluded on codes. Of the 296 procedures on diagnosis was missing. The M:F was 65.8:34.2; mean age at diagnosis was 70 years (range 28-94). The symptoms at time of diagnosis included anaemia/weight loss/dysphagia in 78.4%, epigastric pain (without alarm symptoms) in 10.1%, dyspepsia/reflux in 3.4%. Of the 685 patients with adenocarcinoma 48% had AST between 1st GP consultation and diagnosis and in 67% this was initiated immediately. Overall a cancer diagnosis was suspected by the GP in 38.3% of cases. For those treated prior to gastroscopy the mean time from 1st GP visit to diagnosis was 26.7 weeks compared with 8.8 in those not treated (p=0.001). Of the 357 patients not treated with AST prior to diagnosis only 12.6% had a previous gastroscopy within 3 years of diagnosis, whereas of the 228 prescribed AST prior to diagnosis this figure was 42.4% (p=0.001). Overall, 35.5% of patients had a previous upper GI investigation within 3 years of diagnosis (75.7% OGD, 14.8% barium studies, 9.5% US.) 28% had investigations more than 3 years previously.

Conclusion: 1 in 2 patients receive AST prior to diagnosis increasing the mean time from 1st GP visit to diagnosis by 17.9 weeks. 35% of cancers were not diagnosed at the time of their first investigation. As 22% had only benign symptoms at diagnosis decisions regarding treatment or investigation should not be based solely upon symptoms but on an overall assessment of risk.
(overall 20.6, with AST 31.6, without AST 8.6 weeks), strictures being delayed by 11.1 weeks (overall 13.6, with AST 19.9, without AST 8.8 weeks) and the cancers presenting as tumour masses being delayed by 8.8 weeks (overall 12.1, with AST 17.5, without AST 8.7 weeks). Of the ulcer cancers 24.2% had had a previous gastroscopy within 3 years of the diagnosis compared with 27.9% of the mucosal abnormalities, 24.2% of the strictures and 19.5% of the cancers presenting as a tumour mass (p=0.008).

Conclusion: The results show that AST therapy is associated with a delay in the diagnosis of all morphological types of oesophago-gastric adenocarcinoma through all modes of referral including OP clinics and open access. Ulcer-cancers and mucosal abnormalities are more likely to have received AST and are more likely to have had a previous gastroscopy (within 3 years of diagnosis). This suggests more potential to diagnose these types of oesophago-gastric cancer earlier by avoiding AST treatment and performing a gastroscopy earlier.

**043** PREDICTIVE VALUE OF ALARM SYMPTOMS IN DYSPEPSIA FOR SIGNIFICANT UPPER GASTROINTESTINAL PATHOLOGY

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Background and Aim: Alarm symptoms in dyspepsia are thought to predict significant pathology at endoscopy (OGD). However few studies have assessed their predictive value. Our aim was to determine the predictive value of alarm symptoms for significant pathology.

Methods: Consecutive outpatients with dyspepsia undergoing OGD were studied prospectively. Inpatients with acute upper GI haemorrage were excluded. Patient demographics, OGD indications, all symptoms including alarm symptoms, ie. vomiting, weight loss, dysphagia, haematemesis, melaena, anaemia were prospectively recorded. Logistic regression analysis with backward elimination was used to determine which symptoms were significantly associated with particular pathologies and the odds ratios were determined.

Results: 449 patients were recruited. Dysphagia was significantly associated with oesophagitis (odds ratio [OR] 2.9). Vomiting, weight loss, dysphagia, haematemesis, melaena, anaemia were prospectively recorded. Logistic regression analysis with backward elimination was used to determine which symptoms were significantly associated with particular pathologies and the odds ratios were determined.

Conclusions: Alarm symptoms of dysphagia, haematemesis, melaena, anaemia were predictive of significant pathology at endoscopy. In particular dysphagia was strongly predictive of oesophageal cancer. Vomiting and weight loss were not predictive of significant pathology. Non alarm symptoms such as chest pain and atypical dyspepsia were predictive of oesophagitis.

**044** CLO™ TESTING: OPTIMAL NUMBER OF BIOPSIES REQUIRED TO DIAGNOSE HELICOBACTER PYLORI INFECTION BASED ON ITS TOPOGRAPHICAL DISTRIBUTION

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Background: Due to increasing demand, there is immense pressure to perform more numbers of gastroscopies (OGD) per list in busy DGHs. Accurate diagnosis of H. pylori is critical to optimal management of patients undergoing OGD. It is customary to put 1 antral biopsy in a CLO™ well, though it is known that increasing the numbers & sites of biopsies increases the diagnostic accuracy. We suggested that Fibrin Glue (FG) injection improves the final outcome.

Methods: We recruited consecutive patients over the age of 18 years undergoing OGD in a busy DGH who had evidence of gastritis, duodenitis, gastric or duodenal ulcers.

Results: 100 patients underwent CLO testing. 30 patients were CLO positive. Of these 28 were positive in CLO & all 30 in CLO.

Assuming a gold standard of 100% sensitivity for CLO™ (based on our previous publication), the sensitivity of CLO™ is 93.3% (95% CI=78.7% to 98.2%) [see table].

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Conclusion: While it may be preferable to take 2 antral and 1 body biopsies for a CLO™, if due to time constraints or patient restlessness, less number of biopsies are taken, we propose at least 2 topographically different biopsies for CLO™ testing.

**045** FIBRIN GLUE INJECTION FOR THE TREATMENT OF ACUTE UPPER GASTROINTESTINAL BLEEDING


Introduction: The rebleeding rate from bleeding peptic ulcers is still very high despite a range of available treatments. It has been suggested that Fibrin Glue (FG) injection improves the final outcome.
For the treatment of acute upper gastrointestinal bleeding, from high risk upper GI lesions.

Methods: Retrospective case note audit of clinical outcome, of the patients treated with FG injection for spurring or oozing bleeding or due to the presence of a visible vessel following an acute upper GI bleeding, were reviewed. The complication rate, the rebleeding rate, the need for radiological or surgical interventions and the mortality rate were recorded.

Results: From August 1999 to October 2001, 54 patients, 35 men and 19 women were treated with FG injections in 57 admission episodes. Mean age was 62 years (range 17–90). The source of bleeding was oesophageal in 20%, gastric in 27%, duodenal in 49% and multiple in 4% of the cases. A visible vessel was clearly seen in 81% of the cases, was highly suspected in 13% and in 6% spurring or oozing bleeding was present. In addition to FG, in 63% and 5% of the cases, adrenaline 1:10,000 and ethanolamine oleate respectively were injected. Twenty patients were re-injected in total, ten during a second look endoscopy and 10 due to rebleeding. There were no complications related to the treatment. There were 16 (28%) rebleeding episodes, 3 (5%) patients underwent embolisation after rebleeding, 4 (7%) patients had a surgical intervention (2 primary failures and 2 after further rebleeding) and 6 (11%) patients died, one of them having not rebled. From the patients who died, 2 had advanced malignancies and 2 died from post operative complications. Overall control of the bleeding episode with endoscopic treatment was 82%.

Conclusion: In our experience, FG injection is an effective way of treating upper gastrointestinal bleeding from high risk lesions. A prospective study is needed to investigate whether it offers better results than other endoscopic treatments.

ENDOSCOPIC CLOSURE WITH METALLIC CLIPS FOR MUCOSAL DEFECT AFTER ENDOSCOPIC MUCOSAL RESECTION IN PATIENTS WITH INTRAMURAL TUMOURS OF THE STOMACH

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Background and Aims: Endoscopic mucosal resection (EMR) is widely used for treating intramural gastric tumours. The success of this local treatment requires negative margins. To achieve this requirement, the area of the mucosa resected by EMR has been increasingly larger in recent years. The larger the mucosal defect, however, the greater is the risk of complications such as bleeding or perforation after the procedure. The purpose of this study was to clarify if endoscopic closure with metallic clips for mucosal defect by EMR was able to decrease the rate of bleeding.

Methods: The population of the study consisted of 150 patients who underwent EMR for intramural tumours of the stomach. Patients were divided into two groups. The first group was the patients without endoscopic mucosal closure, and the second was the patients treated with endoscopic mucosal closure using metallic clips after EMR.

Results: The number of patients of the first group was 94. In 11 (12%) patients of this group, bleeding following EMR was observed. In patients with mucosal defect less than 20 mm in diameter in this group, bleeding was not detected. The number of patients of the second group was 56. The complete closure rate was 96% (54/56). In this group, bleeding following EMR was encountered in only two (3.6%) patients. Those two patients had been unsuccessful in complete closure of the mucosal defect, because the size of the defect was over 40 mm in diameter.

Conclusions: Endoscopic closure with metallic clips for mucosal defect after EMR was useful for decreasing the bleeding following EMR, especially in large defects over 20 mm in diameter.

INTENSIVE CARE ENDOSONOGRAPHY AND GUIDED FINE-NEEDLE ASPIRATION FOR DIAGNOSIS AND MANAGEMENT OF POSTERIOR MEDIASTINITIS

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Background: Tissue diagnosis of splenic lesions is usually obtained using CT or US guidance, but is limited to a size of approximately 1.5 cm. It may be dangerous if the lesion is adjacent to the splenic hilum or not surrounded with sufficient residual splenic tissue to protect the puncture site. However, tissue diagnosis is essential in a variety of diseases to direct therapy. We used EUS-FNA to perform in real time conditions in unknown splenic foci to reveal tissue diagnosis.

Methods: EUS-FNA was performed in 12 patients, when US- or CT-guided biopsy failed to achieve the diagnosis (n=5), was not attempted due to the small size of the lesions (n=5, size of foci: 0.9–1.4 cm), or was supposed to be too dangerous due to the fear of it being a hemangioma, or covered by insufficient residual splenic tissue. EUS and EUS-FNA was carried out using a linear echo-endoscope and 22 gauge needles for cytology. In each of the patients a separate pucture for bacteriology was carried out in addition to that for cytology.

Results: The age of the patients was 19–68 years (median: 32; 7 males). The size of the lesions was 0.8–4.2 cm; median: 1.4 cm. Cytology was inadequate in 1 patient, in whom only blood was aspirated. Bacteriology was positive for staphylococcus in 2 patients and cultures were positive for mycobacterium tuberculosis in two. Final diagnosis was tuberculosis in 2, Hodgkin’s disease in 2, sarcoidosis in 2 and metastasis of colon cancer, abscess, infection and exclusion of a recurrent non Hodgkin’s lymphoma in each one. All patients with or exclusion of a suspected malignancy were followed up for at least 6 months. Those with benign diseases were followed up to check that other techniques including bacteriological culture, confirmed diagnosis. There were no complications despite the fact that 2 patients had severe septicemia and one agranulocytosis.

Conclusion: EUS-FNA cytodiagnosis in patients with unknown splenic lesions seems feasible even in very small foci, when CT- or US guided biopsy fail. Additional material for bacteriology may show benign diseases such as abscesses or tuberculosis.

Inflammatory bowel disease free papers 049–062

ALTERED COLONIC GLYCOPROTEIN EXPRESSION IN UNAFFECTED MONOZYGOTIC TWINS OF INFLAMMATORY BOWEL DISEASE PATIENTS

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Introduction: Alterations in epithelial glycoprotein expression in inflammatory bowel disease (IBD) include increased expression of the epithelial glycoprotein CD15. We have previously reported that a 65 kDa glycoprotein is increased in the apical or basolateral membrane of cultured Caco-2 cells in response to 25-OH vitamin D3, and to tumour necrosis factor α (TNFα). While increased expression of this protein has been reported in patients with active disease, no studies of unaffected monozygotic twins of inflammatory bowel disease (IBD) patients have been reported.

Aims: To review our experience with Fibrin Glue (FG) injection for the treatment of acute upper gastrointestinal bleeding, from high risk upper GI lesions.
oncofetal carbohydrate antigens, TF (galactose-1,3N-acetylgalactosamine) and sialyl-Tn (sialyl 2,6N-acetylgalactosamine). Previous chromatographic colonic mucin analysis in monozygotic twins with IBD suggested a possible genetic basis for these changes (Tysk et al, Gastroenterology 1991;100:419). The present study aimed to explore this further by assessing mucosal expression of specific glycoprotein epitopes amongst IBD twins.

Methods: Formalin-fixed rectal biopsies from 22 monozygotic twin pairs with IBD were studied (6 pairs concordant for UC or CD; 16 healthy twins). Affected twins were in clinical and endoscopic remission. Expression of sTn and TF was assessed by indirect immunohistochemistry using a specific monoclonal antibody and peanut lectin respectively, and compared with expression in rectal biopsies from normal mucosa (irritable bowel syndrome) controls (n=14 sTn; n=17 TF) with investigators blinded for diagnosis. TF positivity was scored from 0 to 3.

Results: Compared to histologically normal controls, unaffected twins showed significantly greater TF positivity and a trend towards greater sTn positivity (table). Of the 5 unaffected twins who were sTn positive, 4 had twins with UC and 1 with CD. One of the sTn-positive/TF positive healthy twins has subsequently developed UC.

Conclusions: The positive findings in unaffected twins support previous evidence of a biochemical mucin defect. This could be the result of a direct genetically determined alteration in glycosylation or of a secondary, eg cytokine-mediated, alteration in glycosylation. The altered glycosylation could be relevant in determining changes in the mucosal-associated bacterial flora.

050 IL-10 GENE THERAPY AMELIORATES TNBS INDUCED COLITIS

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Introduction: Recent therapeutic strategies for Crohn’s disease (CD) have focused on modulating the immune response by targeting cytokines and their receptors. For example, daily injections of recombinant IL-10, a pivotal immunoregulatory cytokine, are safe and well tolerated, but have shown limited benefit in clinical trials. An alternative therapeutic approach using adenoviral vectors to deliver IL-10 has proven superiority over daily IL-10 injections in IBD-/- mice with colitis.

Aims: The oetiology of CD is more complex than the deletion of a single immunoregulatory gene. Thus, we investigated the therapeutic efficacy of adenoviral vectors encoding IL-10 (AdvmuIL-10) in mice with trinitrobenzenesulfonic acid (TNBS) induced colitis, a Th1 dependent disease that is also unresponsive to daily IL-10 injections.

Methods: Balb/C mice received a single i.v. injection of 1x10^9 PFU AdvmuIL-10, empty cassette virus (Adv0) or PBS. After 24 hours colitis was induced by two intra-rectal doses of 0.5 mg TNBS or vehicle separated by seven days. Mice were sacrificed 48 hours after the second dose of TNBS.

Results: Mice treated with AdvmuIL-10 suffered significantly less weight loss over time than Adv0 or PBS controls after TNBS administration (p<0.0001 by 2 way ANOVA). In addition, AdvmuIL-10 therapy led to a significant reduction in stool pro-inflammatory cytokine levels and acute phase response. Finally, the histological score of mice with TNBS colitis treated with AdvmuIL-10 was significantly lower than Adv0 or PBS treated controls (7.1±0.9 compared to 10.4±1.0 and 10.8±1.3 respectively; p<0.05). The therapeutic efficacy of AdvmuIL-10 was associated with a decrease in the TNF-α, IFNγ and IL-6 levels detected in colonic homogenates from mice with TNBS colitis. AdvmuIL-10 had no effect on cytokine release from stimulated systemic lymphocytes.

Conclusion: AdvmuIL-10 offers superior therapeutic efficacy to daily IL-10 injections in the TNBS model of colitis. Gene therapy strategies using adenoviral vectors encoding IL-10 may prove to be a potent therapy for chronic inflammatory conditions such as Crohn’s disease.
independent of TNF-1031C. Subgroup analysis of HLA-B*51, B*57 negative patients however revealed that the association with TNF-1031C remained (P=0.024; RR=1.9 CI 1.1–3.2).

Conclusions: (1) TNF-1031C is associated with susceptibility to Caucasian BD independently of the recognised association with B*51 and the novel association with B*57. (2) Transracial and functional studies are required to dissect out the complex linkage disequilibrium demonstrated by this study.

053 THE MOLECULAR CLASSIFICATION OF THE CLINICAL MANIFESTATIONS OF CROHN’S DISEASE

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Background: Crohn’s disease (CD) is characterised by extensive heterogeneity in terms of disease location, behaviour and response to treatment. The major focus of recent genetic research in CD has been the identification of susceptibility rather than phenotype determining genes. NOD2 on chromosome 16 and the HLA region on chromosome 6 have been associated with disease overall but there are no data regarding contribution to specific disease subtypes.

Methods: We studied 240 accurately characterised Caucasian CD patients who had been followed up at a single centre for a median time of 16 years and 354 healthy controls. Three NOD2 variants (Arg702Trp, Gly908Arg, Leu1007fsinsC) were studied and linkage disequilibrium mapping applied across 340 HLA polymorphisms, broken down into 24 discrete gene haplotypic blocks (alleles). Genetic comparisons were made between CD patients and healthy controls.

Results: The NOD2 variants were associated with ileal disease only (P<0.0001; RR=4.1). All 42 patients who possessed Leu1007fsinsC had ileal disease (P=0.0001). The risk of ileal disease was greatest in compound heterozygotes and homozygotes (P<0.0001; RR=37.4). Early age of onset was associated with carriage of Leu1007fsinsC (P=0.006) and compound heterozygosity (P=0.03). In contrast alleles on specific extended HLA haplotypes determine overall susceptibility (Cw*0802, P=0.0004, RR=3.05; DRB1*0701, P=0.03, RR=1.61), location (Perianal: MICA*010, P=0.01, RR=2.1; Colonic: BATIA1, P=0.0003, RR=3.6) and behaviour (Fistulating disease: DRB1*0103, P=0.02, RR=3.4).

Conclusions: (1) The clinical heterogeneity of CD may be defined by genetic background. (2) Patient stratification by such a molecular classification may lead to a better understanding of the different mechanisms that underlie this clinical heterogeneity.

054 BEHÇET’S OR CROHN’S DISEASE? COMBINATION HLA-B*51 AND NOD2 MOLECULAR TYPING MAY HELP DECIDE

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Background: BD is a chronic multisystem inflammatory disorder that shares many clinical features with Crohn’s disease (CD), including gastrointestinal inflammation, oral ulceration, uveitis and erythema nodosum. There are however important differences in prognosis and treatment. Association with HLA-B*51 and susceptibility to BD has been reported worldwide although in Caucasian BD this allele is present in only one third of patients. Three groups have reported associations between variants in the NOD2 gene and susceptibility to CD.

Methods: We studied 580 accurately characterised Caucasian BD patients and 350 healthy Oxfordshire control subjects were studied.

Results: HLA-B*51 was significantly associated with BD only; 32.4% vs. 9.9%; P=2x10^{-6}. No association was found between NOD2 LRR variants and susceptibility to BD despite stratification by B*51 status. When BD and CD patients were compared possession of a NOD2 variant without HLA-B*51 carried a likelihood ratio (LR) of CD rather than BD of 6.8. Conversely possession of HLA-B*51 without a NOD2 variant carried a LR of 4.7.

Conclusions: Individuals with NOD2 LRR variants may be used to molecularly distinguish BD from CD. (3) Polymorphisms in other regions of the NOD2 gene need to be studied in BD before NOD2 can be excluded as a susceptibility gene for BD.

055 IMPORTANCE OF DIFFERENT NOD2 MUTATIONS IN UK CAUCASIAN CROHN’S DISEASE.


Introduction: NOD2 has recently been identified as the susceptibility gene for Crohn’s disease on chromosome 16. Three distinct NOD2 mutations (Arg702Trp, Gly908Arg and Leu1007fsinsC) have been reported to be independently associated with Crohn’s disease in European Continental and North American populations. NOD2 is a monocyte protein, which recognises intracellular bacterial components and through NF-kB activation stimulates cytokine production.

Aims: To assess the relative importance of the three NOD2 mutations previously associated with Crohn’s disease (CD), in the UK population.

Methods: We genotyped 587 IBD families (containing 252 UC, 294 CD trios, 321 unrelated CD cases) and 239 healthy controls (HC) (all UK Caucasian). Family based (ASPEX transmission disequilibrium test, TDT) and case-control association analyses were performed on unrelated cases were selected one per family, at random, and an average taken of 1000 such selections). Population attributable risk (PAR) was calculated.

Results: Significant associations with Crohn’s disease were seen for the Arg702Trp (TDT Transmitted/Untransmitted 65/37, P=0.01, allele frequency in unrelated CD cases 10.6% vs. HC 2.8%) and Leu1007fsinsC (47/9, P=0.001, 7.1% vs. 2.2%) mutations. No association was seen with Gly908Arg (11/12, P=0.1, 1.9% vs. 0.7%) mutations of PAR were Arg702Trp 14%, Leu1007fsinsC 10%, all tested mutations 23%. Genotype relative risks of Crohn’s disease were: Arg702Trp heterozygotes 3.5, homozygotes 58.9; Leu1007fsinsC heterozygotes 2.7, homozygotes 53.7; possession of any 2 mutant alleles 38.2.

Conclusion: The Arg702Trp variant is the most common NOD2 mutation in UK Crohn’s disease, and carries the greatest relative risk and population attributable risk. The biological function of the Arg702Trp mutation is unknown. The Leu1007fsinsC mutation is also common in UK Crohn’s disease, whereas the Gly908Arg mutation is extremely rare. The PAR calculation suggests there would be 23% less Crohn’s disease in the UK if these NOD2 mutations had not arisen.

056 HAPLOTYPIC ANALYSIS OF HEAT SHOCK PROTEIN 70 (HSP70) SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) IN SUSCEPTIBILITY AND PHENOTYPE OF INFLAMMATORY BOWEL DISEASE (IBD)

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Background: The HSP70 gene family comprises three genes (HSP70-1, HSP70-2 and HSP70-Hom) located in the HLA class III region, an area implicated in determining disease susceptibility and phenotype in both Crohn’s disease (CD) and ulcerative colitis (UC). The encoded proteins, expressed in response to cellular stress, are involved in intracellular protein folding and the chaperoning of peptides through the endoplasmic reticulum.

Aims: To determine whether haplotypes constructed from SNPs in two HSP70 genes are associated with disease susceptibility, location and behaviour of IBD.

Methods: We studied 580 accurately characterised Caucasian BD patients [263 CD, 317 UC] and 341 healthy controls. Three synonymous HSP70-1 SNPs [A-110C, G190C, C438T] and two non-synonymous HSP70-Hom SNPs [T2437C, G2763A] were studied using PCR-SSP.

Results: Six HSP70 gene haplotypes were constructed from the five biallelic SNPs. H1 [AGTCG] conferred protection to CD overall
(p=0.04, RR 0.7, CI 0.5–0.9). H5 (CCCTG) was associated with colonic disease (p=0.01, RR 1.6, CI 1.1–2.3) and H2 (AGCCG) with ileal disease (p=0.03, RR 1.8, CI 1.05–3.2). A negative association with H1 and perianal disease (p=0.008, RR 0.53, CI 0.3–0.8) was also found. When disease behaviour was analysed, H4 (AGCTG) (p=0.04, RR 1.51, CI 1.02–2.1) was associated and H1 (p=0.04, RR 0.65, CI 0.4–1.0) protective for stenotic ileal disease. No association was found with HSP70 gene haplotypes and UC susceptibility or phenotype.

Conclusion: Specific HSP70 gene haplotypes are associated with clinical CD phenotypes. Functional studies are required to clarify whether these associations are due to linkage disequilibrium with SNPs in other HLA genes.

CHINESE PATIENTS IN SINGAPORE WITH LATE ONSET ULCERATIVE COLITIS HAVE MORE SEVERE DISEASE

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Introduction: The clinical features and natural course of ulcerative colitis (UC) in older patients is controversial. Reports in Western literature before 1980 suggested that UC in older patients is more aggressive, but recent studies suggest the opposite. There have been no reports on Orientals.

Aim: Describe and compare the features and disease course of Chinese UC patients in Singapore diagnosed before and after 50 years of age.

Methods: The notes of all Chinese UC patients followed up in the Singapore General Hospital for the last 30 years were reviewed. Late onset colitis was defined as UC diagnosed at or after 50 years of age. Extensive colitis was defined as UC extending proximal to the splenic flexure. Severity was determined using Truelove and Witts criteria.

Results: One hundred and thirty eight patients were diagnosed before 50 years of age (92 men 46 women, mean age 32), and 37 diagnosed at or after 50 (19 men 18 women, mean age 60). They were followed up for at least 1 year. Mean time to diagnosis from symptom onset was 8 months for younger patients, and 14 months for older patients. Significantly more older patients had extensive disease at diagnosis, 18(50%) versus 36(26%) in younger patients (p=0.019). Thirteen (9%) younger patients had severe disease at diagnosis, compared with 9(24%) older patients (p=0.023). Nine (25%) patients with late onset colitis only had the initial attack of colitis versus 51(37%) of younger patients. A greater proportion of older patients (22%) were steroid dependant or needed a steroid sparing agent compared with younger patients (12%). These did not reach statistical significance. Nine (24.1%) patients with late-onset colitis required proctocolectomy for fulminant colitis or poorly controlled disease versus 15 (10.9%) patients with early-onset disease (p=0.034).

Conclusions: Chinese patients with late onset UC have significantly more severe and extensive disease at onset. They are more likely to require surgery for fulminant colitis or poorly controlled colitis compared with younger patients.

IN SCOTLAND, MONTH OF BIRTH IS NOT LINKED TO RISK OF CROHN’S DISEASE IN CHILDHOOD

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Introduction: The incidence of juvenile onset Crohn’s disease (CD) continues to rise in Scotland over the past 3 decades. A recent Danish report on Orientals.

Data on outcome of in-patient management of severe colitis is mainly available from single-centre studies in specialist hospitals. In preparation for a national clinical trial, prospective centres were asked to record clinical details of all patients admitted for intensive treatment of ulcerative colitis (UC) between May 1 and July 31 2001.

Methods: Data forms were sent to 45 centres intending to participate in the trial, and data collected on UC extent, duration, severity, outcome of treatment, and for patients undergoing colectomy – reasons for surgery.

Results: 116 patients, 53% male (median age 42, range 17–100) from 29 centres were reported. All received steroids. In 32 (28%) it was the first attack, and 78 (68%) fulfilled Truelove and Witts’ criteria for a severe attack at admission. 47 (41%) responded completely (stool freq. <3), 36 (31%) had a partial response to treatment (stools >3, or visible blood), and 33 (28%) had a colectomy during that admission. On admission, median stool freq. (10/day), pulse (90bpm), temp. (37.0°C) and haemoglobin (12.3g/dl) did not differ significantly between the three groups. Admission CRP (n=78, median 63mg/l) did not predict response, but admission ESR (n=44) was significantly higher in the colectomy group (median 65mm/hr) vs complete response [34mm/hr] or partial response [20mm/hr] groups (Kruskall-Wallis, p=0.005). Outcome was not influenced by disease extent, duration or other factors. 15 received ciclosporin, with 9 avoiding colectomy. Follow-up questionnaires were received for 26 colectomy patients, who had surgery after a median 10 days in hospital. Four (15%) had toxic dilatation, and 1 (4%) had perforation. The commonest reason for surgery was failure to remit after 7 days (77%). Three had procto-colectomy, 23 had subtotal colectomy. Conclusions: A colectomy rate of 28% for severe colitis across the UK is similar to that reported from single centres. At admission, ESR was more predictive of outcome than CRP. Duration, previous attacks, extent or severity of symptoms on admission did not predict outcome. Recruitment of 116 patients in 3 months makes large trials on severe colitis potentially viable.

Objective: To investigate the influence of birth date on the development of CD later in life.

Methods: From the Scottish Hospitals Discharges Linked Database we identified 438 patients with juvenile onset CD (age of symptom onset before or at 16 years of age) between 1981 and 1995. This covered the entire Scottish population. All case notes were retrieved and the diagnosis verified. The month of birth distribution of the CD cases was compared to that expected from population statistics obtained from the General Register Office for Scotland. Seasonal trends were analysed using the von Mises distribution.

Results: The table shows the seasonal pattern by month of birth. The value within brackets gives the expected number of CD births. 52% were born in the first half of the year; there were 226 observed CD births between January and June against expected number of 220 (obs/exp = 1.03). 48% were born in the second half of the year; there were 212 observed CD births between July and December against expected number of 219 (obs/exp 0.96). 26% were born in winter (Dec-Feb), 23% in spring (Mar-May), 27% in summer (Jun-Aug) and 24% in autumn (Sept-Nov). Seasonal analysis using the von Mises distribution gave $\chi^2 = 3.67$, $p = ns$.

Conclusion: Our data, inclusive of the entire Scottish population aged 0–16 years, do not support significant influence of in utero or perinatal exposure to seasonal environmental/infectious agents in the later onset of juvenile CD.

OUTCOME OF IN-PATIENT MANAGEMENT OF SEVERE COLITIS: A BSG IBD CLINICAL NETWORK SURVEY

A.B. Hawthorne, S.P.L. Travis, and BSG IBD Clinical Network. 1University Hospital of Wales, Cardiff; 2John Radcliffe Hospital, Oxford, UK.

Data on outcome of in-patient management of severe colitis is mainly available from single-centre studies in specialist hospitals. In preparation for a national clinical trial, prospective centres were asked to record clinical details of all patients admitted for intensive treatment of ulcerative colitis (UC) between May 1 and July 31 2001.

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Abstract 058

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(38) (33) (30) (35) (32) (52) (30) (37) (29) (42) (40) (41)
060 NO EVIDENCE OF SEASONALITY IN MONTH OF BIRTH OF BRITISH IBD CASES: A NATIONWIDE PROSPECTIVE POPULATION BASED STUDY OF UNDER 20 YEAR OLDS

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Background: Pre-natal or early neonatal exposures have been postulated to alter the risk of IBD later in life. The risk of Crohn’s disease has been reported to vary with season of birth in cases reported from large UK referral centres. We report birth data from the 1998/9 BPSU-BSGRU UK incidence survey of IBD in those aged less than 20 years (Lancer 575,093–4).

Methods: The number of cases born in each of the 12 calendar months was corrected for the effect of variation in birth rate of the population of England and Wales for the 21 years during which the cases were born. The resulting monthly ‘rate’ (numbers of cases born per month for each 100,000 live-births over the 21 years) was modelled using periodic regression.

Results: There were 659 cases of newly diagnosed Crohn’s Disease (CD) and 297 cases of Ulcerative Colitis (UC). The periodicity of their births (fig 1) appeared similar to that of the total population. The periodicity regression models showed some evidence for residual periodicity after correction for this. (R^2 = 0.29 for CD and 0.43 for UC). However a likelihood ratio test showed these models not to be a significant better description of the data than a straight line (chi^2 (6df) = 4.11, P = 0.6613 for CD, chi^2 (6df) = 6.83, P = 0.3271 for UC).

Conclusion: In this study, the largest population survey of childhood and adolescent IBD to date, we could not detect significant periodicity in month of birth of either CD or UC cases.

061 TREATMENT OF SEVERE CORTICOSTEROID UNRESPONSIVE ULCERATIVE COLITIS BY SELECTIVE GRANULOCYTE AND MONOCYTE APHERESIS

H. Hanai1, H. Arai1, T. Furuta1, K. Yoshida1, A. Sanabadi1, F. Watanabe2, I. Matsuhashi1, K. Takeuchi1, T. Iida2 (introduced by B. Danesh). 1Dept of Medicine, Hamamatsu University; 2Japan Immunoresearch Laboratories, Takasaki; 3Dept of Gastroenterology, Fujueda Municipal General Hospital, 4Dept of Gastroenterology, Seirei General Hospital; 5Gastroenterology Centre, Hamamatsu South Hospital, Hamamatsu, Japan

Ulcerative colitis (UC) is an inflammatory bowel disease associated with activation of the immune system and inflammatory responses. Factors which initiate and perpetuate the inflammatory responses are not well understood. However, several recent reports have provided strong evidence for a major role by granulocytes and monocytes in the mucosal inflammation and UC relapse. Accordingly, we thought that patients with corticosteroid unresponsive severe UC might respond to granulocyte and monocyte apheresis (GMCAP). For GMCP, we used a column of 335 mL capacity filled with 220g cellulose diaceate beads of 2 mm in diameter as the column adsorptive carriers (Adacol). The carriers selectively adsorb granulocytes and monocytes. Thirty one patients with prednisolone unresponsive severe UC and 8 corticosteroid naive patients with severe UC received 10 GMCP treatment sessions, one session/week for 10 consecutive weeks. During a session of one GMCP session was 60 minutes, flow rate 30 mL/minute. The efficacy of GMCP was assessed by measuring UC clinical activity index, UC disease activity index and Mads’ classification index of endoscopic mucosal appearance at baseline, week 6 and week 12.

Patients who improved were given 6-mercaptopurine (30mg/day) to maintain remission. At week 12, 80.6% of corticosteroid unresponsive and 87.5% of corticosteroid naive patients were in remission. Another 6.2% and 12.5% respectively, had their UC symptoms improved. Further, during the mean observation time of 8.8 months, no serious adverse side effects attributable to GMCP were observed which is remarkably in contrast to cyclosporin A therapy for corticosteroid unresponsive UC. The major findings of this new treatment for UC are the following; a) induced remission in patients with severe steroid refractory UC; b) reduced the number of patients who needed surgery; c) dramatically reduced the use of corticosteroids.

062 MYCOPHENOLATE MOFETIL IN INFLAMMATORY BOWEL DISEASE


Background: Mycophenolate mofetil (MMF) has been claimed to be effective and well tolerated in refractory IBD although there is relatively little information regarding its use in clinical practice, particularly with reference to steroid sparing, toxicity, and longer term efficacy.

Aims: To review our experience in achieving and maintaining remission in refractory IBD and to document tolerability, major toxicity, and steroid sparing.

Methods: A retrospective audit of the records of 20 patients treated with MMF over a 30-month period.

Results: Twenty patients (M=6 F=20, ages 18 to 72) were identified of whom 17 had Crohn’s disease and 3 ulcerative colitis. All patients had been intolerant of, or had not responded to Azathioprine, and 19 were taking corticosteroids when MMF therapy was instituted. The median dose of MMF was 1.5g/day and mean duration of therapy was 10.7 months. MMF was discontinued in 12 patients –7 due to intolerance (4 non-specific symptoms, 1 joint aches, 1 lethargy, 1 skin rash) and 5 because of lack of efficacy. Of the 8 still on treatment at the end of the study period (mean duration of therapy 23.8 months) 6 were in remission (5 Crohn’s, 1 UC) and off all steroid therapy, but 2 had relapsed and were being considered for alternative therapy. No major haematological, hepatic, renal, or GI toxicity was noted and there was no major sepsis. No predictors of response to MMF could be identified.

Conclusions: Approximately one third of patients with severe and refractory IBD achieved both remission and complete steroid withdrawal on MMF therapy. 35% of patients could not tolerate the drug, and a further third did not respond. No major toxicity was recorded. MMF therapy should be considered for patients refractory to steroids and Azathioprine, but longer term controlled studies are required.

Nutrition/Coeliac/Small bowel free papers 063–076

063 CLINICAL RESULTS OF WIRELESS CAPSULE ENDOSCOPY

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Background: The development of wireless capsule endoscopy allows painless imaging of the gastrointestinal tract. The clinical utility and performance characteristics of this examination are unknown.

Aim: To assess the clinical efficacy and technical performance of wireless capsule endoscopy in a series of 55 patients.

Methods: A wireless capsule endoscope measuring 11 x 27 mm was used. It contained a light source, CMOS imager, colour television transmitter and silver oxide batteries encapsulated in a strong plastic container with a transparent optical dome window. The 50,000 transmitted images are received via an array of 8 aerials and stored on a portable solid-state recorder, which is carried on a belt.

Results: In a subset of 38 patients push-enteroscopy was compared with capsule endoscopy. A bleeding source was discovered in the small intestine in 21 of 38 patients (55%). These included angiodysplasia (11), fresh blood (5), ileal ulcer (1) tumour (2), Meckel’s diverticulum (1) vasculitis (1). Active intestinal bleeding was seen
in 3. No additional intestinal diagnoses were made by enteroscopy. The yield of push-enteroscopy in evaluating obscure bleeding was 30% (12/38). The capsule found significantly more intestinal bleeding abnormalities than push enteroscopy (p < 0.05). A source of bleeding was identified beyond the reach of the push enteroscope in 9/21 (42%). Therapy was altered in 50% and in 3 patients, who had required medical treatment 100 units of blood. Directed surgery caused a markedly reduced (1) the bleeding. Patients always preferred capsule endoscopy to push-enteroscopy (p < 0.001). There were no complications. Preparation with piroxicam improved images in patients on iron or oral blood in the intestine. 7 patients had no push-enteroscopy. Studies in volunteers (7) and patients with chronic abdominal pain (3) were mostly normal – erosions in 1, lymphangectatic cysts in 3.

Conclusions: This study shows that capsule endoscopy provides small intestinal imaging comparable to push-enteroscopy and can diagnose intestinal bleeding at sites beyond the reach of push-enteroscopes. It was safe and well tolerated.

### 064 THE RELATIONSHIP OF ADULT COELIAC DISEASE WITH IRITRIBLE BOWEL SYNDROME, IRON DEFICIENCY ANAEMIA AND FATIGUE: A PRIMARY CARE CROSS-SECTIONAL STUDY

D.S. Sanders, D. Patel, T.J. Stephenson, A. Milford Ward, E.V. McCluskey, M. Hadjivassiliou, A.J. Loban. Supra-Regional Protein Reference Unit, Northern General Hospital & Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Sheffield, UK

Background and Aims: Our aim was to determine the prevalence of undiagnosed adult coeliac disease in the general population of mainland United Kingdom. We also sought to establish the relationship in primary care between coeliac disease, irritable bowel syndrome, iron deficiency anaemia, fatigue and other coeliac related conditions.

Methods: A cross-sectional study using immunoglobulins, IgA/IgG antigliadin antibodies and endomysial antibodies to initially recognise coeliac disease. 1200 volunteers were recruited (January 1999 to June 2001) from Five General Practices in South Yorkshire. Any participant with a positive IgA antigliadin antibody, positive endomysial antibody or only IgG antigliadin antibody in the presence of IgA deficiency was offered a small bowel biopsy to confirm the diagnosis of coeliac disease.

Results: 12 new cases of coeliac disease were diagnosed from 1200 samples. The prevalence of coeliac disease in this general population sample is 1% (95% CI 0.4–1.3%). The prevalence of coeliac disease in participants with irritable bowel syndrome was 3.3% (4/123), for iron deficiency anaemia 4.7% (3/64) and for fatigue 3.3% (3/92).

Conclusions: This is the first study to establish the prevalence of undiagnosed adult coeliac disease in a general population from England. Underdiagnosis of coeliac disease is common in primary care. A case finding approach would avoid delays in diagnosis and the associated morbidity or potential complications of coeliac disease. A low threshold for serological screening of patients with coeliac associated symptoms or conditions would be an optimal strategy in primary care.

Acknowledgements: We wish to acknowledge the support of Action Research. This study was entirely funded by Action research. Dr Sanders is an Action Research Training Fellow.

### 065 SEROPREVALENCE, CORRELATES AND CHARACTERISTICS OF UNDETECTED COELIAC DISEASE IN ENGLAND

J. West1, R.F.A. Logan3, P.G. Hill1, C.A. Lloyd1, S. Lewis1, R. Reader1, G.K.T. Holmes3, K.T. Khw1. 1Divin of Public Health and Epidemiology, University Hospital, Nottingham, Dept of 2Chemical Pathology and Medicine, Derbyshire Royal Infirmary, Derby; 3Medical & Surgical Sciences, Nottingham City Hospital, “Clinical Gastroenterology Unit, Addenbrooke’s Hospital, Cambridge, UK

Background: Recent studies using various antibody tests to screen for undetected coeliac disease have shown that the prevalence of coeliac disease (CD) in several countries is between 0.5–1.0% of the population. So far the numbers detected have been small and information as to the characteristics and consequences of undetected CD is limited. We have examined the seroprevalence of undetected CD in a large population sample from the Cambridge area.

Methods: The Cambridge General Practice Health Study identified individuals aged 45–74 from the age-sex registers of 11 general practices and invited them for a health survey and a bone density scan between 1990–1995. We tested 7550 of the serum samples collected for antidiomysial antibody (EMA) and used multivariate analyses to compare EMA positive and negative subjects.

Results: The seroprevalence of undetected CD in this general population sample was 1.2% (95% CI 0.9–1.4) and did not vary significantly with age or sex. EMA+ve subjects (n=87) were 2.2 kgs lighter (p < 0.07) and 0.1 cms shorter (p = 0.09), were more likely to have reported their general health as being “good to excellent” (Odds Ratio (OR) 1.8, 95% CI 0.9–3.5), and were less likely to report being a current or ex-smoker (OR for current versus never 0.36, 95% CI 0.14–0.90). Undetected CD was associated with a 8% reduction in mean serum cholesterol (0.5mmol/l, p<0.01) and small reductions in mean haemoglobin (0.3g/dl, p<0.01), total protein (1.0g/l, p<0.05) and corrected serum calcium (0.02mmol/l, p<0.05). There was an increased prevalence of osteoporosis in the EMA+ve group (OR 3.1, 95% CI 1.3–7.3) and of mild anaemia (OR 4.6, 95% CI 2.5–8.2). Five EMA+ve+ (+6%) had died, a proportion similar to that in EMA-ve (8%).

Conclusions: Undetected coeliac disease is likely to affect about 1% of the population of England, a figure similar to several other countries. Although affected subjects report no increase in “poor or moderate” health they have an increased prevalence of osteoporosis and mild anaemia. In contrast they have a favourable cardiovascular profile which is likely to afford substantial protection from ischaemic heart disease and stroke.

### 066 WHAT FACTORS INFLUENCE COMPLIANCE WITH A GLUTEN-FREE DIET: A COMPARISON OF WHITE CAUCASIAN AND SOUTH ASIAN COELIAC PATIENTS

J.R. Butterworth1, L. Banfield1, T.H. Iqbal1, B.T. Cooper1. 1Department of Gastroenterology and 2Department of Dietetics, City Hospital NHS Trust, Dudley Road, Birmingham B18 7QH, UK

Introduction: Lifelong and strict adherence to a gluten-free diet is mandatory in patients with coeliac disease (CD) to improve nutrition and prevent long-term complications. Little is known about what factors influence compliance with a gluten-free diet.

Aims: To identify factors that may influence compliance to a gluten-free diet amongst Caucasians and South Asian patients with coeliac disease.

Methods: A questionnaire survey was sent to 130 coeliac patients followed-up at our unit, (90 Caucasians and 43 South Asian).

Results: Eighty seven (66.9%) of the 130 questionnaires were returned- 66 from the Caucasians, and 21 from the South Asian patients (p=0.003). Patients own assessment of their strictness to a gluten-free (GF) diet was significantly correlated with both small bowel histological recovery and negative endomysial antibody status among the Caucasian patients (p<0.001 and <0.0001 respectively), but not amongst the South Asians. In the Caucasian patients, eight factors appeared to correlate with compliance with a GF diet: 1.Membership of the Coeliac Society (p<0.0001). 2.Understanding food labelling (p=0.014). 3.Obtaining GF products on prescription (p=0.047). 4.Affordability of GF products (p=0.01). 5.Getting sufficient prescription GF products (p=0.017). 6.A detailed explanation of CD by a physician (p=0.006). 7.Having a follow-up small bowel biopsy (p=0.03). 8.Regular dietetic follow up (p=0.01). No factors were identified amongst the South Asians, who were less likely to attend dietetic clinics (p=0.005), or be members of the Coeliac Society (p=0.02) and were more dissatisfied with information provided by doctors (p=0.026) and dieticians (p=0.011) compared with the Caucasian coeliac patients.

Conclusions: In contrast to the South Asians, a number of factors seem to influence compliance with a GF diet amongst Caucasian patients with CD. Compliance seems poor amongst South Asian patients, and a different approach is required in terms of education and dietetic supervision compared to the Caucasian patients with CD.

### 067 DETECTION OF GLUTEN IN ALCOHOLIC BEVERAGES IS FEASIBLE USING DRY STRIP IMMUNOCHEMISTRY IN THE “GLUTEN HOME TEST” KIT

M.M. Skelly, C.J. Hawkey. Division of Gastroenterology, University Hospital, Nottingham, UK

Introduction: It is unclear which cereal-based alcoholic drinks are suitable for coeliac patients. A gluten “home test” (GHT) detection kit has been developed utilising dry-strip immunochromatography format with a
range of detection of wheat gluten from 50 to 1200 ppm. Recommended acceptable levels are <20ppm for food naturally gluten free and <200ppm for food rendered gluten free.

**Aim:** To demonstrate that the gluten content of a number of alcoholic beverages can be determined by Gluten Home Test kit.

Method:
Alcoholic beverages were tested with the GHT and ELISA. Control samples contained known quantities of gluten (starch) or were not cereal based (Coca-Cola). Test samples are as reported. The GHT strip contains antibodies specific for omega gliadin, a stable gluten protein, which bind to gliadin in the test beverage. When the beverage is overlayed on the strip, a gliadin-antibody-blue latex particle combination migrates along the strip until it is trapped by immobilised gliadin antibody in one of three positions. The positions indicate gluten level less than 50ppm (“Negative test”), 50–200ppm or greater (“Positive”) and more than 10% gluten (“Strong positive”). Gliadin correlated of the test and control samples was determined using a direct sandwich ELISA that utilised a monoclonal antibody to omega gliadin. See table.

### Table: GHT and ELISA Results

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<th>Beverage</th>
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<th>ELISA Rating</th>
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<tr>
<td>Stella Artois</td>
<td>0.1578</td>
<td>Positive</td>
</tr>
<tr>
<td>Newcastle Brown Ale</td>
<td>0.4715</td>
<td>Strong positive</td>
</tr>
<tr>
<td>Bass</td>
<td>0.029</td>
<td>Positive</td>
</tr>
<tr>
<td>Budweiser</td>
<td>0.116</td>
<td>Strong positive</td>
</tr>
<tr>
<td>Whisky (blend)</td>
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<td>Negative</td>
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<tr>
<td>Whisky (malt)</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Guinness</td>
<td>0.49</td>
<td>Strong positive</td>
</tr>
<tr>
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</tr>
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</tr>
<tr>
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**Summary:** Gluten can be readily detected in alcoholic beverages using dry strip immunochemistry. Results from GHT and ELISA broadly correlated. We may be useful for coeliacs to guide choice of alcoholic beverage.

**069 IN-VIVO TOXICITY OF AMINO ACIDS 57–75 OF ALPHA-GLIADIN IN COELIAC DISEASE**

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**Background:** Peptides from α-gliadin have been used to characterise the immunodominant coeliac toxic cereal epitope in vitro. Following incubation with a peptide corresponding to amino acids 57–73 of α-gliadin, peripheral blood mononuclear cells from coeliac patients secrete IFN-γ, gluten-specific small intestinal T cell clones proliferate in vitro to peptides corresponding to residues 57–68 and 62–73 of α-gliadin.

**Aim:** We wished to investigate whether a peptide corresponding to residues 57–75 of α-gliadin exacerbates coeliac disease (CD) in vivo.

**Methods:** We studied four unrelated Caucasian patients with known CD, all of whom were on a gluten-free diet. The patients underwent three separate challenges. One g peptic-tryptic gliadin (PTG) served as a positive control. Twenty to 100mg of the test peptide was studied on a separate occasion, and on the third a negative control peptide from casein, which comprised 20 amino acids incorporating the same residues as the test peptide, but which were in a different order, was assessed. Following sedation, a Quinton hydraulic multiple biopsy capsule was placed into the duodenum. The peptides were instilled into the duodenum over 2 hours. Biopsies were taken before the infusion, 2, 4 and 6 hours after commencement of the infusion. The biopsy specimens were assessed blindly for villus height to crypt depth ratio and enterocyte surface cell height. We used the Mann-Whitney U test, with 95% confidence intervals, for statistical analysis.

**Results:** The negative control peptide caused no significant changes to villus morphology or small intestinal villus enterocytes in any of the patients. The villus height to crypt depth ratio and the enteroocyte surface cell height fell significantly 4 to 6 hours after commencing the infusions with both PTG and the test peptide, compared to the initial biopsy, in all subjects (n=4).

**Conclusion:** A peptide corresponding to residues 57–75 of α-gliadin, exacerbates coeliac disease in vivo.
OSTEOPOROSIS AND COELIAC DISEASE: IS THE 1500 MG/DAY GUIDELINE FOR CALCIUM ACHIEVABLE BY DIET?

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Background: Guidelines for treating and preventing osteoporosis in coeliac disease (CD) were published in 2000 in the international journal Gut. These guidelines recommend that patients with CD should achieve a calcium intake of 1500 mg/day and adhere to a strict gluten-free (GF) diet. UK dietary surveys have shown that >50% of female adults in the general population fail to achieve the Reference Nutrient Intake (RNI) of 700 mg/day (DoH, 1998). In addition, GF diets have been shown to reduce intake of foods that contribute dietary calcium. Consequently the 1500 mg target may be difficult to achieve by diet alone. Our aim was to establish the intake of dietary calcium in patients with CD.

Methods: 26 patients with CD; age range 33 – 71 yrs, 8 males, 18 females, were recruited via gastroenterology out patient clinics and the local coeliac society. Median duration on a GF diet was 10 yrs, range 3–33yrs. Dietary calcium and compliance to a GF diet were determined using a 10-day weighed method, Dietetic interview and a dietary calcium and compliance programme using data from MAFF (Dietplan) and food manufacturers.

Results: 25/26 adhered to a strict GF diet (96% compliance). Median calcium intake was 1209 mg/day (range: 539 – 1898 mg/day). 31% (8/26) achieved the 1500 mg/day. 11% failed to achieve the RNI of 700mg/day, all were female and following a restricted energy intake for the purpose of intentional weight loss. Dairy products provided a median of 57% of dietary calcium, which is similar to the non-coeliac population. 2/26 adhered to a milk-free diet but achieved a calcium intake >1400 mg/day using calcium-enriched GF breads. 42% used the new generation calcium-enriched GF breads. Median contribution of calcium from GF bread/soya products. 42% used the new generation calcium-enriched GF breads. Median contribution of calcium from GF bread was 27% in those using the calcium-enriched GF breads, compared to 8% in those using standard GF breads.

Conclusions: Whilst it is possible to achieve a calcium intake of 1500 mg/day on a strict GF diet, careful dietary assessment is required in the majority of patients to identify those with sub-optimal intake (up to 2/3 of patients) and improve calcium intake through diet and/or supplements. The new generation calcium-enriched GF breads may help achieve dietary intakes of 1500 mg of calcium/day.

MORTALITY RISK FACTORS AND TRANSPLANTATION INDICATIONS FOR PATIENTS ON HOME PARENTERAL NUTRITION (HPN)

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The overall mortality for HPN in the UK is 8% per year and reports suggest that 80–90% of these deaths are attributable to the underlying disease. We performed a retrospective analysis of all patients who died on HPN over the last 5 years at St Mark’s and all patients who had undergone intestinal transplantation (ITx) at Cambridge.

Results: At St Mark’s, 37 patients died on HPN since 1996 and 33 complete sets of notes were traced (89%). These patients had a median age of 58 years (30–77) and a median time on HPN of 543 days (7–677) [20F:13M]. 25 patients (76%) died from their original disease (HPN-disease), 4 (12%) died from complications of HPN (HPN-comp) and 4 (12%) died from other causes (HPN-other). HPN-comp deaths were sepsis [11] and liver failure [3], 2 of the 3 patients who developed liver failure had chronic cholestasis and received >1g lipid/kg/day. In Cambridge, 9 patients had ITx since 1991. 1 set of notes could not be traced and 1 patient did not have HPN prior to transplantation. The remaining 7 had a median age of 25.8 years [21–42 years] and a median of 730 days on HPN (14–2920 days) prior to transplantation [25:SM]. Indications for ITx were recurrent thromboses [4], recurrent central venous catheter (CVC) sepsis [3] and Pseudomembranous enteritis disease [2]. See table.

Conclusions: HPN patients die predominantly of their underlying disease. ITx patients had a higher frequency of infectious and thrombotic complications prior to transplantation and perhaps HPN patients with similar complications should be considered earlier for transplantation.

EFFECTS OF LOW FIBRE DIETS AND VITAMIN CONTENT ON NEOPLASIA AND CELL PROLIFERATION IN THE MIN MOUSE

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Background: Loss of APC and the production of a truncated APC protein leads to familial adenomatous polyposis (FAP) in man and multiple intestinal neoplasia (Min) in the mouse. Both phenotypes are characterised by multiple intestinal polyps. The Min mouse is thus a useful model for the study of exogenous factors on gut biology and tumour progression.

Methods: We have used the Min mouse (C57BK/6;ApcMin) to investigate the effect of dietary fibre and fibre-free semisythetic diets on polyp progression, cell proliferation and crypt fission. The semisythetic diet was then used to investigate the actions of altered vitamin content (lowered to a third of the RDA and a SS diet where the vitamin content was increased fivefold [except for retinol and folate which were doubled], 60 Min mice and wild type littermates, 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 later (number*volume = burden), as was the number of native mitoses and the percentage of branching crypts.

Results: The guts of the chow fed mice were heavier, and all Min groups had heavier guts. The intestines of the low and high vitamin groups were heavier than the SS control. There were fewer polyps and the tumour burden was lower in the SS group. Both low and high vitamin levels lead to increased polyp number, especially in the proximal small intestine. There was more proliferation and crypt fission in the SS group, and this was reduced in the low and high vitamin groups. The effect of vitamins was most pronounced in the proximal intestine.

Conclusion: Low fibre semisythetic diets may reduce polyp formation, suggesting that the lack of ‘fibre’ may be beneficial. Alteration of vitamin content can enhance polyp number and tumour burden. Both low or high vitamin content may be a risk factor.

IS THE CURRENT SERVICE FOR THE INSERTION OF ENDOCOSCOPIC FEEDING TUBES APPROPRIATE AND ACCEPTABLE? A UK SURVEY

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We were concerned that gastroenterologists may be putting themselves in a vulnerable position, in terms of clinical risk, by inserting PEGs purely as a service for other clinicians. A questionnaire was therefore sent out to hospitals in the UK to clarify current practice. Responses were received from 196 of 242 units (>80%). The number of PEGs placed ranged from 1 to 100/100,000 population covered/year with a median of 22 with most placed by medical gastro-enterologists. 59% of responding hospitals have a nutrition team but in 22% of these the patients are still assessed for suitability of PEG only by their own team. The endoscopist does not know what assessment has been made of patients attending for PEG placement in 25% of hospitals. In the hospitals where patients are assessed by a gastro/nutrition team the endoscopist is unaware of the details of the assessment in <3%.

Consent is clearly a difficult issue as many patients are mentally incapacitated but despite this <50% of hospitals have an appropriate, known consent policy for this group. Time from referral to insertion of PEG is >1 week in 33% of patients and this delay may well impact on physical wellbeing and also on bed occupancy.
Gastroenterology follow up is rare. >70% of hospitals do not provide any routine review or a review mechanism should complications arise post PEG insertion. <10% of patients are followed up beyond 1 week. 80% of patients are followed up in the community, often only by district nurses.

Current practice for PEG insertion is highly variable and in many hospitals it does seem to be either appropriate or acceptable. We believe many endoscopists are exposing themselves to potential risk by acting as technicians and feel that national minimum standards should be considered.

075 COLONIC MUCOSAL INJURY FROM NATURAL AND SYNTHETIC SULPHATED POLYSACCHARIDES

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Undegraded lambda lambdaCarrageenan (λCgN) is widely used as a food additive but is chemically related to the pro-inflammatory agent dextran sulphate sodium (DSS). This study tests the hypothesis that λCgN has pro-inflammatory effects in colon.

Methods: Acute and subchronic oral administration of λCgN vs DSS vs drinking water only control against colonic disease activity and mucosal inflammation in 2 species viz mice and rats. λCgN, DSS (1–4%) or drinking water control were administered for 2–72 days to Balb/c mice (n=225) and Sprague-Dawley rats (n=45) which were maintained on AIN76A antioxidant and mutagen-free diet. Disease activity was assessed by stool consistency, blood loss, weight loss and length. Mucosal injury was assessed histologically by semiquantitative scores of crypt loss, shortening, distortion, hyperplasia, and inflammatory infiltration.

Results: Both λCgN and DSS induced colonic inflammation, crypt injury and crypt hyperplasia in mice and rats. Effects on mucic function and mucosal injury were dose dependent and increased with duration of exposure. DSS had greater adverse effects on disease activity than CgN in doses of 3–4% in mice and 1–3% in rats.

Conclusion: Although less toxic than DSS, λCgN produced cumulative dose dependent colonic mucosal injury and adverse effects on colonic function of 2 species.

076 OUTCOMES IN HOME PARENTERAL NUTRITION IN A NATIONAL UNIT

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Hope Hospital is one of the UK's two largest units covering patients on Home Parenteral Nutrition (HPN). In 1998 it was decided to review all new patients commencing on HPN, to study morbidity and mortality. A mean of 27 patients started HPN each year and no patients were lost to follow-up. 85 patients commenced HPN between 15th February 1998 and 15th May 2001, aged 19 years 11 months – 76 years 11 months, (mean 50.2 years ±16.8 months) (50 females). 19 patients were <40 years, 43 were 40–60 years and 23 were >60 years. 76 patients were entirely self-caring for their line, 9 requiring input from family or outside care e.g. district nurse. The main diagnoses in these patients were Crohns (29), mesenteric vascular disease (20) and surgical complications e.g. short bowel syndrome after surgery for e.g. ulcerative colitis or malignancy (18). Conditions e.g. radiation enteritis, scleroderma and volvulus made up smaller numbers. 2 patients were treated for a diagnosis of active malignancy.

Of these 76 were alive, 57 on HPN, 19 have discontinued HPN and 9 have died. Mortality rates were 0% at 1 year and 10.6% at 3 years, compared to 1-year and 3-year mortality rates of 7–15% and 30–32% in published series. 4 patients died of malignancy (3 previously recognised and 1 new case), and 5 of unrelated conditions i.e. 3 patients died of their underlying diagnosis and 6 of unrelated causes. No deaths were related to HPN. 19 patients (22.3%) developed a confirmed line complication - 10 (11.8% with catheter-related) and 7 (patients developed >1 complication). No patients developed significant liver disease.

19 (22.3%) patients came off HPN during this period with an average duration of 9.15±1.05months (range 4–21 months). No clear diagnosis was associated with an increased chance of discontinuing HPN, but 10 patients had surgery (9 reanastomosis) prior to discontinuing. Patients who discontinued HPN were younger (47years±37.5 months) than those who died (55.3 years±64.4 months) and those that continued on HPN (50.8years±19.4), but this was not significant.

Over this time we treated increasing numbers of patients and included patients previously thought not appropriate for HPN e.g. those not self-caring and older age groups. Despite more patients being considered suitable for HPN and new methods e.g training carers, mortality and complication rates are low and there were no HPN-related deaths. We appear to be widening the net without worsening outcome.

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077 THE EFFECT OF ZAPRINAST, A PHOSPHODIESTERASE TYPE 5 INHIBITOR, ON THE SHEEP ISOLATED INTERNAL ANAL SPHINCTER

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Introduction: Neurogenic relaxation of the internal anal sphincter is mediated by elevation of cyclic GMP, following activation of soluble guanylyl cyclase by nitric oxide. Since the activity of the cyclic nucleotide is also regulated by phosphodiesterase 5, we have examined the effect of zaprinast, an inhibitor of the enzyme, on the sheep isolated internal anal sphincter.

Method: Strips of isolated sheep internal anal sphincter were suspended in 5ml organ baths containing warmed and oxygenated Krebs and isometric tension recordings made. Preparations were exposed to a cumulative concentration of zaprinast (3x10^-10 to 3x10^-6M), firstly paired with time controls and then in the presence and absence of N'-nitro-L-arginine methyl ester (LNAME, 100µM), a nitric oxide synthase inhibitor. In a separate series of experiments the effect of sodium nitroprusside, a direct activator of soluble guanylyl cyclase, was examined in the absence and presence of a sub-maximally effective concentration of zaprinast (3x10^-6M).

Results: Zaprinast caused a concentration-related relaxation of the sheep anal sphincter with the highest concentration giving a mean effect of 92.3%±2.6 (n=7) compared to 11%±3.2 loss in time controls over the same period. In the presence of 100 µM LNAME, the response to higher concentrations of zaprinast was significantly reduced (p<0.05, Student's t-test) but not abolished: 30 µM zaprinast (LNAME) (72.4%±4.9 (n=7), SNP caused a concentration-related relaxation of the sphincter (EC50 3x10^-6M) that was enhanced in the presence of zaprinast (EC50 1x10^-6M) (n=6).

Conclusion: Zaprinast acts as a PDE 5 inhibitor to relax the sheep internal anal sphincter, however its actions are only partly dependent on the basal release of nitric oxide from the tissue. Further experiments with more selective PDE 5 inhibitors are warranted in order to assess their possible role clinically in conditions related to sphincter hypotonia.

078 SURVEY OF ANO-RECTAL SYMPTOMS AMONGST PATIENTS OBTAINING TOPICAL HAEMORRHOIDAL PREPARATIONS FROM COMMUNITY PHARMACIES

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Rectal bleeding is a common symptom amongst the adult population. Whilst most often due to benign ano-rectal disorders, it may be the only symptom of colorectal carcinoma. The incidence of rectal bleeding amongst people purchasing topical haemorrhoidal preparations (BNF Sections 1.7.1, 1.7.2) over the counter (OTC) from community pharmacies is unknown.

A survey of ano-rectal symptoms was conducted in 20 participating community pharmacies within Ayr, Prestwick and Troon LHCC during February 2001. Sixty-five patients returned completed questionnaires of whom 36 (55%) had filled a prescription (FP10) and 29 (45%) had purchased OTC. Only 8 of the 29 (28%) purchasing OTC had sought the pharmacist’s advice. Twenty-eight patients (43%) were over 60 years of age.

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Thirty patients (63%) reported rectal bleeding in association with anal symptoms (itch, pain or a lump), 29 (45%) reported anal symptoms with no bleeding and 5 (8%) had rectal bleeding without other symptoms. Four of the five patients with rectal bleeding alone had purchased OTC medications and only one had consulted their GP about their symptoms. Three of these 5 patients might be considered to have “suspicous symptoms” (age >60 years - 2, passing dark blood - 1). A high incidence of rectal bleeding (54%) was found amongst patients obtaining topical haemorrhoidal preparations (61% of those filling prescriptions vs 45% of those purchasing OTC). The majority of patients (86%) reporting bleeding had associated anal symptoms and were considered low risk for cancer. The majority (69%) reporting bleeding had consulted their GP about their symptoms. A small number reporting bleeding and purchasing OTC topical haemorrhoidal preparations should be consulting their GPs. Community pharmacists need to be aware of the possibility of patients treating themselves inappropriately.

**Analisis of Symptomatology of Patients Presenting to the Rectal Bleeding Clinic: Need for Better Referral Guidelines**

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Introduction: Rectal bleeding clinics (RBC) act as the pick-up point for colorectal cancers ideally in their early stages. Referral guidelines for RBC vary and are yet to be formalised on a national scale. Appropriately, referral guidelines will facilitate patient selection for RBCs.

Methods and Results: 2597 patients were seen in the RBC over a six-year period between October 1994 and September 2000. Patients were referred by their general practitioners. All patients had a detailed history, clinical exam and flexible sigmoidoscopy (FS). 1231 (53%) were diagnosed as having colorectal cancer (mean age 70, range 45 – 90). 390 (15%) patients had polyps (mean age 62, range 19 – 94) and were referred for formal colonoscopy. A total of 15 symptoms were recorded in these patients and analysed in separate groups (cancer, poly, sex and age). The incidence of change in bowel habit (CIBH), loose stool (LS), mucous discharge (MD), blood mixed with stool (BS), weight loss, palpable abdominal mass and mass palpable per rectum were significantly (p < 0.05) increased in the cancer group. Further, in the cancer group, symptoms of CIBH, LS, MD and BS were significantly (p < 0.05) present in patients over 70 years. Interestingly, abdominal pain, constipation and fresh bleeding per rectum were not significantly associated with the diagnosis of malignancy or polyps.

Discussion and Conclusion: This study demonstrates and is in agreement with other studies that the symptomatology of colorectal cancer is distinctive and should be incorporated into the RBC referral guidelines. In this series only 5% of the referred patients had colorectal cancer and 15% had polyps. More stringent RBC referral guidelines based on these symptoms and related to age would aid in selection of patients for rectal bleeding clinics.

**A Double-Blind, Placebo Controlled Pilot Study to Assess the Effects of a Probiotic on the Response of the Intestinal Microflora to Helicobacter pylori Eradication Therapy**

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Introduction: Antibiotic therapy can detrimentally alter the intestinal microflora. Probiotics are preparations of non-pathogenic intestinal bacteria which may be beneficial to human health. The effects of supplementation with probiotics days 1–15 (n=6). Patients provided stool samples on days 1, 7, 12, 17 & 27. Specimens were analysed using standard microbiological techniques.

**Results:** Administration of antibiotics alone resulted in a significant increase in numbers of aerobes between days 1 and 7 (p=0.001). When probiotics were given after antibiotics, numbers of aerobes fell significantly between days 7 and 27 (p=0.021), a change not observed with antibiotics alone. When antibiotics were supplemented with probiotics, there was a decrease in the numbers of enterobacteriaceae between days 7 and 27 (p=0.068); these organisms were below limits of detection at day 27. There were no differences between levels of lactic acid bacteria between the three groups.

Conclusions: Probiotic supplementation may be able to prevent some of the alteration to the intestinal microflora resulting from broad-spectrum antibiotic therapy. This may be of importance in the prevention of antibiotic-related diseases.

**A Comparative Study on the Quality of Life in Patients with Ileostomy Versus Colostomy**

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Background: The choice of an ileostomy as the preferred option for proximal diversion over colostomy, has been a recent topic of interest. This study evaluated the quality of life of patients with an ileostomy and compared it with that of patients with a colostomy.

Methods: Life quality of 25 patients with an ileostomy (median age 42 years, range 22–76 years) was compared with 25 patients with a colostomy (median age 44 years, range 18–70 years). A self-administered structured questionnaire was used with responses obtained for ten life quality questions on visual analogue rating scale (0–100mm) and graded good (71–100), satisfactory (51–70) or poor (0–50).

Results: Purchase of the stoma appliance was without much difficulty in 22 (88%) patients with an ileostomy compared with 16 (64%) patients with a colostomy (P=0.09: x²:NS). Effluent was tolerable in 18 (72%) patients with an ileostomy as compared with only 7 (28%) patients with a colostomy (P=0.002: x²). Appetite was not significantly affected in all patients with an ileostomy (100%), compared with 64% of patients with a colostomy (P=0.002: x²), travel by public transport was not affected in 32% of patients with ileostomy of 28% with colostomy (NS), dress in 20% of patients with an ileostomy of 24% with colostomy (NS) and daily activities 28% of patients with an ileostomy of 24% with colostomy (NS). Furthermore, 68% with an ileostomy did not have a problem with personal hygiene, compared with 40% with a colostomy (NS), while 95% with an ileostomy abstained from sexual activity compared with 81% with a colostomy (NS).

Conclusion: Both ileostomy and colostomy resulted in significant impairment of quality of life in patients. However, with an ileostomy, the effluent was more tolerable, had less of an impact on personal hygiene and preserved appetite compared with patients with a colostomy. There were no differences in appetite, travel, dress, daily chores and sexual activity between the two groups.

**Adenoma Prevalence and Ileal Mucosa in Pouch vs Neoterminal Ileum**


Introduction: The recent findings of adenomas of ileal origin in up to 42% of FAP pouches has caused some concern as to the subsequent long-term risk of ileal pouch cancers. The development of ileal adenomas in FAP may be a phenomenon restricted to the pouch, occurring as a result of environmental changes. We aimed to describe polyp burden and determine the characteristics of FAP pouch/ neoterminal ileal mucosa.

Methods: A video-flexible sigmoidoscope was used to compare the ileal mucosa within the pouch to 20cm of neoterminal ileum proximal to the pouch in 32 consecutive FAP patients (18M, 14F, median age 37, IQR 31–44). The number and size of polyps were counted and 4 polyp biopsies/ 4 normal biopsies were taken from each area. Biopsies were examined for presence of adenoma and were also scored for acute and chronic poulchitis by an experienced pathologist using the Moskovitz criteria.

Results: Adenomatous polyps were seen and confirmed by biopsy in 17/32 (53%) pouches compared to just 1/32 (3%) adenomatous polyps in the neoterminal ileum of the same patients. The median number of pouch adenomas was 4 (range 1–50) and median size was 3mm (range 1–40mm). 12 patients (75%) had tubular adenomas with mild dysplasia and 5 patients (25%) had adenomas with either
villous or tubulovillous architecture or moderate dysplasia. There was no severe dysplasia and there were no cancers. Acute pouchitis (median score 1, range 1–5) was found in 5/32 (16%) patients and chronic pouchitis (median score 2, range 1–4) in 18/32 (56%). Chronic pouchitis, score 4, was found in the neo-terminal ileum of 1/32 (3%) patients but in all other cases the neo-terminal ileal mucosa was normal. The presence of pouchitis did not predict presence of adenomas which occurred in 9/17 (53%) patients with, compared to 8/15 (53%) without pouchitis.

**Conclusion:** The development of ileal adenomas in patients with FAP is almost exclusively restricted to the pouch, with the spectrum of severity being similar to that seen in the duodenum of FAP patients. Mild pouchitis occurs, but is not predatory of adenoma formation.

**083 RESULTS OF NON STIMULATED GRACILIS MUSCLE TRANSPOSITION FOR RESTORATION OF ANAL CONTINENCE**

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**Background:** Stimulated gracilis muscle transposition is now widely practised. However, it is expensive and is also associated with a high postoperative complication rate. Our aim was to assess the efficacy of non-stimulated gracilis transposition and to compare the outcome with a published series of stimulated graciloplasty.

**Method:** Between November 1997 and May 2000 13 patients (11 males and 2 females) aged 22 years (range 11 to 40) underwent 15 gracilis transpositions (2 bilateral) without vascular delay. The Cleveland Continence Score (0–20), Maximum Resting Pressure (MRP) and Maximum Squeeze Pressure (MSP) were assessed before and after operation. Follow up was for a median (range) of 12 months (6 to 36 months).

**Results:** There were 3 (20%) complications (wound infection; fistula-1). There were no complications associated with stoma closure. There was a significant improvement in continence score (Preop; median (range) – 20 (19–20) vs Postop: 11(7–12) – P< 0.001 Wilcoxon Rank Sum Test) Significant improvement was also seen in MRP and MSP after operation. (Median MRP, Preop vs Postop – 10 mm Hg vs 29 mm Hg – P< 0.007 and Median MSP, Preop vs Postop – 18 mm Hg vs 62 mm Hg – P<0.005 – Wilcoxon Rank Sum test). Compared with a collected series of stimulated graciloplasty, non-stimulated gracilis transposition showed a comparable improvement in continence scores and anal manometry but revealed a lower overall complication rate. (20% vs 57%; Non-stimulated vs Stimulated).

**Conclusion:** Gracilis transposition without stimulation is cost effective, associated with low postoperative morbidity and results in significant improvement in continence.

**084 FUNCTIONAL OUTCOME OF RECTOPEXY FOR OBSTRUCTIVE DEFAECATION: WHAT DO THE PATIENTS THINK?**

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**Introduction:** Obstructive defaecation (OD) is characterised by prolonged straining at stools and a sense of incomplete emptying. This may be secondary to intra-rectal intussusception and rectopexy has been used to correct this abnormality in attempt to improve OD. The aim of this study is to assess patient’s perspective of the functional outcome of rectopexy.

**Methods:** Thirty-six patients (male 2; female 34, median age 54 years, range 20–71) who underwent rectopexy for OD were identified. Their symptoms before and after operation were analysed. A simple functional assessment questionnaire was sent to 35 patients by post. Twenty-seven patients (77%) responded.

**Results:** Symptoms of prolonged straining and incomplete evacuation improved in 40% of patients while 25% had no change noticeable and another 25% had worsening of these symptoms after operation. Vaginal and rectal digitation resolved in only 10% of patients whereas 30% reported some improvement, 40% no change and 20 % were worse after rectopexy. Ten patients (37%) were satisfied with the outcome of surgery. Five patients (19%) would recommend a rectopexy to someone with similar symptoms, while 10 (37%) would not and the rest (44%) were unsure.

**Conclusion:** Persisting or worsening of symptoms was observed in a quarter of patients after rectopexy for OD. The overall patient satisfaction following rectopexy for OD is less than ideal. Hence careful patient selection and counselling prior to surgery is essential.
Cyclooxygenase-2 expression and dysplasia in human colorectal adenomatous polyps

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Introduction: Cyclooxygenase-2 (COX-2) is a target of aspirin and other non-steroidal anti-inflammatory drugs and is implicated in the pathogenesis of colorectal cancer. The objective of this study was to evaluate the extent of COX-2 in pre-malignant colorectal polyps and to assess the relationship between COX-2 and the level of dysplasia in these lesions.

Methods: Whole polypctomy specimens were retrieved by endoscopic or surgical resection. Following formalin fixation and paraffin embedding, the polyps were histologically evaluated for size, type and grade of dysplasia. The extent of COX-2 expression was measured by avidin biotin immunohistochemical technique using a monoclonal COX-2 antibody. The extent of COX-2 expression was graded according to percentage epithelial COX-2 expression.

Results: Polyps were retrieved from 109 patients (72 males). The mean age was 65 years (range 33-85). The polyps were of the following histological types: 10 hyperplastic, 35 tubular adenomas, 55 tubulovillous adenomas and 9 villous adenomas. Nineteen showed mild dysplasia, 63 moderate dysplasia and 17 focal or severe dysplasia (including 2 with focal invasion). The average polyp size was 1.24 cms (range 0.2-6.0 cms). Nine hyperplastic polyps were COX-2 negative and 1 was positive (This patient had a co-existing adenocarcinoma elsewhere in the colon). In 8% of the adenomas, adjacent normal colon weakly expressed COX-2. COX-2 expression was more extensive in larger polyps (p=0.01) and in those with a higher villous component. Polyps with mild dysplasia expressed COX-2 in 35% of the epithelial cells whereas severely dysplastic polyps expressed COX-2 in 60% of the cells (p=0.03). Within a polyp, there was a corresponding increase in COX-2 expression with epithelium showing higher grade of dysplasia.

Conclusion: COX-2 is directly related to polyp size and grade of dysplasia in colorectal polyps. This suggests that the role of COX-2 in colorectal cancer may be at an early stage in the adenoma-carcinoma sequence and non-steroidal anti-inflammatory drugs may be useful chemopreventative agents for this disease.

Flat and depressed neoplasms: matched pair study between a UK and a Japanese population

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Background: Flat and depressed colorectal neoplasms may have more malignant potential than polypoid lesions, and may occur more frequently in Japan than in Western countries. As differing definitions are used, the incidence of these lesions is ill-defined. We examined the proportion of such lesions detected in UK & Japan in patients undergoing colonoscopy performed by a single colonoscopist.

Methods: 164 patients found to have polyps on colonoscopy at St. Mark’s Hospital, UK (SMH) were age and sex-matched with 164 patients who had previously had polyps detected by the same colonoscopist (NSy) at Osaka City University Hospital, Japan (OCU). FAP, HNPCC and IBDS patients were excluded. Polyp characteristics (shape, location, size and histology) were documented.

Results: 255 polyps were confirmed histologically in the 164 SMH patients, compared with 260 in the 164 OCU patients (see table). Of the 43 flat & 3 depressed lesions in SMH, no severely dysplastic or cancerous lesions were seen; whereas of the 35 flat & 6 depressed lesions in OCU, 10 (24%) showed severe dysplasia (P) or invasive cancer (I).

Conclusion: There was no significant difference in the proportion of flat & depressed neoplasms detected in UK & Japan when the colonoscopy was performed by the same endoscopist using the same definition. (2) The difference in rate of malignancy on these lesions needs to be further investigated.

The influence of antibiotics on irritable bowel syndrome: a randomised controlled trial

P. Moayyedi1, S. Duffett1, S. Mason3, J. Brown4, A.T.R. Axon. 1City Hospital, Dudley Road, Birmingham; 2Introduction: Observational studies have suggested that irritable bowel syndrome (IBS) occurs after infective gastroenteritis and antibiotic prescription. This suggests alteration of the intestinal bacterial flora may be involved in the pathogenesis of IBS. Observational studies, however, are difficult to interpret as results could be due to confounding factors. We were interested in this hypothesis in a randomised double blind placebo controlled trial.

Methods: This trial represents a secondary outcome from a trial of H. pylori screening and treatment in the community. Subjects between the ages of 40-49 years were invited to attend their local general practitioner for H. pylori infection assessment by 13C-urea breath test and positive individuals were randomised to omeprazole 20 mg bd, clarithromycin 250 mg bd and tinidazole 500 mg bd for one week or identical placebos. Randomisation was performed at a central clinical trials unit using computer generated random numbers. A research nurse interviewed subjects with an IBS questionnaire at baseline, 6 months and two years. Participants were defined as having IBS if three or more Manning’s criteria were present.

Results: 1,713/2329 (74%) participants attended at two years with complete questionnaires. 1,439 subjects did not have IBS at baseline and at two years IBS was present in 63/721 (9%) receiving placebo and 41/718 (6%) allocated antibiotics (odds ratio for those taking antibiotics = 0.63, 95% CI = 0.42 to 0.95; p=0.03). Evaluating individual IBS symptoms suggested frequent stool (OR = 0.55; 95% CI = 0.30 to 1.0; p = 0.03) and loose stool (OR = 0.43; 95% CI = 0.20 to 0.7; p = 0.002) were significantly less frequent in subjects given antibiotics. 274 participants had IBS at baseline. At two years 54/129 (42%) of the placebo group and 61/145 (42%) of the antibiotic group still had IBS (OR = 1.0; 95% CI = 0.6 to 1.6; p=1.00).

Conclusion: This randomised controlled trial does not support the hypothesis that clarithromycin and tinidazole exacerbates IBS. Indeed, in those subjects without IBS at baseline, antibiotic prescription appears to be protective.

Is the p53-apoptotic pathway significant in the short course radiotherapy?

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Aim: Selection of patients who will benefit from preoperative adjuvant radiotherapy for operable rectal cancer remains problem. p53 is believed to play a significant role in apoptosis after radiation. Concentrating on short course radiotherapy, we have examined relationship between apoptotic cell death, proliferative activity, and the expression of apoptosis-regulating proteins.

Methods: 26 patients underwent operation from June 1982 to October 1984 after short course radiotherapy (15Gy). Patients’ aged was between 27 and 77 years (median 57.1) were male. Tumours stages were (Dukes) A (2), B (11), C (13). Sections of paired biopsies and post-irradiated surgical specimens of each tumours were immunohistochemically stained for p53, Bcl-2, BCLXL, Bax, Ki67, & P21/WAF1. The proliferative index (PI) was the percentage of cells positive for Ki67. The TUNEL method was used to identify apoptotic cells, the apoptotic index (AI) being the percentage of positive tumour cells.

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Abstract 088

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<th>Polypoid</th>
<th>Flat</th>
<th>Depressed*</th>
<th>Adv. Cancer</th>
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<td>OCU—Japan (%)</td>
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*P=0.7151 Fisher’s Exact test
**HELICOBACTER PYLORI UPREGULATES MMP-7 IN EPITHELIAL CELLS IN A CAG-DEPENDENT MANNER**

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**Background:** MMP-7 (matrilysin) is a member of the metalloproteinase family of enzymes, which are important in normal and pathological remodelling of epithelial-matrix interactions. Several studies have shown increased expression of MMP-7 in gastric cancer tissue compared to non-cancer tissue. More virulent strains of *H. pylori* possess PAI (encoding a Type IV secretion system) and an active form of VacA, a toxin that induces vacuolation in vitro. This study examines the effect of *H. pylori* on MMP-7 expression in HT29 cells.

**Methods:** *H. pylori* strains 60190 (cagPAI+, vacA s1/m1), Tx30a (cagPAI+, vacA s2/m2) and the VacA and CagE isogenic mutants of 60190 were co-cultured with HT29 cells for 24 hours. Cell pellets were assessed for MMP-7 levels assessed for MMP-7 levels (and GAPDH) by Real Time PCR.

**Results:** Results: *H. pylori* pathogenic strain 60190 increased MMP-7 RNA levels (13-fold vs untreated, p=0.06, unpaired T-test) more than non-pathogenic strain Tx30a. Use of isogenic mutants showed this effect to be CagA-dependent but CagE-independent. Western blot gave a 29kDa band for 60190 and its VacA mutant. Casein zymography revealed a 29kDa band of activity for all samples but reduced intensity for strain Tx30a and the 60190 cagE mutant. This band corresponded to the predicted size for pro-MMP-7. Gelatin zymography showed no differences between treatments.

**Conclusion:** In HT29 cells *H. pylori* co-culture leads to upregulation of MMP-7 at both RNA and protein level. This upregulation is partly MMP-7 dependent on an intact Cag Type IV secretion apparatus but is not VacA-dependent. This is a further example of subversion of host systems through CagA-dependent signalling and we speculate that it may be important in the pathogenesis of *H. pylori*.

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**IS THERE A ROLE FOR MMP19 IN GUT INFLAMMATION?**

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**Introduction:** Matrix metalloproteinases (MMPs) comprise a family of 26 enzymes, which remodel components of the extracellular matrix (ECM). There is evidence that MMPs 1, 2, 3 & 9 are over expressed in the gut in inflammatory bowel disease (IBD). The gene encoding MMP19 lies on chromosome 12q14 close to the IBD 2 susceptibility locus. We therefore investigated the expression of MMP19 protein in normal and diseased gut by immunohistochemistry.

**Methods:** Biopsy specimens were obtained at endoscopy from patients with Ulcerative Colitis (n=6), Crohn’s Disease (n=11), Colonic Carcinoma (n=2), Pseudomembranous Colitis (n=2), Coeliac Disease (n=3) and normal controls (n=15). Immunohistochemistry was performed on paraffin embedded sections using a polyclonal rabbit anti-human MMP19 hinge region antibody (Sigma) in accordance with standard techniques.

**Results:** In normal tissue, staining for MMP19 was observed in the cytoplasm of epithelial cells in surface and crypt mucosa. Within the crypt, we also identified cytoplasmic staining of cells of neuroendocrine origin. Some pigment was seen in the stroma and lamina propria, including the cytoplasm of mononuclear cells. This pattern was consistent in the rectum, colon, ileum, duodenum, stomach. In the colon, the cytoplasm of pericryptal fibroblasts was prominently stained. In the duodenum, the cytoplasm of Brunners gland cells was stained. The specimens from IBD and coeliac patients demonstrated increased staining of surface and crypt mucosal epithelial cells and stromal tissue. This was not observed in colonic carcinoma or pseudomembranous colitis. No differences were seen between crohns disease and ulcerative colitis.

**Discussion:** This is the first demonstration of MMP19 protein in the gut. We have identified expression in epithelial cells of the mucosal stromal tissue including mononuclear cells and pericryptal fibroblasts. Increased expression of MMP19 was identified in IBD and coeliac disease.

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**ATTENUATION OF THE HEPATIC INFLAMMATORY RESPONSE TO PORTAL ENDOXOXAEMIA IN OBSTRUCTIVE JAUDICE USING A NOVEL ANTI-ENDOTOXIN PEPTIDE.**

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**Background:** In obstructive jaundice (OJ), hepatic proinflammatory cytokines such as TNFα and IL-6 are released in response to portal...
endotoxaemia. Exaggeration of this response may occur following a “second hit” such as surgical intervention, leading to organ dysfunction. The aim of this study was to develop novel anti-endotoxin peptides and assess their efficacy in reducing the hepatic proinflammatory response to a second hit of portal endotoxaemia in OJ.

**Methods:** Endotoxin specific peptides were generated using biopanning of a pVIII random linear phage library with Lipopolysaccharide from Salmonella minnesota Re595. A test peptide, P6, was developed which was shown to inhibit LPS-induced TNFa secretion by human monocytic cells. Bile duct ligation was performed on 9 Male Wistar rats who were randomised to receive either (a) endotoxin (LPS) alone (n=4) or (b) LPS + P6 peptide (n=5), during in-situ hepatic perfusion performed 1 week post surgery. Aliquots of effluent perfusate were collected for cytokine analysis at 80, 100 and 120 minutes.

**Results:** See table.

**Conclusion:** This novel anti-endotoxin peptide offers an exciting new therapeutic strategy for preventing an exaggerated endotoxin-induced inflammatory response at the time of surgery in patients with OJ.

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**095 THE CD14+/CD16+ BLOOD MONOCYTE SUB-SET AND NOT GENETIC PRE-DISPOSITION INFLUENCES THE INCREASED SOLUBLE CD14 RECEPTOR EXPRESSION ASSOCIATED WITH SEVERE ACUTE PANCREATITIS**


**Background:** The soluble form of CD14 (sCD14) is derived from a 55kDa membrane bound glycoprotein on monocytes, and enhances endothelial cytokine responses to lipopolysaccharides (LPS). It is a mediator of the systemic inflammatory response syndrome (SIRS). We investigated the role of sCD14 expression in the SIRS associated with acute pancreatitis (AP), to determine if altered expression was due to a C260T polymorphism in the CD14 promoter gene, or attributable to an altered monocyte subpopulation.

**Methods:** Peripheral blood samples in patients with AP were assayed for sCD14 (24 and 72 hr from onset) and correlated with clinical severity (Atlanta Criteria), and SIRS (Acute Physiology Score, APS). Peripheral blood mononuclear cells (PBMC) were isolated to identify immunophenotypes using immunofluorescence flow cytometry. Leukocyte DNA was genotyped for the CD14 polymorphism using PCR.

**Results:** Severe AP (n=20) was associated with an early sustained increase in plasma sCD14 median 67pg/ml (R:25–216) compared to mild attacks (n=70) median 30ng/ml (R:24–103), p<0.001, and healthy controls (n=40) median 5.1ng/ml (R:23–78), p<0.001. Soluble CD14 strongly correlated with APS at 24hr r=0.38, p<0.001 and 72hr r=0.56, p<0.001. The proportion of monocytes in PBMC isolates was increased in severe attacks (p<0.005), but the early increase in CD14 only correlated with the relative expansion in the population of CD14+/CD16+ monocytes r=0.57, p<0.001. No differences in CD14 genotype were detected between 245 patients with AP (68 severe) and 143 controls even after stratification for disease severity.

**Conclusions:** Severe AP is associated with increased sCD14 expression that may be secondary to alterations in monocyte sub-sets, possibly in response to LPS, but appears not to be genetically pre-determined.
Results: Almost all mouse T cells freshly isolated from mesenteric (MLN) and peripheral lymph nodes stained weakly for α4β7 but a subpopulation became α4β7⁺ upon activation with anti-CD3 in a cycle-length and accessory-cell dependent manner. Precursor frequency analysis revealed that a small proportion (1.6±0.5%) of the starting cells gave rise to α4β7⁺ cells after culture. Both the proportion and number of dividing cells expressing α4β7⁺ was consistently greater for MLN than PLN (five experiments). Typically 2–3 fold fewer PLN than MLN were α4β7⁺. Peyer’s patch cultures displayed intermediate values. In crossover experiments using highly purified T cells, MLN DC induced significantly (p<0.01) more α4β7⁺ cells than PLN DC irrespective of the source of responding T cells.

Conclusions: In addition to their other immunoregulatory roles, dendritic cells can shape immune responses by influencing the homing of the lymphocytes they activate. Modulating lymphocyte migration and development of mucosal vaccines.

098 STEROID ENHANCING EFFECT OF THE INTERLEUKIN-2 ANTAGONIST BASILIXIMAB ON LYMPHOCYTE STEROID SENSITIVITY

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Up to 30% of patients with severe ulcerative colitis (UC) fail to respond to steroid therapy. We have previously shown that lymphocytes from these patients (and approximately 20% of normal subjects) have a steroid enhancing effect. We therefore hypothesised that basiliximab (BAS), a clinically well-tolerated chimeric monoclonal IL-2 receptor blocking antibody might enhance lymphocyte steroid sensitivity in resistant subjects.

Methods: Peripheral blood lymphocytes were isolated from 32 subjects (25 healthy volunteers and 7 patients with quiescent UC), on 41 occasions, using buoyant density centrifugation. Lymphocyte steroid sensitivity was assessed by measuring the antiproliferative effect of dexamethasone (DEX) on phytohaemagglutinin stimulated lymphocytes. Maximum steroid induced suppression was expressed as a % of control lymphocyte proliferation (I₃₀). I₃₀ was measured in the absence and presence of BAS (1mg/l).

Results: The addition of BAS significantly enhanced the anti-proliferative effect of DEX (Wilcoxon signed-rank test, p < 0.0001) [see table]. All 8 steroid-resistant subjects (I₃₀ <60%) were modulated (p<0.0001) (see figure) by DEX (Wilcoxon signed-rank test, p < 0.0001) (see figure).

Conclusion: BAS has a marked in vitro steroid enhancing effect. As we have previously demonstrated an association between lymphocyte steroid resistance and poor response to steroids in severe UC, this raises the possibility that BAS may be an effective adjunctive therapy in steroid-resistant subjects. A clinical trial of basiliximab in steroid-resistant UC is planned.

099 EXPRESSION OF TUMOUR NECROSIS FACTOR α (TNFα) AND LYSOZYME IN NECROTIZING ENTEROCOLITIS (NEC)

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Background: NEC is an acute inflammatory disease of premature neonates. Risk factors for NEC include prematurity, bacterial colonisation, formula feeding and hypoxia, but its aetiology remains unknown.

TNFα is a potent proinflammatory cytokine associated with the development of NEC in animal models. In neonates with NEC, plasma TNFα levels are not consistently elevated and do not correlate with disease severity. However plasma TNFα levels do not accurately reflect cellular activity. We therefore analysed TNFα gene expression in situ in intestinal tissue from neonates with severe NEC (Bell stage III), and compared this with the expression of lysosome, an antibacterial enzyme produced by Paneth cells in the small intestine.

Methods: We performed in situ hybridisation, using digoxigenin labelled riboprobes, on paraffin embedded intestinal tissue from eight neonates with NEC and four control subjects. Sense and anti-sense probes were used, and macrophages were identified immunohistochemically using an antibody to CD68.

Results: The intestinal architecture was disrupted in all cases of NEC and necrosis, ulceration and haemorrhage were the dominant histopathological features. Increased TNFα expression was present in all cases of NEC (8/8) whilst normal intestinal tissue and control NEC sections showed no TNFα expression. TNFα expression was most intense in infiltrating macrophages in the lamina propria and around areas of neutrophil infiltration. TNFα expression was also noted in Paneth cells, epithelial cells and circulating macrophages, and correlated with the histological severity of NEC. Lysosome gene expression was noted in sections containing Paneth cells.

Conclusions: Increased TNFα expression characterises acute NEC and this expression is sustained in established disease. These findings support data implicating TNFα in the pathogenesis of NEC in animal models. Treatment of NEC with anti-TNFα monoclonal antibodies may therefore be justified in the setting of a controlled clinical trial.

100 A PRO-INFLAMMATORY CYTOKINE COCKTAIL INCREASES CCK RELEASE FROM STC-1 CELLS VIA AN EFFECT ON INTRACELLULAR CALCIUM

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Background: How mucosal inflammation produces anorexia is poorly understood. Modulation of enteroendocrine cell function is a plausible mechanism. Cholecystokinin (CCK) produces symptoms of nausea and satiety when infused parenterally and is involved in IL-1 induced anorexia.

Methods: The CCK secreting cell line, STC-1 was incubated with the pro-inflammatory cytokines IFN-γ, IL-1β and TNF-α alone or in combination. CCK secretion was measured by radioimmunoassay. As CCK secretion is mediated by increases in intracellular calcium ([Ca²⁺]), changes in [Ca²⁺] in response to 70 nM K⁺ (a receptor-independent stimulus of secretion) were assessed using a dual wavelength ratio imaging technique (Fura-2). To look at effects on gene expression we studied the effects of combined cytokines on activity of CCK promoter-reporter constructs using a luciferase assay system and luminometry.

Results: Pre-incubation with the single cytokines IFN-γ, IL-1β and TNF-α for 2 hours produced small increases in basal CCK secretion. IFN-γ (6.25U/ml) produced a 38.4±4.6% increase in CCK secretion compared to control (p=0.02), IL-1β (0.125ng/ml) produced a 16.9±1.5% increase (p=0.005) and TNF-α (5ng/ml) produced an 13.7±1.83% increase (p=ns). However when a cocktail of IFN-γ, IL-1β and TNF-α was pre-incubated together this produced an increase of 109.4±24.0% over basal secretion after 2 hours incubation (p=0.001). This increase was maintained after 4 hours with a 70.7±24.7% increase (p=0.02) but diminished at 8 hours to a 43.6±8.0% increase (p=0.055). The cytokine cocktail had no effects on basal [Ca²⁺], but pre-incubation for 2 hours produced a 23.9±2.9% (p=0.03) increase in the [Ca²⁺] response to K⁺ compared to control. However the cytokine cocktail did not stimulate CCK promoter-reporter activity during the same period of pre-incubation.

Conclusions: Short-term incubation with a cocktail of the pro-inflammatory cytokines IFN-γ, IL-1β and TNF-α has a synergistic effect increasing basal CCK secretion in the STC-1 cell line. This occurs via a mechanism involving changes in intracellular calcium. This may have implications for symptom genesis, particularly anorexia in proximal GI inflammation.

Dr Leslie is sponsored by the Wellcome Trust & Dr McLaughlin by the DFF.
FUNCTIONAL IL-18 RECEPTOR EXPRESSION BY HUMAN INTESTINAL EPITHELIAL CELLS REQUIRED FOR INHIBITION OF CRYPTOSPORIDIUM PARVUM DEVELOPMENT BY IL-18

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Introduction: IL-18 is a cytokine with both Th1 polarising and proinflammatory actions. IL-18 binds the heterodimeric IL-18 receptor (R) to mediate its action. We have previously observed infection of intestinal epithelial cells (IECs) by the intracellular parasite C. parvum may be inhibited by proinflammatory cytokines (IFN-γ, TNF-α and IL-1β). We hypothesised IECs expressed functional IL-18R and parasite development could thereby be directly inhibited by IL-18.

Methods: mRNA transcripts of the receptor sub-units IL-1Rrp and A28 BSG abstracts were measured by semi-quantitative PCR in the transformed IEC lines Caco-2, HCT-8, and HT-29 and freshly isolated human IECs. The specificity of the PCR reaction was confirmed by restriction digest or sequence analysis. The action of a panel of proinflammatory cytokines on receptor sub-unit expression by IECs was similarly determined. Finally, the action of exogenous IL-18 (2–200 ng/mL) on C.parvum development in IECs was studied using a previously described in vitro model of infection (Gastro 119: 1234).

Results: Transcripts of IL-1Rrp, AcPL and MyD88 were detectable in all transformed IEC lines tested. Expression of the receptor sub-units by isolated human IECs was variable and dependent on the origin of the cells. Restriction digests confirmed the specificity of the PCR products for the receptor sub-units. Functionality of the IL-18R expressed by HT-29 and HCT-8 cells was also demonstrated. Significant exogenous IL-18 significantly inhibited parasite development (p<0.0001)

Conclusion: We describe for the first time functional expression of the IL-18R by both cultured and isolated human IECs. We speculate IL-18 has a previously unknown proinflammatory action on enterocytes and may be an important innate mucosal defence mechanism in the control of intracellular enteric pathogens. Further work is required to confirm this action in vivo.

RCGP funded by a Wellcome Trust Research Training Fellowship.

SPECIFIC CYTOTOXIC T LYMPHOCYTE IMMUNITY AGAINST TELOMERASE IN COLORECTAL CANCER

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Background: Characterisation of the cytotoxic T lymphocyte (CTL) activity against tumour antigens is crucial for understanding cancer immune surveillance mechanisms. Although telomerase activity is found in 90–100% of colorectal cancers, there is insufficient data on the prevalence of specific anti-telomerase immunity.

Methods: The CTL response against two HLA-A2-restricted epitopes of human telomerase reverse transcriptase (hTERT) was studied ex vivo in 16 HLA-A2+ colorectal cancer patients and 6 healthy subjects. An interferon gamma (IFN-γ) ELISPOT assay was used to quantify the amplitude of the specific CTL response against telomerase, after incubation of peripheral blood mononuclear cells (PBMC) with hTERT peptides. PBMC incubated with or without phorbol 12-myristate 13-acetate (PMA) served as positive and negative controls, respectively. The level of the specific CTL response against HLA-A2-restricted peptides of Influenza A and CEA was also determined to allow comparison.

Results: Specific CTL against one of the two hTERT peptides were found in 6 (38%) of the 14 colorectal cancer patients, with 4 (25%) of these recognising both peptides. The frequencies of telomerase-specific CTL were between 15–45/10^6 PBMC. In addition, 11 (69%) patients presented CTL reactive with the Influenza A peptide and 6 patients (31%) had CTL that responded to stimulation with the CEA peptide. CTL active against telomerase were found both in patients with disseminated disease, as well as in patients with early disease. None of the healthy volunteers studied presented CTL capable of recognising telomerase and/or CEA antigens, but three (50%) recognised Influenza A.

Conclusions: The present study demonstrates that patients with colorectal cancer are capable of mounting a specific cellular immune response against telomerase antigens. Our findings suggest that the lack of an effective immune response against tumour cells that possess telomerase activity is not due to the absence of CTL directed against telomerase epitopes, but probably to a defective presentation mechanism for these antigens.

INCREASED MUCOSA-ASSOCIATED & INTRA-EPITHELIAL BACTERIA IN COLON CANCER

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Introduction: It has been suggested that mucosa-associated bacteria may be important in the pathogenesis of colon cancer (Swidinski et al., Gastroenterol. 1998;115:281). Such bacteria are suspected to act as a result of interaction between bacterial adhesins and the altered colonic mucosal glycoconjugates found in colon cancer and pre-cancer.

Methods: Mucosa-associated and intra-epithelial bacteria were isolated from biopsies taken from patients with colon cancer and from histologically normal controls using the gentamicin protection method. Bacteria were cultured on MacConkey agar, identified using API 20E bacterial identification kits and assayed for agglutination of sialidase-treated red blood cells which express the TF cancer-associated carbohydrate antigen, GaGa1-3GalNAcα.

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<thead>
<tr>
<th>Bacteria</th>
<th>Cancer (tumour) n=19</th>
<th>Cancer (distant mucosa) n=19</th>
<th>Normal n=24</th>
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<tr>
<td>Mucosa-associated</td>
<td>14 (74%)*</td>
<td>10 (53%)</td>
<td>8 (33%)</td>
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<tr>
<td>Intra-epithelial</td>
<td>11 (58%)†</td>
<td>6 (32%)</td>
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Data expressed as number of cases from each group positive for any bacterial growth. Significant difference from normal, *p<0.004, †p=0.04.

Results: A significant increase of mucosa-associated and intra-epithelial bacteria was found in colon cancer [see table]. 73% of intra-epithelial bacteria were identified as being Gram-negative (mostly E. coli), bacteria from the cancer cases, including 2 from...
the distant mucosa, but none of the normal controls, tested positive for TF adhesin activity. This is the first report of TF-binding intestinal bacteria in humans. Further studies on an isolate of TF-binding non-pathogenic E. coli (HM44), which we have shown to lack conventional pathogenicity islands, from a colon cancer case show that it is able to invade HT29 human colon cancer cells.

Conclusion: These results support the hypothesis that altered mucosal carbohydrate expression (such as TF antigen) in colon cancer and distant “unaffected” mucosa may lead to recruitment of E. coli. Bacteria which lack conventional markers of pathogenicity but which can invade intestinal epithelial cells could be relevant to carcinogenesis.

Symposium: Gut flora in IBD—practical importance 105–107

105 DIAGNOSIS OF CROHN’S DISEASE IS ASSOCIATED WITH INCREASED LEVELS OF ANTIBIOTIC USE OVER THE PRECEDEING FIVE YEARS

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Background: Although it is generally accepted that Crohn’s disease has both genetic and environmental determinants, few environmental determinants are well established. In view of the widely supported notion that dysfunction of the gut is inter-linked with its flora, we explored the potential importance of the use of antibiotics as a risk factor.

Methods: We selected records of incident cases of Crohn’s disease from the General Practice Research Database. All cases were diagnosed after 1992, had no history of Ulcerative Colitis and at least five years of GPRD data prior to diagnosis. Controls with five years complete data were randomly selected. Data were extracted on smoking, presentation to GP with a diagnosis of infection, oral contraceptive use (OCP) and antibiotic use 3–5 years prior to the date of diagnosis of Crohn’s disease (and for a comparable period for controls). Data on antibiotic use was restricted in time to exclude those that could have been prescribed as treatment of premonitory symptoms. Logistic regression was used to investigate the relationship between antibiotic use and Crohn’s disease.

Results: 601 Crohn’s disease and 1460 controls were available for analysis. We found statistically significant associations between Crohn’s disease and use of OCP in the year before diagnosis (Odds ratio 1.7, P=0.003) and smoking (Odds ratio 1.5, P=0.001) despite incomplete data for the latter (these are consistent with the literature). Antibiotic use 3–5 years pre-diagnosis was significantly greater in cases than controls. Only 29% of cases compared to 42% of controls received no antibiotics (P<0.001), and the mean number of courses was 2.6 in cases and 1.9 in controls (P<0.0001). Adjusting for age, sex, smoking and use of OCP, antibiotic use had an odds ratio of 1.6 (1.3–2.0) (P<0.001). There was a highly significant trend with increasing numbers of courses (P=0.001). The population attributable fraction for antibiotic use was 28% (18–36%).

Conclusions: There is a highly significant association between Crohn’s disease and prior antibiotic use in this data. This is unlikely to be explained by reporting bias in view of the prospective recording of all prescriptions in GPRD. If this association is causal then it may explain about a quarter of all Crohn’s disease.

106 MICROBIAL CELL WALL OLIGOMANNAN INHIBITS THE NEUTROPHIL RESPIRATORY BURST: A POSSIBLE MECHANISM FOR GRANULOMA FORMATION IN CROHN’S DISEASE?

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Background: Crohn’s like intestinal lesions occur in Chronic Granulomatous Disease, a condition caused by a defect in phagocyte function. Crohn’s disease patients commonly have serum antibodies to Salmonella enteritidis mucosal cell wall oligomannan. The epitope for this antibody is oligomannan which is present in bacterial and yeast cell wall. Our hypothesis is that oligomannan, shed by intramucosal bacteria, may inhibit neutrophil and macrophage function within the mucosa, leading to the granulomatous lesions seen in CD.

Methods: The effect of S. cerevisiae oligomannan on phorbol ester (PMA) induced-respiratory burst of neutrophils from healthy volunteers was measured by luminol-amplified and isoluminol-amplified chemiluminescence and by the cytochrome c reduction method. Neutrophils were isolated using a one-step centrifugation method and suspended in HBSS buffer.

Results: See fig 1. At the highest concentration used (1 mg/ml), oligomannan inhibited luminal dependent chemiluminescence by 68% (±5%, n=6). Luminal chemiluminescence measures the combined activities of the neutrophil NADPH oxidase and myeloperoxidase, and so the oligomannan could be acting on either or both of these activities. However, oligomannan (at 1 mg/ml) also inhibited PMA-stimulated isoluminol-amplified chemiluminescence and cytochrome c reduction. As oligomannan and cytochrome c reduction largely measure extracellular superoxide secretion, the oligomannan may have an effect on NADPH oxidase activity.

Conclusion: S. cerevisiae oligomannan causes dose-related inhibition of the PMA-induced respiratory burst. It has extracellular and probably intracellular effects. This supports the hypothesis that microbial oligomannans impair mucosal phagocyte function, thus generating the granulomatous phenotype of Crohn’s disease.

107 REDUCED BIFIDOBACTERIA AND INCREASED E. COLI IN RECTAL MUCOSA-ASSOCIATED FLORA IN ACTIVE INFLAMMATORY BOWEL DISEASE

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Background: Colorectal bacteria probably contribute to the pathogenesis of IBD. To test the hypothesis that potentially protective bacteria are reduced and pathogenic flora increased, we have compared the mucosa-associated flora in IBD and controls.

Methods: Snap-Frozen rectal biopsies were taken at routine colonoscopy from patients with ulcerative colitis (UC), Crohn’s and controls with normal colorectal mucosa. Fluorescent in situ hybridisation was used separately to count numbers of mucosa-associated bifidobacteria, lactobacillus, E.coli, clostridia and sulphate-reducing bacteria.

Results: Bacteria were sited on, and superficially within rectal mucosa. Mucosa-associated bifidobacteria counts (median 14/hpf (range 4–65), n=13) in active UC were lower than in controls (79 (0–146), n=24, P=0.008), the difference from quiescent UC (38 (0–118), n=19) did not reach statistical significance (P=0.07). Conversely, E.coli counts were higher in active UC (80/hpf (30–186)) than in controls (0 (0–16), P=0.0002) and inactive disease (2 (0–144), P=0.003). Similar results were found in patients with active Crohn’s colitis (n=4). In 6 patients with UC who had biopsies from 2 sites, inflamed mucosa always showed fewer bifidobacteria (P=0.008) and more E.coli (P=0.008) than normal looking more proximal colon. There were no differences, between IBD and controls, of quantitative counts of other bacteria.

Conclusions: The reduction in mucosa-associated bifidobacteria and increase in E.coli in active IBD supports the hypothesis that a deficiency of potentially beneficial bifidobacteria and excess of E.coli could play a role in the causation of IBD.
LOCAL IL-10 GENE THERAPY INDUCES COLONIC IL-10 RELEASE AND IS THERAPEUTIC FOR MURINE COLITIS

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Introduction: Interleukin-10 knockout (IL-10 -/-) mice spontaneously develop a Th1 T cell mediated colitis with many similarities to Crohn’s disease. Daily injections of IL-10 are unable to induce remission in mice with established disease. In contrast, the intravenous administration of snRNA viral vectors encoding full-length IL-10 (AdvmuIL-10) induces hepatic IL-10 release and leads to long-term disease suppression with profound systemic immunoregulatory changes.

Aims: To determine whether the rectal delivery of AdvmuIL-10 will induce localised colonic IL-10 expression without systemic immunosuppression. To assess its therapeutic efficacy in IL-10 -/- mice with established colitis.

Results: A single rectal infusion of 5x10^8 PFU AdvmuIL-10 to 10 week IL-10/-/- mice induced a median of 27.3 pg/mg IL-10 in colonic homogenates harvested after one week. In contrast, the IL-10 concentration of liver and spleen homogenates did not differ significantly from the background seen in PBS treated controls. IL-10/-/- mice with established colitis were treated with 5x10^8 PFU AdvmuIL-10, empty cassette adenovirus (Adv0), or PBS vehicle by rectal infusion (n=10/group). The median clinical score in the AdvmuIL-10 group fell from 1.8 ± 0.13 to 0.16, whereas the clinical scores increased from 1.4 ± 0.27 to 2.5 ± 0.27 and from 1.8 ± 0.22 to 2.6 ± 0.13 in the PBS and Adv0 treated groups respectively (p<0.001, 2-way ANOVA). In addition, the stool concentration of IL-10 increased over the four-week expression period significantly higher in mice treated with saline or Adv0 than those treated with AdvmuIL-10 (p<0.01). Finally, local AdvmuIL-10 therapy had no effect on TNF-a release from stimulated splenocytes.

Conclusion: Local AdvmuIL-10 therapy reverses colitis in IL-10 -/- mice without the systemic effects seen after intravenous administration. Gene therapy strategies using adenoviral vectors encoding immunoregulatory cytokines may prove to be a potent approach to the treatment of chronic inflammatory diseases such as Crohn’s disease.

INFLAMMATORY BOWEL DISEASE IS ASSOCIATED WITH FUNCTIONAL TNF POLYMORPHISM AFFECTING OCT1/NF-KB INTERACTION


Introduction: The tumour necrosis factor-alpha (TNF) gene lies within a replication defective inflammatory bowel disease (IBD) genetic susceptibility locus (6p21, IBD3); and TNF is clearly implicated in IBD pathogenesis.

Aims: To assess genetic associations of TNF promoter variants in IBD and study the functional biology of associated variants.

Methods: Association studies of the common TNF polymorphisms (-1031, -863, -857, -308). Two independent cohorts were used (set A, 457 IBD families; 294 Crohn’s disease (CD) trios, 252 ulcerative colitis (UC) trios; set B 130 IBD families and 278 healthy controls (HC)). Functional studies of –857C/T used: LPS stimulated whole blood TNF ELISA in 46 healthy controls; monocyte nuclear extract/promoter construct electro-mobility shift assays; in vitro GST pull-down assays of transcription factors OCT1, NF-kB, and deletion mutants; in vivo COS cell immuno-precipitation and COS cell luciferase reporter gene analysis.

Results: TNF –857C was associated with IBD in both set A and replication set B, using case control and family based (TDT) association analyses. Numbers homozygous for TNF-857C were 857C homozygotes show higher TNF production. We have identified a molecular mode of action, through allele specific binding of OCT1 to the TNF promoter and interaction between OCT1 and NF-kB.

Conclusion: The TNF-857C allele is associated with IBD, and TNF-857C homozygotes show higher TNF production. We have identified a molecular mode of action, through allele specific binding of OCT1 to the TNF promoter and interaction between OCT1 and NF-kB.

SUSCEPTIBILITY TO PRIMARY SCLEROSING CHOLANGITIS IS ASSOCIATED WITH A POLYMORPHISM OF THE MMP-9 (GELATINASE B) GENE


Background: Primary sclerosing cholangitis (PSC) is a disease of the intrahepatic and/or extrahepatic bile ducts which is characterized by concentric obliterative fibrosis and bile duct strictures eventually leading to biliary cirrhosis. The matrix metalloproteinase family of zinc-containing proteolytic enzymes is involved in mediating extracellular matrix degradation. An association between a functional polymorphism of MMP-3 (stromelysin) and susceptibility to PSC has recently been described. MMP-9 polymorphisms have been described in association with progression of coronary atherosclerosis and cancer metastasis. This study assessed carriage of MMP-9 polymorphisms in relation to susceptibility to PSC.

Method: DNA was extracted from 69 patients with well-documented PSC, 71 patients with ulcerative colitis, and 92 healthy controls. Primers were designed to examine 8 polymorphisms in the MMP gene using a SSP/PCR method. PCR products were run on 1% agarose gels and read under UV light. PSC and UC patients were compared with controls using 2x2 contingency tables and a χ² test (with Yates correction). A Bonferroni correction for multiple comparisons was made using a factor of 8 (the number of polymorphisms tested).

Results: The R279Q polymorphism was significantly associated with susceptibility to PSC compared with controls. The frequency of the mutant allele was 32% in the PSC patients compared with 17% in controls (p = 0.008). There was a trend towards increased carriage in the ulcerative colitis group but this did not reach statistical significance after correction (p = 0.16). No associations were seen with any of the other polymorphisms tested.

Conclusion: There is increased carriage of the R279Q polymorphism in PSC patients. This polymorphism is in the catalytic region of the gene and may therefore influence the function of MMP-9. Studies...
are currently being undertaken to address the possible functional effects of this polymorphism.

### PRIMARY BILIARY CIRRHOSIS (PBC): NO SPECIFIC ASSOCIATION WITH MICROCHIMERISM

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**Background:** Some diseases may result from immunocompetent fetal cells acquired during previous pregnancies (allo-immunity) and persisting in the mother for decades (microchimerism). In women with scleroderma who have had male children, male DNA is found in skin and peripheral blood more frequently than in control women. Primary biliary cirrhosis (PBC) mainly affects older women and has similarities to graft versus host disease, consistent with a role for alloimmunity. Studies on the association of PBC with microchimerism have been small (<20 PBC liver specimens) and results have been conflicting.

**Aim:** To address the association of PBC with microchimerism in a larger cohort.

**Methods:** We studied (a): blood (2 extractions x 2 PCR= 4 PCR) from 55 women with PBC and 49 normal control women (irritable bowel or G-O reflux; normal liver enzymes) and (b): archived needle liver biopsies (1 extraction x 2 PCR = 2 PCR) from 42 women with PBC, 21 women with normal liver histology or mild steatosis (normal controls), and 32 women with autoimmune hepatitis (AIH) (disease controls). All had >1 male child and none met ARA criteria for scleroderma or had had a blood transfusion or a liver transplant when tissue was obtained. Male DNA was assayed by PCR using specific Y chromosome primers; lower detection limit = 1/3 of DNA in 1 cell (2pg).

**Results:** The table shows subject numbers (% with 0, 1 and >2 PCRs positive for male DNA.

<table>
<thead>
<tr>
<th>Blood</th>
<th>PBC</th>
<th>Normal</th>
<th>Liver</th>
<th>PBC</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>27 (49)</td>
<td>19 (35)</td>
<td>9 (16)</td>
<td>9.86</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>13 (27)</td>
<td>15 (31)</td>
<td>21 (43)</td>
<td>&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1 (2)</td>
<td>10 (24)</td>
<td>31 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIH</td>
<td>3 (14)</td>
<td>7 (33)</td>
<td>11 (52)</td>
<td>4.56 ns*</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>5 (16)</td>
<td>6 (19)</td>
<td>21 (65)</td>
<td>4.32 ns*</td>
<td></td>
</tr>
</tbody>
</table>

*: vs PBC livers.

**Conclusion:** PBC showed an unexpected negative association with microchimerism in blood and no significant association (compared to either control group) in liver. This, the largest study to date, does not support a role for microchimerism in the pathogenesis of PBC.

### FASTING INSULIN, 31,32 SPLIT PRO-INSULIN AND INSULIN RESISTANCE IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER

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**Introduction:** Nonalcoholic fatty liver (NAFL) is associated with insulin resistance and an increased risk of type II diabetes (T2DM). Development of T2DM results from either insulin resistance or defective insulin processing/secretion or both. Insulin resistance leads to increased lipolysis and flux of fatty acids (FFA) to the liver, which in turn may increase hepatic glucose output. Insulin processing involves enzymatic conversion of proinsulin to insulin through a series of site-specific cleavages. Recent development of specific assays allows different molecules of the proinsulin processing pathway to be measured separately. 31,33 split proinsulin is the predominant form of proinsulin, known to be elevated in T2DM and impaired glucose tolerance. Fasting levels have also been shown to predict development of T2DM.

**Methods:** We measured fasting insulin, intact proinsulin and 31,33 split proinsulin levels in patients with NAFL (n=24) compared to a healthy reference group (n=14). Insulin resistance index (IRI) was calculated from fasting plasma glucose and insulin levels using the well recognised mathematical model of glucose-insulin interactions - the ‘homeostatic model assessment’ (HOMA). Body composition was assessed by BMI, waist hip ratio and bioelectrical impedance analysis (BIA).

**Results:** Patients with NAFL were obese according to BMI: 31.19 +/- 0.81 vs 26.55 +/- 0.81, p<0.004. The NAFL group had higher insulin levels than reference: 21.44 +/- 7.64 mU/l vs 9.07 +/- 3.11 mU/l, p=<0.0014 and higher 32,33 split proinsulin levels: 18.50 mU/l +/- 1.85 mU/l vs 8.55 +/- 0.73 mU/l, p<0.0003. The NAFL group were also significantly insulin resistant using HOMA, p<0.0015. These results were independent of BMI and body fat assessed by BIA.

**Conclusions:** NAFL is associated with hyperinsulinaemia, elevated 32,33 split proinsulin levels and insulin resistance. Patients with NAFL are at increased risk of developing T2DM. Measurement of 32,33 split proinsulin may help to select individuals with the highest risk for targeted intervention. Insulin resistance causes an increased flux of FFA to the liver leading to fat deposition if metabolic competence for disposal is exceeded. Increased FFA flux may also result in hepatic overload of metabolic pathways that are incompletely understood.

### INHIBITION OF APOPTOSIS OF ACTIVATED HEPATIC STELLATE CELLS BY TIMP-1 IS MEDIATED VIA EFFECTS ON MMP INHIBITION: IMPLICATIONS FOR REVERSIBILITY OF LIVER FIBROSIS

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**Introduction:** The activated hepatic stellate cell (HSC) is central to liver fibrosis as the major source of collagens I and III and the tissue inhibitors of metalloproteinase-1 and -2 (TIMPs). During spontaneous recovery from liver fibrosis there is a decrease of TIMP expression, an increase in collagenase activity and apoptosis of HSC, highlighting the potential role of TIMP-1 and -2 in HSC survival.

**Aims:** To determine if TIMP-1 and TIMP-2 directly inhibit HSC apoptosis in tissue culture and in models of liver fibrosis in vivo.

**Methods:** Effects of recombinant TIMPs and mutated TIMP-1 on cultured activated HSC were examined after induction of apoptosis by cycloheximide in vitro. Rat and murine models of experimental liver fibrosis induced by CCl4 were examined during spontaneous recovery. HSC number, TUNEL staining and TIMP-1 mRNA were assessed.

**Results:** TIMP-1 and 2 demonstrated a consistent, significant and dose dependent anti apoptotic effect on HSC activated in tissue culture. A non-functional mutated TIMP-1 (T2G mutant) did not inhibit apoptosis indicating that inhibition of apoptosis was mediated through MMP inhibition. Studies of experimental liver fibrosis in the rat demonstrated that loss of activated HSC correlated with a reduction in TIMP-1 mRNA expression by PCR. Persistence of TIMP-2 mRNA expression did not correlate with MMP activity suggesting that TIMP-2 is an MMPI inhibitor in vivo. TIMP-1 knockout mice demonstrated significantly more HSC apoptosis relative to wild type mice at 3 and 7 days of spontaneous recovery.

**Conclusion:** TIMP-1 and -2 inhibit apoptosis of activated HSC. The anti apoptotic effect of TIMP-1 is mediated via MMP inhibition.

### DISTRIBUTION OF THE CONSTITUTIVE (COX-1) AND THE INDUCIBLE (COX-2) CYCLOOXYGENASE IN HUMAN LIVER CIRRHOSIS: A POSSIBLE ROLE OF COX-2 IN PATHOGENESIS OF LIVER CIRRHOSIS

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Several mediators of systemic vasodilatation and inflammation in liver cirrhosis have been reported. Among these are prostaglandins (PGs), which have been proposed as one of the main mediators during inflammation. In this study, liver biopsies from fifteen patients with clinically and pathologically diagnosed liver cirrhosis secondary to hepatitis B and C, were taken. In addition 3 liver biopsies from healthy controls were used. The protein expression of the constitutive (COX-1) and the inducible (COX-2) cyclooxygenase was investigated using immunocytochemistry.
We have shown that COX-2 was completely absent from the control group but was highly expressed in the cirrhotic livers. COX-2 was seen mainly in the inflammatory cells infiltrating the liver, sinusoidal cells, vascular endothelial cells and epithelial lining of bile ducts. On other hand COX-1 was expressed in normal and cirrhotic livers. COX-1 was exclusively seen in sinusoidal cells and vascular endothelial lining cells. There were no significant differences in COX-1 expression between normal and cirrhotic livers.

It is therefore clear that COX-2 is induced in liver cirrhosis and this could contribute to the overproduction of prostaglandins which could be a major contributor to hyperdynamic circulation associated with liver cirrhosis. High production of COX-2 in cirrhotic liver could explain the occurrence of hepatocellular carcinoma since COX-2 is believed to be carcinogenic. Finding that COX-2 and not COX-1 is markedly upregulated in cirrhosis could provide a possible new line of treatment using selective COX-2 inhibitors to treat the inflammation and also to minimise the occurrence of HCC in cirrhotic patients.

**114 EXPRESSION OF NITRIC OXIDE SYNTHASE ISOFORMS IN HUMAN LIVER CIRRHOSIS**


Several mediators of systemic vasodilatation in liver cirrhosis have been reported. Among these is nitric oxide (NO), which has been proposed as one of the major mediators. In this study sera and liver biopsies from fifteen patients with clinically and pathologically diagnosed liver cirrhosis were taken. In addition sera from 7 and 3 liver biopsies from healthy controls were used. Serum levels of nitrate [the end product of nitric oxide] were measured using Griess reaction and the protein expression of the inducible nitric oxide synthase (iNOS) and constitutive nitric oxide synthase (ecNOS) was investigated using immunocytochemistry. We have shown that the serum nitrite levels (94 ± 9.8 µmol/L) in cirrhotic patients were significantly [P <0.05] increased by comparison to the control (36.6 ± 1.03 µmol/L). iNOS was completely absent from the control group but was highly expressed in the liver of the cirrhotic group. iNOS was seen mainly in the inflammatory cells infiltrating the portal tracts, blood monocytes, hepatocytes, sinusoidal cells and vascular endothelial lining. However, iNOS was only seen in the vascular endothelial lining of both the control and cirrhotic groups but much higher in the latter. It is therefore clear that NO is augmented in cirrhotic patients and it is mainly produced by induction of iNOS. Moreover, NO upregulation is dependent on the inflammatory stage of liver cirrhosis. ecNOS production could be a normal chronic adaptation mechanism of the endothelium to the chronically increased splanchic blood flow secondarily to portal hypertension. In the near future, the appropriate inhibition of NO synthesis by using selective iNOS inhibitors may provide a novel strategy for the treatment of patients with liver cirrhosis or at least improve the fate of cirrhosis.

**115 SPLENCHNIC VASCULAR HYPOREACTIVITY IN HUMAN CIRRHOSIS IS RELATED TO DISEASE SEVERITY AND MEDITED BY NITRIC OXIDE AND CARBON MONOXIDE**

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Cardiovascular changes of cirrhosis correlate with disease severity and are associated with vascular hyporesponsiveness to vasoconstrictive stimuli and splanchic vasodilatation. The effect of disease severity on intravascular reactivity and the mechanisms involved in humans have not been studied.

Methods: We studied endothelial-denudated rings of human hepatic artery from patients undergoing orthotopic liver transplant for cirrhosis (n=5) and from organ donors and patients undergoing hepatic resection (controls: n=6). Decompensated cirrhosis was defined as Child Pugh score > 8 (n=5) and compensated cirrhosis ≤8 (n=4). The response to 80 mmol/L potassium chloride was recorded. Rings were then incubated with either 0.1 mM L-NMMA (a non-selective nitric oxide synthase inhibitor), 0.1 mM ZnPp (a non-selective haem oxygenase inhibitor) or vehicle control for 30 min. Cumulative dose response curves to phenylephrine (PHE) were constructed.

Results: Decreased maximal response to PHE was seen in decompensated cirrhosis compared with controls (P<0.002) and compensated cirrhosis (P<0.002) (Figure). In compensated cirrhosis, the maximal response was not different from controls. L-NMMA or ZnPp improved the maximal response in decompensated cirrhosis toward control values (1.11+/−0.19 mg/g and 0.93+/−0.10 mg/g respectively). Neither inhibitor affected the PHE response in compensated cirrhosis or controls.

**Conclusions:** Hepatic artery hyporeactivity to PHE occurs only in patients with decompensated cirrhosis and not those with compensated cirrhosis. Restoration of PHE responsiveness by LNMA or ZnPp in these endothelial-denuded vessels suggests that smooth muscle derived nitric oxide and carbon monoxide may be important and induced only in advanced disease.

**116 ACUTE LIVER FAILURE SERUM CAUSES APOPTOTIC CELL DEATH BY DOWN-REGULATION OF β1-INTEGRIN ACTIVITY**

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Integrity of the cytoskeletal axis is important for the maintenance of cellular differentiation, adhesion and viability. Disruption of this axis in acute liver injury may limit the role of stem cell/hepatocyte transplantation.

Aim: To study the effects (and mechanisms) of acute liver failure (ALF) serum on hepatocyte adhesion/cell death.

Methods and Results: HepG2 cells were cultured in media supplemented with 10/20% ALF or Normal human (NS) serum. Culture with 20% ALF serum led to significant increases in apoptotic cell death (Feulgen staining/TEM) after 24 [4%] and 48 [7.5%] hrs compared with negligible levels of apoptosis seen in culture with NS. Cellular adhesion (attachment to collagen coated plates after culture in either ALF or NS) was significantly decreased in cells grown in ALF serum. Of note this effect became pronounced after just 4 hours culture, well before apoptosis was observed (see table). Using Scanning Electron Microscopy cells cultured in ALF serum were strikingly more rounded in appearance and appeared far less adherent. Flow cytometric expression of the common integrins (β, α, λ) on HepG2 cells was carried out, and after 24 hours culture levels were seen to be higher on cells cultured in ALF serum (β log mean fluorescence: 2.61 in ALF vs 2.25 in NS). We then studied the activation level of the β-integrin using a flow cytometric assay. After 24 hours culture, ALF serum significantly reduced the activity of the β-integrin compared with control cultures (33.6 +/- 6.2 (ALF) vs 69 +/- 10.1 (NS)).

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<th>Abstract 116</th>
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<tbody>
<tr>
<td><strong>Culture duration</strong></td>
</tr>
<tr>
<td>4 hours</td>
</tr>
<tr>
<td>24 hours</td>
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<td>48 hours</td>
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www.gutjnl.com
Conclusion: Down-regulation of β3-integrin activity appears to be an early event in cells exposed to ALF serum, which precedes impaired cellular adhesion and apoptotic cell death, thus negating the possible therapeutic benefits of cell transplantation in liver injury. Modulation of integrin activity may be important in optimising cell transplantation.

[117] IS THE PROTHROMBIN TIME STILL USEFUL FOR ASSESSING FULMINANT HEPATIC FAILURE?


Prothrombin markers, such as prothrombin time, are important in guiding management in patients with Fulminant Hepatic Failure (FHF). The measurement of PT has recently changed from the Manchester method to the Innovin method, which utilises recombinant reagents and as such should provide less variability.

Aim: To study whether the two methods provide similar results when tested on samples taken from patients with FHF admitted to the Scottish Liver Transplantation Unit (SLTU).

Methods and Results: We prospectively studied 96 samples from 42 patients (35 paracetamol, 3 Non-A Non-B, 2 autoimmune, 1 Budd-Chiari Syndrome & 1 drug reaction) admitted to the SLTU from August 2000 to March 2001 with acute liver injury. Of these 17 developed encephalopathy (and thus FHF) and 9 met the King's College criteria for FHF. The equation derived by linear regression to relate the two values is Manchester prothrombin time = 0.61 + (1.72 x Innovin prothrombin time) (R^2=0.766, p<0.001). Whilst there is a strong association between these methods it is clear that there is not equivalence. Significantly the Innovin measured PT consistently records times greater than the Manchester measured PT, and thus usage of the Innovin PT could potentially lead to patients not being considered for liver transplantation as they would not meet KCPP criteria. Indeed in our cohort no patients had an Innovin PT of greater than 150 seconds and 57.8 seconds as measured by the Innovin corresponds to 50 and 100 seconds as measured by the Manchester method.

Conclusions: Our study demonstrates that Innovin measured PT is different from that measured with the Manchester reagent, and therefore its usage in FHF, as per the KCPP criteria, cannot be recommended. Widespread usage of the Innovin PT in FHF will require validation in larger studies before it can be recommended. This finding has important implications in the management of FHF.

[118] PENTOXIFYLLINE IMPROVES SHORT TERM SURVIVAL IN SEVERE ACUTE ALCOHOLIC HEPATITIS

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Background and Aims: Pentoxifylline (PTX), an inhibitor of Tumor Necrosis Factor, has been reported to improve the outcome of acute alcoholic hepatitis. The aim of the current study was to review our experience with this drug and to compare the results with a large control population.

Methods: The treatment group comprised of 8 consecutive patients with severe acute alcoholic hepatitis with Maddrey discrimination factor (MDF) >32 who were consecutively treated with PTX (400 mg orally 3 times/day) for 4 weeks. A group of 35 patients who were admitted before PTX was used in our unit with similar MDF score served as the control group. There were no statistical significant differences between the two groups as regards the demographic and clinical criteria or laboratory values, with the exception of an elevated serum creatinine, which was significantly more common in the control group (p < 0.05).

Results: The four week mortality in the treatment group was 0% as compared with the control group with a 4 week mortality of 77.1% (p < 0.0001). Hepato-renal syndrome developed in 50% of patients in the treatment group compared with 80% of the control group. Serum creatinine, MDF, and liver function tests in the treatment group. Serum alkaline phosphatase were three independent factors associated with mortality. Serum bilirubin and MDF showed significant improvement over 4 weeks in the PTX treated group (p < 0.03 and 0.02 respectively). The drug was well tolerated in all the patients and all received 4 weeks therapy. 5 of the patients in the treated group died subsequently on follow up 2 and 3 months later.

Conclusions: Treatment with pentoxifylline was well tolerated and appears promising in improving short-term survival in patients with severe acute alcoholic hepatitis. Such improvement in survival rate appeared to be related to the significant decrease in the risk of development of hepatorenal syndrome.

[119] ACUTE SICKLE CELL HEPATOPATHY: A NEW CONTRAINICATION TO PERCUTANEOUS LIVER BIOPSY

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Background: Percutaneous biopsy of the liver is an invaluable diagnostic tool in the investigation of liver pathology and is associated with a low incidence of complications. The mortality rate post-liver biopsy is approximately 0.1%. Following recent experience of complications including mortality following liver biopsy in paroxysmal nocturnal haemoglobinuria (PNH) we undertook a systematic review of our clinical experience in this population.

Methods: Sixteen patients with sickle cell disease who underwent a percutaneous liver biopsy were identified. Clinical records, pathology records, and the Coroner’s death register were reviewed. Demographics, duration of disease, frequency of sickling crises, sickle cell genotype, haematological and biochemical indices, and histopathological findings were correlated with course after biopsy and clinical value of data yielded by biopsy.

Results: Five of 16 patients (31%) suffered serious haemorrhage, and four died (80%/25%). None of the eleven patients without biopsy complications was in acute sickling crisis at the time of biopsy; four of the five patients with complications were. Four of these five patients underwent biopsy for an emergency indication. Chronic venous outflow obstruction, marked hepatic sequestration of erythrocytes, and sinusoidal dilatation were strongly associated with complications. Data obtained by biopsy in patients who suffered complications were assessed as not of substantial value in clinical management, nor likely to have been of value had patients survived. Five patients (80%) had hepatic sequestration crisis. In most of those (8/11; 73%) who did not suffer complications, however, the biopsy data were useful.

Conclusions: Percutaneous liver biopsy in patients with acute sickle cell haemoglobinopathy complicating sickle cell anaemia carries a high risk. To recognise acute sickle cell hepatitis is important; such a condition may represent a newly identified contraindication to percutaneous liver biopsy.

[120] COST EFFECTIVENESS OF HISTOACRYL GLUE VS. TIPS IN THE MANAGEMENT OF ACUTE GASTRIC VARICEAL BLEEDING

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Introduction: The management of bleeding gastric varices (GV) has not been standardised. Although TIPS is used in most centres, endoscopic treatment with histoacryl glue has been shown to be effective recently. Cost-effective analyses of these methods are lacking.

Methods: Review of results of patients who were treated for bleeding gastric varices in this institution initially by TIPS and later with histoacryl glue injection. Cost analysis, based on hospital charges, for a fixed financial year and comparison between the two groups were made for up to a period of 6 months, liver transplantation or death for each patient.

Results: 20 patients with bleeding GV had TIPS from January 1995 to December 1999 whilst 23 patients had histoacryl glue injection from January 2000 to October 2001. There were no significant differences in age, sex, diagnosis, Child-Pugh classification and transfusion requirement between the two groups. The TIPS group had 13 cases of GOV 1 and 7 with GOV 2, with 15 cases of GOV 1 and 8 with GOV 2 in the glue group (p=NS). In the TIPS group, 15/20 patients had the procedure within 24 hours of haemorrhage and 90% of stent insertions were successful. Complications consisted of three cases of pulmonary oedema, two cases of severe encephalopathy and a 15% stenosis rate at 6 months. In the glue group, there were 3.1 ± 5 endoscopies and 2 ± 1 injections per patient with a 96% haemostasis. There was one case of fatal (glue)
Genetic Haemochromatosis (GH): Where are all the patients?

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Background: Genetic haemochromatosis (GH) is the most common genetic disorder of Caucasian populations. A single autosomal recessive gene mutation (C282Y) accounts for over 90% of cases of GH in the UK. The highest carrier frequency reported for this mutation (approximately 1 in 10) is observed in North European or Celtic populations. Therefore there is likely to be a high prevalence of patients with GH in Scotland, but data are scarce.

Aims: To (1) estimate the gene frequency of the C282Y mutation in healthy control populations in Glasgow; (2) establish the prevalence of known cases of GH in Glasgow; (3) estimate the number of patients with diagnosed GH in Glasgow.

Methods: C282Y mutation frequency was established anonymously in two healthy control populations from Glasgow: umbilical cord blood samples from consecutive newborn infants and randomly selected healthy elderly controls. All patients in the Greater Glasgow Health Board area homozygous for the C282Y mutation up to 1st August 2001 were identified. The prevalence of GH was estimated from the frequency of GH in controls and the known GH population. The number of patients with undiagnosed GH was estimated from this figure and the number of known cases of GH.

Results: 340 controls (163 infants, 177 elderly controls) underwent C282Y testing. The C282Y mutation gene frequency was 7.4% (6.4% and 8.2% respectively) with a carrier rate of 1 in 10. An estimated 1 in 183 (5.5 per 1000) were homozygous, which equates to 4942 cases of GH within the 904,000 population of the GGHB area. Only 240 (0.26 per 1000) C282Y homozygotes are recognised. This represents 4.9% (240 / 4942) of the estimated number of C282Y homozygotes in the area.

Conclusions: As expected the C282Y mutation gene frequency is high in the control groups studied. Only a small minority (4.9%) of the estimated 4942 individuals with GH in Glasgow are recognised. Whether this reflects lack of biochemical or clinical penetrance of the C282Y mutation, or a failure of diagnosis requires further study.

Hepatitis C: Why have so few patients been treated?

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Hepatitis C (HCV) is a chronic illness for which a relatively effective anti-viral therapy exists. Many sufferers are referred to liver clinics with long waiting lists but a significant number do not receive active therapy.

A retrospective review of all HCV positive patients attending an outpatient liver clinic was conducted to determine the number who commenced anti-viral therapy and the reasons why patients did not. From Oct 1994-Dec 2000 all those attending clinics were documented. Those seen from Oct 1994 - Oct 1997 were reviewed in detail to determine the reasons why patients did not receive treatment (see table). Of 490 HCV patients [298M/192F] seen from Oct 1994-Dec 1997, 174 received anti-viral therapy (interferon alone or with ribavirin) and 316 did not. 27% of females were treated compared to 41% males. Predominant risk factors for HCV in either group were IVDU (63%) and 85 blood products (17%). Primary reasons for not receiving therapy: 105 (35%) did not meet Government criteria, 67 (21%) last to follow up after visit 1 or 2, 54 (17%) health, 45 (14%) herbal, 22 (7%) social and 23 (7%) chose no treatment. Of the 1104 patients seen over the 7 years, only 405 (37%) received anti-viral therapy.

Conclusions: Only 37% of HCV patients attending our clinic received anti-viral therapy. The major reasons for non-treatment were related to inadequate education and education pre-referral. This did not change with time. We have now provided referral checklists to general practitioners, established a new patient review clinic run by our clinical nurse consultant and we will evaluate the effect of these changes on treatment uptake rates. As HCV will continue to place major demands on busy liver clinics there remains a need to optimise use of clinic time.

Using the joint British societies coronary risk prediction charts to calculate coronary heart disease risk after liver transplantation

D.A.J. Neal1, P. Flynn1, A.E.S. Gimson1, P. Gibbs1, G.J.M. Alexander1. Department of Medicine and 1University Department of Surgery, Addenbrooke’s NHS Trust, Cambridge, UK.

Background: Hypertension, hypercholesterolaemia and weight gain are common after liver transplantation. It is not known whether development of these complications alters the cardiovascular risk profile after liver transplant.

Methods: The case notes of 110 consecutive adult liver transplant recipients surviving beyond one year were reviewed.

Results: Median follow-up was 52 months (range 6–90 months). 74 % of patients developed hypertension compared with 3 % being hypertensive before transplant (P<0.001). Hypercholesterolaemia was present in 16 % before and 60 % after transplant (P<0.001). 29 % were overweight at the time of transplant compared with 58 % after transplant (P<0.001). Diabetes mellitus was present in 8 % before and 12 % of patients after transplant. There were 3 non-fat cardiovascular events: 1 myocardial infarct, 1 heart failure and 1 cerebellar infarct. The Joint British Societies Coronary Risk Prediction Charts categorise 10-year coronary risk (on the basis of total cholesterol:high density lipoprotein cholesterol ratio, systolic blood pressure, smoking, diabetes mellitus, age and gender) as < 15 %, 15–30 % and > 30 %. Using these charts we categorised coronary heart disease risk before and after transplant (see table). If we assume patients require therapeutic intervention aimed at reverting risk when risk is 15 – 30 % or greater, 20 patients (18 %) would require treatment before transplant compared with 52 (47 %) after transplant.

Conclusions: Coronary heart disease risk increases after liver transplant. The number of observed cardiovascular events is low. We would expect more events than we have seen.
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124 BONE MARROW DERIVATION OF PERICYCRIPTAL PARACRINE COX-2-MEDIATED SIGNALLING BY MYOFIBROBLASTS IN THE MOUSE AND HUMAN SMALL INTESTINE AND COLON

S.J. Forbes1,2, T. Hunt3, M. Brittan3, R. Jeffery3, R. Poulsom3, K. Hodivala-Dilke1, M.R. Alison1,3, N.A. Wright1,4

Background: The intestinal sub-epithelial myofibroblasts (ISEMF) are found in the lamina propria of the intestine under the epithelial cells, and are of critical importance in epithelial-mesenchymal interactions. It has been suggested that the origin of ISEM/F might be from the neural crest, or locally from mesenchymal stem cells sited in the muscularis mucosae.

Aims/Methods: In order to establish whether extra-intestinal cells contribute to the turnover and repair of gastrointestinal tissues we studied: (i) the colon and small intestines of female mice that had received whole body irradiation followed by a male bone marrow transplant, (ii) gastric sub-mucosal myofibroblasts in patients that had undergone a male bone marrow transplant and then developed graft versus host disease. In situ hybridisation for the Y-chromosomes was combined with immunohistochemistry to define the phenotype of these cells of donor (bone marrow) origin.

Results: In female mouse recipients of male bone marrow grafts we observed clusters of Y-chromosomes positive/alpha-smooth muscle actin positive myofibroblasts. While few of these were present at 7 days after bone marrow transplantation, they were numerous at 14 days and by 6 weeks, whole columns of pericryptal myofibroblasts could be seen surrounding crypts in both the small intestine and colon. These columns appeared to extend into the villi in the small intestine. In the human intestine we confirmed that the bone marrow-derived cells within the intestine exhibited a myofibroblast phenotype.

Conclusions: Our data suggest that the bone marrow contributes to the regeneration of intestinal myofibroblasts after damage. This axis of gut regeneration may have therapeutic potential.

125 PITUITARY ADENYLYL CYCLASE-ACTIVATING POLYPEPTIDE REGULATES THE HISTIDINE DECARBOXYLASE PROMOTER VIA DUAL SIGNALLING MECHANISMS AND A DISTINCT RESPONSE ELEMENT

J.T. McLaughlin1, N.F. Sinclair, R. Callucci, R. Raychowdhury, T.C. Wang, T.J. Koh [introduced by Q Aziz]1, 2

Overall, our data suggest that the bone marrow contributes to the regeneration of intestinal myofibroblasts after damage. This axis of gut regeneration may have therapeutic potential.

Background: The gastric enterochromaffin-like cell has recently been transfected into PC12 cells, either wild type or stable transfectants

Methods: 1.8kB of the histidine decarboxylase promoter was ligated into a luciferase promoter-reporter construct and transiently transfected into PC12 cells, either wild type or stable transfectants expressing the gastrin-CCK, receptor. The effects of PACAP and gastrin on promoter activity were assessed via a series of 5' deletions and are of critical importance in epithelial-mesenchymal interactions.

Results: Promoter activation by PACAP was found to be dose-dependent and temporally biphasic, with an initial peak occurring at 4-6 hours (5-fold over basal, p<0.01), followed, to a trough of 16 hours, and then rising to a secondary peak at 24 hours (4-fold over basal, p<0.01). The initial peak was shown by inhibitor studies to depend upon activation of both adenyl cyclase and phospholipase C-dependent pathways, while the secondary peak was entirely PKA-dependent. Deletion analysis, block mutation and block phoretic mobility shift assays demonstrated a PACAP response element (PRE) at -177 to -170 (CTCTGAGG), wholly necessary for the effects of PACAP but not gastrin. Gastrin also interacted at key differences in the timing (small peak at 6 hours, major peak at 16 hours) and magnitude (maximally 3.5-fold) of its effects.

Conclusions: The data show that discrete neural and endocrine pathways impinging on histaminergic cells can exhibit different patterns of post-receptor signalling and promoter element activation. As previously described, the PACAP receptor is able to activate both PKA- and PKC-dependent pathways. A newly characterised PRE in the promoter is pivotal in PACAP’s effect on the HDC promoter, and quite distinct from the gastrin response element which has been localised to the +1-+48 region of the first untranslated exon.

126 IDENTIFICATION BY GENE ARRAY OF PLASMINOGEN ACTIVATOR INHIBITOR-2 (PAI-2) AS A NOVEL TARGET OF GASTRIN IN HYPERGASTRINAEMIA


Background and Aim: Gastrin controls acid secretion and the organisation of the gastric mucosa. Some gastrin-regulated events involve changes in gene expression. We sought to identify major, new, gastrin-regulated genes using a gene array.

Methods: A cancer gene array was probed with samples from AGS-cells expressing the gastrin-CCK, receptor stimulated with gastrin. The expression of gastrin-regulated genes was characterised by Western blot and ELISA in tissue and blood of hypergastrinemic patients. Gene expression was studied using promoter-luciferase reporter constructs.

Results: The gene array revealed PAI-2 as a major, previously unreported, gastrin-regulated gene in AGS cells. The relevance was confirmed by showing significantly (p<0.05, t test) elevated PAI-2 in plasma of hypergastrinemic patients (pernicious anaemia (PA): plasma gastrin, 1.20±0.16 nM; plasma PAI-2, 1.42±0.33ng/ml, n = 9; multiple endocrine neoplasia type 1 (MEN-1): gastrin, 0.53±0.09 nM; PAI-2, 2.0±0.2 ng/ml, n = 9; control gastrin, 0.03±0.01nM; PAI-2, 0.62±0.2ng/ml, n = 9). Moreover, PAI-2 was detected as a strong band in Western blots of gastric biopsies of 8 of 9 PA patients, 5 of 7 MEN-1 patients, but was at or below the limit of detection in 9 of 10 controls. To examine cellular control mechanisms we transiently transfected AGS cells with 2.3kb of the PAI-2 promoter in a luciferase reporter construct; gastrin (1nM) increased expression 14.0±1.3 fold over control (p<0.05). Pharmacological agents and dominant negative vectors indicated that responses were mediated partly via protein kinase C, RhoA, and the transcription factors CREB and AP1. Over-expression of the tumour suppressor menin (which is mutated in MEN-1) significantly inhibited gastrin-stimulated PAI-2 expression (p<0.05).

Conclusions: PAI-2 is a novel, gastrin-regulated gene. PAI-2 is thought to inhibit apoptosis and extracellular proteolysis, so the data suggest a novel potential mediator of gastrin-stimulated changes in epithelial organisation.

127 PARACININE COX-2-MEDIATED SIGNALLING BY MACROPHAGES PROMOTES TUMORIGENIC PROGRESSION OF INTESTINAL EPITHELIAL CELLS


Background: The gastric enterochromaffin-like cell has recently been transfected into PC12 cells, either wild type or stable transfectants expressing the gastrin-CCK, receptor. The effects of PACAP and gastrin on promoter activity were assessed via a series of 5' deletions and are of critical importance in epithelial-mesenchymal interactions.

Results: Promoter activation by PACAP was found to be dose-dependent and temporally biphasic, with an initial peak occurring at 4-6 hours (5-fold over basal, p<0.01), following, to a trough of 16 hours, and then rising to a secondary peak at 24 hours (4-fold over basal, p<0.01). The initial peak was shown by inhibitor studies to depend upon activation of both adenyl cyclase and phospholipase C-dependent pathways, while the secondary peak was entirely PKA-dependent. Deletion analysis, block mutation and block phoretic mobility shift assays demonstrated a PACAP response element (PRE) at -177 to -170 (CTCTGAGG), wholly necessary for the effects of PACAP but not gastrin. Gastrin also interacted at key differences in the timing (small peak at 6 hours, major peak at 16 hours) and magnitude (maximally 3.5-fold) of its effects.

Conclusions: The data show that discrete neural and endocrine pathways impinging on histaminergic cells can exhibit different patterns of post-receptor signalling and promoter element activation. As previously described, the PACAP receptor is able to activate both PKA- and PKC-dependent pathways. A newly characterised PRE in the promoter is pivotal in PACAP’s effect on the HDC promoter, and quite distinct from the gastrin response element which has been localised to the +1-+48 region of the first untranslated exon.

JMc supported by MRC Travelling Fellowship and DDF Senior Fellowship.

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was not associated with significant changes compared with control IEC-6 cells. AMC-cultured IEC-6 cells maintained cytokeratin expression but expressed decreased membranous E-cadherin, decreased TGFBRII (associated with resistance to TGFB1) and increased Cox-2 as well as PAI-1 compared with control and NMCC-cultured IEC-6 cells. AMC-cultured IEC-6 cells exhibited anchorage-independent growth in soft agarose as well as increased membrane microsatellite instability (MSI) but were non-tumorigenic in nude mice. The presence of the selective Cox-2 inhibitor SC236 (Pharmacia) during (but not after) RAW264.7 cell activation inhibited AMC-induced IEC-6 cell changes.

Activated macrophages promote phenotypic change of IEC-6 intestinal epithelial cells (compatible with tumorigenic progression) via a paracrine Cox-2-dependent mechanism. These models provide direct in vitro evidence for Cox-2-mediated macrophage-intestinal epithelial cell signalling during the early stages of intestinal tumorigenesis.

**AN N-TERMINALLY TRUNCATED CYTOPLASMIC FORM OF OXYGEN-REGULATED PROTEIN 150 (ORP150), THE MAJOR INTRACELLULAR LIGAND FOR THE ANTIMICROBIAL PROLIFERATIVE MUSHROOM LECTIN, IS ESSENTIAL FOR NUCLEAR LOCALISATION SEQUENCE (NLS)-DEPENDENT NUCLEAR PROTEIN IMPORT IN HUMAN INTESTINAL CANCER CELLS**

L.G. Yu, J.M. Rhodes. Department of Medicine, University of Liverpool, Liverpool L69 3GA, UK

The classical NLS-dependent nuclear import system, which mediates import of large nuclear proteins, is fundamentally important for maintaining nuclear function. Our previous studies have shown that the import of cell proliferation of mushroom Agaricus bisporus lectin (ABL) (Cancer Res 1993;53:4627) is linked to its internalisation and selective blockade of NLS-dependent nuclear protein import (J Biol Chem 1999;274:4890). One of the major intracellular ABL-binding ligands is N-terminally truncated cytoplastic form of ORP150 (Gastroenterology 2001;120(suppl1):3579). ORP150 is a stress-related protein and is up-regulated in tumours and highly expressed in cancer cell lines. In this study we investigated the role of ORP150 in nuclear protein import.

Nuclear protein import was performed in digitonin semi-permeabilized human colorectal cancer HT29 and gastric cancer AGS cells using a fluorescein-conjugated synthetic NLS peptide/bovine albumin complex (NLS-BSA-FITC) as a transport marker. It was found that introduction of an anti-Orp150 antibody, but not other irrelevant antibodies, into the transport system resulted in 57% and 48% reduction of nuclear accumulation of NLS in HT29 and AGS cells respectively. Removal of cytosolic Orp150 from the transport system by immunabsorption caused over 40% reduction of NLS nuclear accumulation. The ras-related nuclear transport factor Ran was identified in the Orp150 immunoprecipitate. Orp150 was also identified by immunoblotting in the immunoprecipitates of Ran but not in the immunoprecipitates of other Ran-associated proteins (RanBP1, RCC1, RanGAP1 and NTF2).

This result suggests that the truncated cytoplastic Orp150 has a crucial role in NLS-dependent nuclear protein import probably by direct interaction with Ran.

**CONTIGUOUS HYPERPLASTIC POLYP (HP), SERRATED ADENOMA (SA) AND COLORECTAL CANCER (CRC): PATHWAYS AND TIMING**

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**Background:** HPs may progress to CRC via the SA [serrated CRC pathway]. In hyperplastic polyposis (HP) this occurs by microsatellite instability (MSI) and chromosomal instability (ICI). In sporadic CRC, the serrated CRC pathway has been suggested to lead to proximal CRC with high levels of microsatellite instability (MSIH). Aims: To investigate the heterogeneity of MSI and K-ras and p53 mutations in contiguous SA/CRC and contiguous HP/SA to help understand the timings and genetic mechanisms driving the serrated pathway.

**Methods:** Paraffin-embedded tissue blocks with contiguous SA/CRC or contiguous HP/SA were selected. Using a haematoxylin-eosin stained section as a reference, tissue components were identified, micro-dissected and DNA was extracted. MSI analysis was done by PCR at Bat 25 and Bat 26 and by immunohistochemistry for the mismatch repair proteins hMLH1 and hMSH2. DNA samples were analysed for point mutations in codons 12 and 13 of the K-ras gene using minisequencing. Abnormal p53 accumulation was identified using immunohistochemistry.

**Results:** 11 contiguous SA/CRC and 2 contiguous HP/SA were analysed. 10/11 SA/CRC samples were MS stable. MSI was seen in both SA & CRC components in 1/11. The CRC but not the SA showed loss of hMLH1. K-ras mutations were detected in 4/11 CRCs. 3/4 contiguous SAAs had the same K-ras mutation [1/4 PCR failure]. The remaining 7 SA/CRCs were wild type. P53 results were available in 10. All 10 CRCs and 5/10 contiguous SAs showed accumulation of mutant p53. Neither of the two HP/SAAs showed MSI or K-ras mutations.

**Conclusions:** All contiguous SA/CRC or HP/SA were concordant in MS and K-ras status. This supports the serrated CRC pathway. K-ras mutation appears to be an early event whereas p53 over-expression (and presumably mutation) a later event. MSI was rare in this predominantly distal tumour series.

**TELOMERASE EXPRESSION IN BARRETT’S, OESOPHAGEAL AND GASTRIC ADENOCARCINOMA**

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Ribonucleoprotein enzyme telomerase is increased in most cancers and is present in small quantities in gastrointestinal epithelia. Telomerase is involved in carcinogenesis but the contribution of the gene encoding its catalytic subunit (hTERT) to the regulation of telomerase activity is unclear. We assessed hTERT expression and telomerase activity in Barrett’s, oesophageal and gastric adenocarcinoma.

**Methods:** hTERT mRNA was quantitated using real-time RT-PCR and telomerase activity measured by the TRAP assay in the following: paired samples from Barrett’s (n=16) and adjacent cardia, paired samples from gastric (n=15) and oesophageal (n=21) adenocarcinoma and adjacent macroscopically normal tissue.

**Results:** (median expressed as arbitrary units) In Barrett’s and adjacent cardia, telomerase activity was 20 and 11 respectively, p = 0.28 and hTERT mRNA was 3.6 and 2.3 respectively, p=0.12. There was no significant difference. In gastric adenocarcinoma, compared to adjacent normal tissue, telomerase activity was increased significantly from 0 to 16, p = 0.01 and hTERT mRNA was increased also from 2.2 to 7.1, p =0.008. In oesophageal adenocarcinoma, compared to adjacent normal tissue, telomerase activity was increased significantly from 5 to 229, p < 0.0001 but hTERT mRNA was not significantly different, 1.7 and 2.5, p =0.48. Comparing oesophageal cancer and Barrett’s, telomerase activity was 229 and 20 respectively, p = 0.001 but hTERT mRNA was not significantly different, 3.5 vs 3.6.

**Conclusions:** Telomerase enzyme activity was increased in cancers but not Barrett’s suggesting that increased enzyme activity occurs late in oesophageal carcinogenesis. In gastric adenocarcinoma, increased hTERT expression was associated with increased enzyme activity suggesting a modest regulatory role of hTERT in this cancer. However, in general, hTERT expression correlated poorly with telomerase activity confirming the complexity of telomerase regulation in malignant and benign tissue of the human foregut.

**TNF-α IN BARRETT’S OESOPHAGUS**

C. Tslepis1, I. Perry1, D. Wakelin1, R. Hardy1, S.J. Darrton1, R. Harrison1, J.A.Z. Jankowski1,2. 1Epithelial Laboratory, Department of Medicine, University of Birmingham, B15 2TH, UK; 2Oesophageal Research Laboratory, Birmingham Heartlands Hospital B9 5SS; 3Department of Pathology, University of Birmingham, B15 2TT, UK

Barrett’s metaplasia of the oesophagus (BM) is an early lesion in the progression from oesophageal inflammation, through dysplasia to the development of Barrett’s adenocarcinoma (BA). Previous work indicates that BM and BA are associated with reduced E-cadherin expression and increased cytoplasmic/nuclear pools of its associated protein β-catenin. β-catenin participates in Wnt signalling and activates oncogene transcription by complexing with T-cell factors (TCF).

Since we have previously shown that TNF-α can down-regulate E-cadherin expression we have assessed TNF-α expression in Barrett’s oesophagus and examine if TNF-α can promote β-catenin mediated transcription of oncogenes in a gastrointestinal model system.
Epithelial expression of TNF-α was determined by immunohistochemistry and Western blot analysis of oesophageal tissue. β-catenin mediated transcription was assessed in TNF-α stimulated cell lines using the TOPFLASH reporter system. C-myc expression was assessed by real time PCR.

Epithelial expression of TNF-α increases with the metaplasia-dysplasia-carcinoma sequence. In an intestinal cell model TNF-α induces c-myc expression, which is mediated through β-catenin regulated transcription, independent of NF-κB activation.

In summary TNF-α is up regulated in the progression of Barrett’s Oesophagus. β-catenin mediated transcription of c-myc is a pathway whereby elevated levels of TNF-α may lead to oncogene transcription in gastrointestinal epithelia.

132 INCREASED EXPRESSION OF THE SRC, MET AND ERBB-2 KINASES IN THE PROGRESSION OF BARRETT’S METAPLASIA TO ADENOCARCINOMA

M.R. Anderson, J.A. Jankowski, D.C. Rowlands, C. Tslepis. The Epithelial Laboratory, University of Birmingham, Edgbaston, UK

Background: The development of oesophageal adenocarcinoma is characterised by progression along the Barretts metaplasia – dysplasia – carcinoma sequence. It is known that the growth factor TGFβ and its receptor, EGFR show increased expression along this sequence. Receptor activation leads to phosphorylation of kinase substrates involved in signal transduction pathways. This may promote cell proliferation and invasion. Further tyrosine kinase receptors may also be involved in dysplastic progression and could provide therapeutic targets. ErbB2, src and met are three tyrosine kinases that may be influenced by such growth factors.

Aims: To investigate the expression of erbb2, src and met along the metaplasia – dysplasia – carcinoma sequence.

Methods: Routine immunohistochemistry staining was carried out on paraffin sections from specimens of normal squamous oesophagus, Barretts metaplasia and oesophageal adenocarcinoma. Staining was scored semi-quantitatively. Western blotting was carried out on biopsy samples of normal oesophagus, Barretts metaplasia and oesophageal adenocarcinoma.

Results: Up-regulation of met was seen along the sequence with strong met expression staining seen in 0/10 normal oesophagus, 4/10 Barretts, 5/10 dysplasias and 7/10 carcinomas. Src is ubiquitously expressed but strong membranous staining was seen in only 3/10 Barretts and 6/10 carcinomas. ErbB2 showed reduced expression in Barretts compared with normal oesophagus, but then showed strong membranous staining in 3/9 dysplasias and 4/10 carcinomas. Western blotting confirmed these patterns of altered expression.

Conclusions: The increased expression of met is an early step in the metaplasia – dysplasia – carcinoma sequence. The increased expression of src and erbb2 appears to be later steps in the sequence akin to EGFR. The altered expression of met, erbb2 and src suggests that whilst there may be some redundancy in tyrosine kinase signaling, one of these could provide a mechanism that promotes the progression from metaplasia to carcinoma, and may be a potential therapeutic target.

133 VARIATIONS IN CYTOKINE EXPRESSION IN THE MALIGNANT PROGRESSION OF BARRETT’S OESOPHAGUS AND FOLLOWING PHOTODYNAMIC THERAPY

P. Sirieux1, T.K.L. Wong1, L.B. Laval1, R.C. Fitzgerald1. 1National Medical Laser Centre, Department of Surgery, Royal Free and University College School of Medicine, London; 2Cancer Cell Unit, Hutchison/MRC Research Centre, Cambridge CB2 2XZ, UK

Background: Oesophagitis has a Th1 cytokine profile in contrast to the Th2 profile (IL-4, IL-10) with low levels of TGF-β of Barrett’s oesophagus (BO). Cytokines influence neoplastic progression via alterations in immune surveillance however this is poorly studied in BO. Patients with high-grade dysplasia in BO can be treated endoscopically by photodynamic therapy (PDT). Post-PDT, the regenerating epithelium is ideally squamous, but BO may persist.

Aims: To compare the cytokine levels in the malignant progression of BO 2. To determine the effect of PDT on cytokine expression in BO.

Methods: Competitive RT-PCR was used to assess the cytokine profile of OE33 (adenocarcinoma cell line) and OE21 (squamous cell carcinoma line) cells and of biopsies from normal squamous oesophagus (NO), high-grade dysplasia (HG-D), non-dysplastic BO (n=50), and Barretts adenocarcinoma (AC, n=3). For PDT patients with high grade dysplasia (n=5), cytokines were determined by semi-quantitative PCR up to 2 months after PDT compared with the pre-PDT biopsies.

Results: TGFβ, IL-1β and IL-8 expression is increased in OE33 cells compared to OE21 (p<0.05, p<0.05 and p<0.005 respectively). In AC biopsies, IL-4 levels are increased (16 fold increase cf. NO, p<0.05) as well as IL-1β levels (>50 fold increase cf. NO and BO, p<0.05). TGFβ expression is decreased in BO (cf. NO p<0.05), but increases again in AC to squamous mucosal levels (8 fold difference, p<0.05). Following PDT IL-10, IL-8, IL-1β and KGF were increased in BO at least 3-fold 24 hours after therapy. 2 months later these cytokine levels reverted to baseline. TGFβ levels in BO were unaffected by PDT. Neo-squamous epithelium had a cytokine profile that was intermediate between NO and BO. The cytokines levels in NO were unaffected by PDT.

Conclusions: Cytokine expression is altered in BO neoplasia and post-PDT. Whether, the cytokine profile has a causal role in the determination of the cell phenotype post-PDT merits further study.

134 LUMINAL NITROSATION POTENTIAL FOLLOWING NITRATE INGESTION IS MAXIMAL AT THE GO JUNCTION

H. Suzuki, K. Iijima, A. Moriya, V. Fyfe, K.E.L. McColl. Dept of Medicine & Therapeutics, Western Infirmary, Glasgow, UK

Background: Acidification of nitrite in the presence of nitrosatable chemicals produces potentially carcinogenic N-nitrosocompounds. The reaction is catalysed by thiocyanate (SCN⁻) and inhibited by ascorbic acid (AA). Saliva contains a high concentration of nitrite (NO₂⁻), derived from dietary nitrate (NO₃⁻), and swallowed saliva is the main source of NO₂⁻ entering the acid stomach.

Aim: To determine if there are regional variations in the nitrosating potential in the upper GI tract.

Methods: We used a validated technique involving microdialysis probes to simultaneously measure the chemicals relevant to nitrosation in the oesophagus, cardia, proximal stomach and distal stomach of 15 healthy volunteers before and following ingestion of 2mmol nitrate (equivalent to a salad portion).

Results: The NO²⁻ ingestion increased median saliva NO₂⁻ from 37µM to 215µM and distal oesophageal NO₂⁻ from 29µM to 182µM (p<0.01 each). Within the acid stomach, the NO₂⁻ concentration progressively decreased and AA concentration progressively increased with distance distal to the GO junction producing the highest acidic NO₂⁻/AA ratio right at the GO junction. Results following NO³⁻ ingestion are shown in table (values are medians).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Saliva</th>
<th>Distal Oes</th>
<th>Gastric cardia</th>
<th>Proximal stomach</th>
<th>Distant stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.0</td>
<td>2.6</td>
<td>1.9</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>SCN[µM]</td>
<td>1378</td>
<td>629</td>
<td>469</td>
<td>651</td>
<td>650</td>
</tr>
<tr>
<td>NO₂[µM]</td>
<td>215</td>
<td>166</td>
<td>20.5*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AA[µM]</td>
<td>7.4</td>
<td>7.8*</td>
<td>19.9</td>
<td>40.4</td>
<td></td>
</tr>
<tr>
<td>NO₂/AA ratio</td>
<td>-5.0</td>
<td>2.7*</td>
<td>-3.0</td>
<td>2.0*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

¹p<0.01 compared to proximal and distal stomach.

Conclusions: 1) Nitrosation within the acid secreting stomach will be maximal at the GO Junction. 2) Dietary nitrate may be involved in the aetiology of mutagenesis and carcinogenesis at this site.

135 SUPPRESSION OF PROLIFERATION AND INDUCTION OF APOPTOSIS IN HUMAN OESOPHAGEAL ADENOCARCINOMA CELLS BY NATURAL AND SYNTHETIC COX-2 INHIBITORS

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Background: Adenocarcinoma arising from Barrett’s oesophagus is the most rapidly increasing cancer in the west. Epidemiological studies suggest that use of NSAIDs is associated with up to 90% decreased risk of developing oesophageal cancer. The main biochemical target for NSAIDs is cyclooxygenase and the isoenzyme

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COX-2 is up-regulated in oesophageal carcinogenesis. The protective effect of NSAIDs may result from inhibition of COX-2. Synthetic COX-2 inhibitors suppress enzyme activity, while the food-borne flavonoid quercetin also suppresses COX-2 mRNA expression. We examined the effects of 3 commercially available COX-2 inhibitors (NS-398, nimesulide and niflumic acid) and quercetin on cell proliferation and apoptosis in the poorly differentiated human oesophageal adenocarcinoma cell line OE-33.

Methods: Cell viability after treatment with COX-2 inhibitors for 24, 48 and 72 h was assessed on 96-well plates using a neutral-red dye technique. Changes in the relative numbers of adherent and floating cells were assessed in culture-flasks, and apoptotic cells among the floating cells were identified using ethidium bromide and acridine orange staining under fluorescent microscopy. Flow cytometric analysis of attached and floating populations was used to quantify apoptotic cells and to examine the effects of the agents on the cell cycle.

Results: Western blot analysis confirmed COX-2 expression in the OE-33 cell line. The selective COX-2 inhibitors and quercetin suppressed OE-33 cells proliferation in a dose- and time-dependent manner, and increased the fraction of floating cells in the population. The majority of the floating cells were identified as apoptotic. The anti-proliferative effects induced by quercetin were significantly greater, and the number of floating cells was significantly higher after quercetin treatment compared with the selective COX-2 inhibitors (p<0.05). Cell cycle analyses revealed that quercetin blocked the cell in S phase while the selective COX-2 inhibitors (NS-398 and Niflumic acid) blocked the cell in G1/G0 interphase.

Conclusion: Selective COX-2 inhibitors are able to suppress proliferation and induce apoptosis in human oesophageal adenocarcinoma cells in vitro. However, quercetin, a food borne COX2 inhibitor, has an even greater inhibitory effect on these cells, and is a potent inducer of apoptosis and cell-cycle arrest.

**Abstract 135**

**ANGIOGENIC POTENTIAL OF HUVEC CELLS IS INCREASED BY AMIDATED AND GLYCINE-EXTENDED GASTRIN-17**

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Introduction: Gastrin peptides directly and indirectly promote the growth of malignant cells. Gastrin modulates expression of heparin binding EGF (HB-EGF), which may play a role in angiogenesis (Miyi-zaki et al., 1999). The aim of these studies was to determine whether gastrin modulates endothelial vessel formation of human umbilical vein endothelial (HUVEC) cells in in vitro culture.

Methods: HUVEC cells were grown in a mixed culture system with irradiated feeder cells in 24-well plates. Amidated human gastrin-17 (G17) and glycine extended G17 were added to the cultures at concentrations of 10nM. Vascular endothelial growth factor (VEGF, 2ng/ml) and suramin (20µM) were used as positive and negative controls. 24, 48 and 72 h was assessed. 96-well plates were set up for each condition, respectively. Media supplementation took place on days 4 and 7. At day 8 the cultures were fixed with ethanol and stained with a CD31 monoclonal antibody. Image analysis was used to quantify tube node formation.

Results: The mean nodes assessed for 2 separate experiments are shown in the table.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean nodes (SEM)</th>
<th>Significance from medium control (p value, Mann Whitney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>15.6 (1.2)</td>
<td>20.5 (1.3)</td>
</tr>
<tr>
<td>Suramin</td>
<td>5.9 (0.5)</td>
<td>6.2 (0.4)</td>
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<tr>
<td>VEGF</td>
<td>29.5 (1.8)</td>
<td>33.5 (1.7)</td>
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<tr>
<td>G17</td>
<td>30.0 (2.1)</td>
<td>27.0 (1.6)</td>
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<tr>
<td>GlyG17</td>
<td>31.0 (1.7)</td>
<td>35.0 (1.7)</td>
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Conclusion: G17 and GlyG17 are able to induce an angiogenic response in HUVEC cells which is equal in magnitude to that induced with VEGF.

**Abstract 137**

**GASTRIC ADENOMATOUS POLyps DEMONSTRATE ACCUMULATION OF MUTANT P53**

G.V. Smith, R. Feakins, A. Ballinger. Adult and Paediatric Gastroenterology and Experimental Pathology, Barts and the London, Queen Mary’s School of Medicine, London, UK

Gastric adenomas are a rare finding at endoscopy, occurring at 1 in 3000 of endoscopies. They are associated with the development of gastric cancers mirroring the adenoma-carcinoma neoplastic pathway in the colon however in the stomach they account for a small proportion of cancers. P53 gene mutations are found in between 40 and 50% of all gastric cancers and occur relatively late in the neoplastic cascade.

**Aim:** To assess the degree of p53 mutation by detecting accumulation of clone DO-7 type mutated p53 in gastric adenomatous polyps.

**Method:** 15 Sequential archived paraffin blocks taken from gastric resections and endoscopic biopsies of gastric adenomas were analysed by immunohistochemistry using a monoclonal antibody raised against p53 clone DO-7 protein (Dako). An avidin-biotin bridge and DAB detection system were employed (Vector).

Positive controls from an oesophageal carcinoma (Dako) and negative controls from an adenocarcinoma (Dako) and normal gastric tissue were also used. Corresponding sections from unselected gastric adenocarcinomas were also assessed. Sections were counterstained with haematoxylin and assessed for the presence or absence of mutated p53 accumulation.

**Results:** All 15 adenomas exhibited p53 accumulation, indicated by nuclear staining, with none of the controls specimen (see table 1).

<table>
<thead>
<tr>
<th>Abstract 137</th>
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<tbody>
<tr>
<td>Normal (15)</td>
</tr>
<tr>
<td>Mutant p53 positive</td>
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Discussion: Mutated p53 accumulation is strongly associated with gastric adenoma, its presence being detectable in a far greater proportion than in gastric carcinomas and normal gastric tissue. This pattern of p53 expression matched gastric resections and replacement of the primary antibody with serum from the host animal were employed. 15 sections from unselected gastric adenocarcinomas were also assessed. Sections were counterstained with haematoxylin and assessed for the presence or absence of mutated p53 accumulation.

**Abstract 138**

**DETECTION OF TELOMERASE ACTIVITY IN CIRCULATING COLORECTAL TUMOUR CELLS**

L. Titu, J. Greenman, V. Jordison, J.R.T. Monson, R.L. Loveday. Academic Surgical Unit, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire HU16 5QJ, UK

Background: Despite an apparently curative resection, up to 10% of Dukes A and 25% of Dukes B colorectal cancer patients relapse and die of metastatic disease within 5 years. This indicates that the metastatic process may already have been established prior to, or at the time of resection, and that the detection of tumour cells in the circulation at this time may have important prognostic or diagnostic implications.

**Methods:** Thirty-six sequentially presenting patients undergoing surgery for colorectal cancer and ten healthy controls were included in the study. Patient blood samples were taken pre-operatively, and 1 and 7 days post-operatively. Peripheral blood mononuclear cells (PBMC) were obtained from whole blood by Ficoll-Hypaque density gradient centrifugation. Circulating epithelial cells were then isolated from PBMC by incubating with the epithelial specific antibody BerEP4 conjugated to magnetic beads. Cells were harvested using a magnetic field, lysed and protein content determined and standardised. Telomerase activity was detected in lysates using TeloTAGG Telomerase PCR ELISA (Roche, UK).

**Results:** We identified 12 (33%) patients who were positive for circulating tumour cells (CTC) pre-operatively, indicating that the method described may have some value as a diagnostic tool. Sixteen patients (44%) were negative for CTC pre-operatively but positive post-operatively, suggesting that surgical manipulation had resulted in the detection of tumour cells in the circulation at this time.
introduction of tumour cells into the circulation. For 11 (67%) of these patients the CTC were still detectable at 7 days after surgery. The presence of telomerase positive CTC did not correlate with the cancer’s stage. None of the healthy controls exhibited telomerase activity in epithelial cells.

**Conclusions**: The method described represents a simple and specific method for the detection of CTC in colorectal cancer patients. The detection of telomerase activity in CTC may have prognostic implications independent of currently established staging systems and the longer term follow up of these patients will assess this.

**[139] CORRELATION BETWEEN UPTAKE OF LABELLED ANTI-CCKB/GASTRIN RECEPTOR ANTIBODIES AND THE OCCURRENCE OF APOPTOSIS IN HEPATOMA CELL LINES**

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**Background**: It has been reported that administration of an anti-CCKB/gastrin receptor (CCK-BR) antibody to mice bearing human xenograft tumours results in increased apoptosis and necrosis (Watson et al., 2000, Cancer Res. 60: 5902–5907). We have previously found that cell lines exposed to an antibody raised against a peptide corresponding to residues 5–21 of the amino terminus of the CCK-BR display endocytosis of the antibody into the cytoplasm and nucleus.

**Aim**: To assess whether the endocytosis of this anti-CCK-BR antibody correlates with the occurrence of apoptosis in these same cell lines.

**Methods**: The anti-CCK-BR antibody was labelled with Alexa Fluor 488 dye (Molecular Probes, USA). HepG2 (human hepatocyte carcinoma), PLC/PRF/5 (human liver hepatoma), MCA RH 7777 (rat hepatoma), HTC (rat hepatoma) and WRL 68 (human liver embryonic) cells were exposed to the labelled antibody at 20 µg/ml for 1 hour at 37°C. The cells were fixed and subsequently costained for apoptosis using anti-CCK-BR antibodies and WTR 68 (human liver embryonic) cells were exposed to the labelled antibody at 20 µg/ml for 1 hour at 37°C. The cells were fixed and subsequently costained for apoptosis using an immunofluorescent rhodamine assay (ApopTag Red kit, Intergen, USA). Cells were imaged using a fluorescent microscope with filters for the Alexa Fluor 488 and rhodamine fluorescence.

**Results**: In all five cell lines, uptake of the labelled anti-CCK-BR antibody was correlated with apoptosis.

**Conclusions**: Here, we demonstrate a direct relationship between the uptake of the antibody and cell death (apoptosis). This observation has important implications in the treatment of CCK-BR positive tumours including hepatomas where there are limited therapeutic options.

**Endoscopy free papers 140–149**

**[140] INTERCOLLEGIATE-BSG NATIONAL COLONOSCOPY (IBNC) AUDIT: THE CONSENT PROCESS PRIOR TO COLONOSCOPY AS REPORTED BY A PATIENT QUESTIONNAIRE**

C.J. A. Bowles1, R. Leicester2, E. Swarbrick3, C.B. Williams4, C. Romaya5, O. Epstein1. 1Royal Free Hospital, London; 2St George’s Hospital, London; 3New Cross Hospital, Wolverhampton; 4St Mark’s Hospital, London; 5Audit Office, B.S.G., London, UK

**Introduction**: Colonoscopy may be complicated by bleeding, peritoneal and sedation related side effects. The General Medical Council guidance on consent states that sufficient information should be provided on the purpose of a proposed investigation or treatment as well as common and serious side effects. Patients should be allowed sufficient time to reflect before making a decision. As part of the IBNC audit a patient questionnaire ascertained details of consent with regard to whether written information was provided, where consent was obtained and whether adverse effects were considered.

**Results**: 1200 patient questionnaires were distributed and 599 (49.9%) returned. Prior to colonoscopy 488/599 (81.5%) patients received written information. In 328/599 (54.8%), consent was obtained in the procedure room, and in 179/599 (29.9%), immediately prior to the colonoscopy but not in the procedure room. In 60/599 (10.0%), consent was obtained as an outpatient and 32/599 (5.3%) patients couldn’t remember or didn’t answer this question. Possible adverse events were reported by 329/599 (54.9%) patients and bleeding and perforation were specifically cited by 95/329 (28.9%) and 96/329 (29.2%) respectively. No mention of adverse events was reported by 196/599 (32.7%) of patients and 56/599 (9.3%) couldn’t remember whether or not they were provided with information on possible adverse events. 18/599 (3.0%) provided no response to the question on adverse events.

**Conclusion**: The majority (81.5%) of patients were provided with written information prior to colonoscopy. Contrary to the GMC advice, patients are frequently consented in the procedure room. Interestingly, 54.9% of patients reported that they had been informed of adverse effects. In the interests of ensuring best practice, endoscopists should be constantly mindful of the GMC guidelines on consent.

**[141] COLONOSCOPY INDUCED PAIN: NURSES ARE BETTER AT ASSESSING THIS THAN DOCTORS**

S. Ramakrishnan, J.Y. Yiannakou, T. Butler, W.R. Ellis, I.M. Bain. Department of Gastroenterology, University Hospital of North Durham, Durham, UK

**Background**: Endoscopists focussed on the technical challenges of colonoscopy may not adequately appreciate patient discomfort.

**Methods**: We conducted a prospective study of 474 colonoscopy procedures most of which were performed by 5 endoscopists. Overall completion rate was 89%. Pain was assessed during the procedure as visual analogue scores (0 to 10) by the nurse, endoscopist (doctor) and patient. All were blind to the others’ scoring. Patients had variable amounts of sedation and analgesia. A Multivariate Linear Regression analysis was performed on 426 data points.

**Results**: Data was complete on 426/474 questionnaires. The average score for doctor, nurse and patient was 2.8 (S.E 0.1), 3.09 (S.E 0.11) and 3.2 (S.E 0.13) respectively. Pain scores of doctors and nurses were compared to that of the patient. The correlation coefficient was 0.42 (p<0.01) and 0.59 (p<0.01) respectively, both highly significantly related to patients’ perception of pain. Indeed nurses appeared to have a better perception of this pain. When using a multivariate analysis, modelling patient pain on both doctors and nurses perception of pain, the doctors have little predictive value over and above nurses, i.e. doctor’s perception is no longer significant when adjusted for nurses’ perception (p>0.39). However nurses’ perception remains highly significant when adjusted for doctors’ perception (p<0.01).

**Conclusions**: The degree of unpleasantness/pain recollected by patients is the most important factor in the acceptability of this procedure. Nurses were able to provide a closer assessment to this than the endoscopist (doctor). This maybe because endoscopists are focussed on the video monitor while nurses are focussed on the patient. This might suggest a need for better training of endoscopists or more active use of nurse’s assessments during the procedure for achieving best results with minimal patient discomfort.
Background and Aims: A recent study suggests the synergistic sedation with a low dose of midazolam combined with propofol for conscious sedation in colonoscopies in a selected group of patients under the age of 60 years. Our study sought to compare the safety and efficacy of the synergistic sedation with a low dose of midazolam combined with propofol versus the standard regimen of midazolam and pethidine for conscious sedation in colonoscopies in a group of patients that included a sufficient number of elderly patients with several comorbidities, representative of the patient profile seen in public general hospitals.

Methods: 120 consecutive patients undergoing colonoscopy were randomly assigned to 1 of 2 medication regimens. Patients in group A (n=64, 33 over 65 years) received intravenously (IV) 2mg (≥70 kg b.w.) or 3mg (>70 kg b.w.) of midazolam and a median dose of 80mg propofol. Patients in group B (n=56, 22 over 65 years) received IV a median dose of 3mg midazolam and 75mg pethidine. The patient’s comfort level was assessed by a four point scale 24 hours after the procedure. The time to recover from sedation was assessed at 5, 10 and 30 min after the procedure by using the Aldrete score.

Results: Multivariate stepwise logistic regression analysis revealed that among sex, age, duration of the test, ASA grade and the sort of sedation, the synergistic sedation with midazolam and propofol was the only factor associated with a higher level of patient comfort (χ²=5.5, p<0.05) and a quicker patient recovery time (χ²=24.5, p<0.01, χ²=51.7 p<0.01 and χ²=148.4 p<0.01 for aldrete in 10, 20 and 30 min respectively). Endoscopist’s satisfaction, the recovery times and carboxygenerative parameters were similar in both groups across all age groups.

Conclusions: Our data suggest that the sedation with midazolam combined with propofol was superior to combination of midazolam and pethidine for colonoscopies as far as the patient comfort and recovery times are concerned.

143 SEDATION FOR COLONOSCOPY: A RANDOMISED, CONTROLLED TRIAL COMPARING PATIENT-CONTROLLED ADMINISTRATION OF PROPOFOL AND ALFENTANIL WITH PHYSICIAN-ADMINISTERED MIDAZOLAM AND PETHIDINE

C. Roseveare, L. Bright, D. Dalgleish, J. Kimble, H. Shepherd. Southampton General Hospital, Royal Hants County Hospital, Winchester, UK

Background: Our previous studies have indicated that Patient-Controlled Sedation (PCS) using propofol and alfentanil provided an effective alternative to a combination of diazepam and pethidine given as a bolus prior to the procedure, with the advantage of shorter recovery time.

Aims: To compare efficacy of sedation and recovery time between PCS and a bolus combination of midazolam and pethidine (M&P); to study further the safety of the technique and to determine the feasibility of PCS being setup and supervised by an endoscopy nurse and endoscopist.

Methods: 67 patients undergoing colonoscopy were randomised to receive sedation with either PCS using propofol and alfentanil or a bolus of midazolam (2.5-5mg) and pethidine (25-50mg). Infusions were connected by the endoscopy nurse with anaesthetist present in an observational capacity only. The anaesthetist only intervened if specific pre-defined criteria were reached. Sedation scores were recorded during the procedure by the endoscopy nurse and pain scores after the procedure by both nurse and patient, using likert scales. Recovery was confirmed using number connection tests. Impact on subsequent daily activity, amnesia and overall satisfaction were established by phone at 24 hours.

Results: Sedation method had no impact on the success, difficulty or duration of the colonoscopy procedure. PCS infusions could be set up by the infusing nurse without causing significant delay. Patients in the PCS group recovered significantly faster (mean 5mins vs 35mins, p<0.0001) and left the endoscopy department much sooner (40mins vs 75mins, p<0.0001). No differences in respiratory or haemodynamic observations were recorded between the two groups. Anaesthetist intervention was required for one patient sedated with M&P, but was not required for any patients sedated with PCS. Overall sedation level was lighter in the PCS group (score 3 vs 4, p<0.05) and verbal contact was lost with only 2 patients using PCS, compared to 9 using M&P. Patients in the PCS group reported significantly more pain (median pain score 1 vs 0, p=0.0005), which may have reflected PCS using M&P. Patients in the PCS group recovered significantly faster (mean 5mins vs 144 mins, p<0.0001 for aldrete in 10, 20 and 30 min respectively). Endoscopist’s satisfaction, the recovery times and cardiorespiratory parameters were similar in both groups across all age groups.

Conclusions: Our data suggest that the sedation with midazolam combined with propofol was superior to combination of midazolam and pethidine for colonoscopies as far as the patient comfort and recovery times are concerned.

144 SYNERGISTIC SEDATION WITH MIDAZOLAM AND PROPOFOL VERSUS MIDAZOLAM AND PETHIDINE IN COLONOSCOPIES: A PROSPECTIVE, RANDOMIZED STUDY

G.A. Paspatis, M. Manolakis, G. Xirochakis, N. Papannikolaou, I. Charoniti, A. Gritzali. Department of Gastroenterology and Anesthesiology, Benizelon General Hospital, Heraklion-Crete, Greece

Background and Aims: A recent study suggests the synergistic sedation with a low dose of midazolam combined with propofol for
THE EFFECT OF TEMPERATURE ON THE FLEXURAL RIGIDITY OF VARIOUS COMMERCIALLY AVAILABLE COLONOSCOPES AND GASTROSCOPES

S. Dogramadzi1, B. Burn2, R. Bicker3, G.D. Bell1. 1Department of Electrical and Electronic Engineering, Newcastle University; 2School of Computing, Engineering and Technology, University of Sunderland; 3Department of Mechanical Materials and Manufacturing Engineering, Newcastle University; 1Medical Sciences Faculty, Sunderland University

Introduction: The rather time consuming simple beam displacement method used to determine flexural rigidity (EI) along the length of an endoscope is reproducible and inexpensive (Gut 2001;49:154). To our knowledge all previous published results for the measurement of endoscope shaft stiffness have been performed at room temperature. We argued that measurements of shaft stiffness at body temperature might be equally important clinically (particularly during a prolonged procedure). We have developed an elegant computer-linked method of rapidly measuring EI such that the stiffness of the entire shaft of a typical 165 cm colonoscope can be determined in less than a minute.

Aims: To measure the EI along the shaft of a number of different commercially available endoscopes at both room temperature and again after 10 minutes immersion in a thermostatically controlled water bath at 40 degrees C.

Methods and Results: We measured EI in a range of different Olympus and Pentax colonoscopes and gastroscopes (=12) that were in use on our Endoscopy Unit. In all cases there was a highly significant (p<0.001) 10-40% reduction in EI at 40 °C compared with room temperature.

Conclusions: Endoscopists need to appreciate that once an endoscope is inserted into a patient it will rapidly become significantly flatter as the endoscope warms up to body temperature. These observations might be particularly relevant to the problems related to recurrent looping that may be observed during a prolonged colonoscopic procedure.

EFFECT OF MAGNETIC ENDOSCOPE IMAGING (MEI) ON ACQUISITION OF COLONOSCOPY SKILLS

S.G. Shah, M. Lockett, S. Thomas-Gibson, J.C. Brooker, M. Vance, C.J. Thapar, B.P. Saunders. Wolfson Unit, St Mark’s Hospital, Harrow, London, UK

Background: Most trainees have little concept of the loops that occur during colonoscopy and have difficulty in appreciating the combination of withdrawal and torqueing manoeuvres, essential to achieving complete colonoscopy. Real-time magnetic endoscope imaging (MEI) allows visualisation of shaft looping, and so makes intuitive the manoeuvres necessary to straighten the colonoscope shaft.

Method: Consecutive routine colonoscopies were performed by a single trainee. Procedures were randomised to be carried out either with the trainee viewing the MEI display, or without the MEI view.

Results: In total 72 procedures were performed. To assess the trend for learning, procedures were analysed in blocks of 24 consecutive examinations (periods 1 to 3). See table.

Conclusions: Real-time colonoscope imaging using MEI appears to enhance the endoscopist’s appreciation of looping, and the learning of manoeuvres to straighten the colonoscope shaft, during training.

ARGON PLASMA COAGULATION: AS EFFECTIVE AS “HOT-BIOPSY”? A RANDOMISED CONTROLLED STUDY

J.C. Brooker, S.G. Shah, M. Vance, A.D. Millar, H.J. Pearson, B.P. Saunders. St Mark’s Hospital, Harrow; North Middlesex Hospital, London; Diana Princess of Wales Hospital, Grimsby, UK

Background: The drawbacks of “hot-biopsy” include a small but important risk of complications and a 15–20% failure rate for adenoma eradication. Cold snare, an alternative technique, may fail to yield a specimen for histology. We hypothesised that simple biopsy followed by destruction with Argon Plasma Coagulation (APC) would be an effective and safe means for destroying small adenomas, whilst guaranteeing a histology specimen. This method was therefore compared with “hot-biopsy” in a randomised controlled trial.

Methods: Consecutive outpatient attending for flexible sigmoidoscopy were included if a suspected adenoma <5mm was detected. Subjects were randomly allocated to one of two groups, either conventional hot-biopsy or cold biopsy and APC. Standard diathermy settings were used (APC:65 Watts and 2L/min gas flow; hot-biopsy:15 Watts coagulating current). Hot-biopsy technique involved tenting the polyp and applying diathermy until visible mucosal whitening occurred at the base (the “Mount Fuji” effect). APC was applied to cauterise the entire polyp surface. A tattoo was placed adjacent to polypectomy sites using sterile India ink. Patients were contacted by telephone at 2 weeks to check for complications and those with confirmed adenomas were followed up with colonoscopy at 1–2 months. At colonoscopy the polypectomy sites were identified and biopsied to check for recurrence.

Results: From 505 examinations (237 male, median age 55[19–93]), 40 suitable adenomas (median size 4mm[2–5mm]; histology: 33 tubular, 7 tubulo-villous) were identified in 33 patients (19 males; median age 63[43–83]). 20 were treated with APC and 20 with “hot-biopsy”. There were no complications. At follow up colonoscopy, a median of 6.4 weeks later (range 3–11 weeks) there were two recurrent adenomas following “hot-biopsy”, but none after APC (p=0.49, Fisher’s exact test).

Conclusions: These results indicate that argon plasma coagulation is at least as effective as “hot-biopsy” for destroying diminutive colorectal adenomas. We propose the development of a single accessory which combines biopsy forceps and Argon Plasma Coagulation together. This could offer a safe and efficient alternative to traditional “hot-biopsy”.

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CLINICAL STUDIES OF WIRELESS CAPSULE COLONOSCOPY

M. Mylonaki, A. Fritsch-Ravens, S. Lewkowicz, P. Swain. Royal London Hospital, Whitechapel, London E1 1BB, UK

Background: Wireless capsule endoscopy has the potential to deliver valuable images of the colon. Slow transit, intermittent rapid movements, larger diameter lumen and capsule transmission times are challenges requiring study.

Aim: To assess colonic images received during experimental, human volunteer and clinical studies. To improve the capacity of wireless capsule technology to image the human colon.

Methods: Colonic views obtained during clinical studies of capsules with a 7.5 hr capsule were reviewed (n=38) human volunteers and patients referred with obscure gastrointestinal bleeding. Studies using experimental long-play with 4 silver-oxide batteries and a potential transmission time of 18 hours were used in 7. Lighter capsules (n=3)[SG = 1.2 vs 1.7], with 2 batteries and a 2 hour rest period moving with the fluid phase were tested. 2 capsules were placed retrogradely into the transverse colon using hydraulic delivery.

Results: In clinical studies performed without colonic preparation (n=38) interpretable images of the human colon were acquired in 35, mucosal detail was seen in 34, faecal material in 35, underillumination in 10. Technical improvements included shorter capsules (27mm, previously 33mm) now transmitting for 7–8 hours using two (previously three) batteries, and experimental capsules with an 12 hour life were tested and occasionally imaged the toilet. Clinical studies in n=13 patients revealed missed colon cancer/polyp (3), bleeding Meckel’s diverticulum (1), ulcerative colitis (2), angiodysplasia (2). Small intestinal transit times were median (4 hr), range (1.2–7.6hrs). Oro-anal transit times were 0.5–8 days. Capsules used in patients with incomplete colonoscopies provided useful clinical information. In patients selected for capsule colonoscopy management was altered in 50%.

Conclusion: Wireless capsule colonoscopy is feasible and has already delivered valuable information in clinical studies. Technical development and better preparation and control over colonic motility is required to extend the range and improve the images of the colon in patients. Capsule colonoscopy was a useful adjunct to conventional colonoscopy especially in patients with difficult recurrent bleeding or incomplete colonoscopy.

Biliary/pancreas free papers

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THE POTENTIAL ROLE OF GASTRIN IN Pancreatic Cancer Progression-RAISED SERUM AMIDATED GASTRIN AND PROGASTRIN LEVELS IN PATIENTS WITH ADVANCED Pancreatic Cancer

A.D. Gilliam, P.A. Clarke, B.J. Rowlands, I.J. Beckingham, S.A. Watson. Academic Unit of Cancer Studies, Academic Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

Aim: To assess the endocrine role of gastrin in pancreatic carcinoma progression.

Method: A prospective study was established in which patients with resectable (n=17) and advanced (n=68) pancreatic carcinoma had their serum assayed for amidated and progastrin. Hormone levels were compared to positive controls (patients undergoing liver resection for colonic metastases, n=24). Gastrin and CCK 2 receptor expression was measured in 17 resected pancreatic tumours and four pancreatic tumour cell lines by RT-PCR, using the SYBR green dye, and immunohistochemical staining or western blotting using antibodies directed against gastrin and CCK2.

Results: There was a significantly greater serum amidated gastrin and progastrin levels in patients with advanced pancreatic cancer when compared to patients with resectable disease (p=0.008* and 0.046*). Patients with advanced pancreatic cancer also had significantly greater amidated gastrin and progastrin levels than patients undergoing liver resection for colonic metastases (p=0.023*). There was, however, no significant difference in amidated gastrin levels in patients with resectable pancreatic carcinoma and patients with metastatic colonic carcinoma (p=0.09*). Gastrin and CCK 2 expression was confirmed at the gene level in 13 pancreatic adenocarcinomas by RTPCR, and immunocytochemistry in 17 pancreatic tumours.

Gasztin and CCK-2 expression was also demonstrated in all four pancreatic tumour cell lines at the gene and protein levels by RT-PCR and western blotting. (*Independent samples Test.)

Conclusion: This study confirms the autocrine, paracrine and endocrine role of gastrin in pancreatic carcinoma progression. Increased plasma levels of amidated gastrin may be a future biomarker for advanced pancreatic cancer. Anti-gastrin therapy may represent a novel therapeutic strategy for the management of pancreatic cancer.

GEMCITABINE DOES NOT INHIBIT THE BIOLOGICAL ACTIVITY OF A HUMAN Pancreatic TUMOR GROWING IN THE Pancreas OF Immunodeficient MICE

A.D. Gilliam, W.J. Speak, R.A. Dean, D. McWilliams, P.A. Clarke, T. Morris, S.A. Watson. Academic Unit of Cancer Studies, Academic Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

Introduction: Gemcitabine (Gemzar), a novel nucleoside analogue, exerts its action by inhibiting DNA synthesis. Gemcitabine is licensed as a first line treatment for patients with locally advanced or metastatic adenocarcinoma of the pancreas and as a second line treatment of patients with 5-FU refractory pancreatic cancer (NICE guidelines 2001). The aim of this study was to assess the effects of gemcitabine on matrix metalloproteinase (MMP), Epidermal Growth Factor Receptor (EGFR), gastrin, Cyclo-oxygenase2 (COX-2) and Cholecystokinin-2 (CCK2) receptor expression of a human pancreatic tumour growing in the pancreas of immunodeficient mice.

Method: The human pancreatic cell line, PAN1, cells were injected into the pancreas in immunodeficient mice (1x10^3 in a 20µl volume). Mice were treated with saline or gemcitabine infusions.

The tumours were examined for MMP 2 and 9, EGFR, COX-2, gastrin and CCK2 receptor expression by real time PCR at the gene level, binding of the SYBR green dye, and by western blotting and zymography at the protein level.

Results: The gemcitabine treated mice had a 40% reduction in their tumour weights (p=0.045*) however there was no significant alteration in MMP gene or protein expression (p=0.1*), EGFR (p=0.48*), gastrin (p=0.15*), COX2 (p=0.33*) and CCK2 receptor (p=0.20*) gene expression. (*Independent samples Test.)

Conclusion: Gemcitabine does not affect the expression of several molecular biological targets suggesting an important potential role for novel biological therapies for use in conjunction with new chemotherapeutic agents in patients with pancreatic cancer.

MANAGEMENT OF ACUTE Pancreatitis IN Wales: HOW GOOD ARE WE?

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Aims: To review the existing practices of Welsh Surgical Consultants in managing acute pancreatitis and compare it with published UK guidelines.

Methods: We designed a questionnaire based on the national guidelines regarding the assessment, indications for intensive management, timing of elective cholecystectomy, ERCP and surgical intervention. This questionnaire was mailed to all the consultants in Wales and the replies were analyzed.

Results: 50 consultants responded. 33 units assess patients with a scoring system and almost all do routine blood gas analysis and liver function tests on admission, but only 29(60%) perform C-Reactive protein to assess prognosis. 10 units managed this problem with a multidisciplinary team approach. 17 of these units did not have access to HDU facilities. CT scan was used by a majority of these units as required by guidelines. Antibiotics were prescribed by most units in severe cases while surprisingly 10(20%) of these units prescribed antibiotics routinely without specific indications even in mild cases. Only one in three of these units routinely performed cholecystectomy within four weeks of an acute attack as recommended. ERCP and percutaneous cholangiograms were not used in accordance with the guidelines.

Conclusion: Consultants in Wales do feel a specialist, multidisciplinary approach is necessary but practical difficulties prevent implementation of the guidelines. However, it is a matter of some concern that despite national guidelines, there is a varied approach across Wales.
PREDICTION OF SEVERITY IN ACUTE PANCREATITIS: A COMPARATIVE STUDY OF RANSON’S SCORE AND 24 AND 48 HOURS APACHE II AND III SCORING SYSTEMS

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Background/Aims: We assessed the prognostic accuracy of Ranson’s, APACHE II, and APACHE III scores in predicting acute pancreatitis (AP) severity in non-intensive care unit (ICU) patients. APACHE III has not been previously evaluated outside ICU settings.
Method: 126 patients with AP (56% gallstone and 9% alcoholic related, 7% secondary, 28% idiopathic) were studied prospectively. Data conforming to scoring systems were recorded 24 (APACHE II and III) and 48 hr (Ranson, APACHE II and III) after admission. Analysis was performed by using Hest, Pearson correlation, receiver operating characteristic (ROC) curves and area under a ROC curve (AUC).

Results: On discharge, 117 patients (76.9%) were classified as mild and 35 (23%) as severe. There were 4 deaths (2.6%). The mean Ranson’s score and the mean 24 and 48 hr APACHE II and III scores of patients with severe AP were each significantly higher than those of patients with uncomplicated outcomes. All five scores correlated strongly with length of stay. When ROC curves were plotted, AUC for Ranson’s score (0.799; cutoff 3; sensitivity, 72%; specificity, 79%; correct, 52%) was found to be larger than AUC for 24 hr APACHE II (0.644; cutoff 8; sensitivity, 53%; specificity, 62%; correct, 55%), 24 hr APACHE III (0.654; cutoff 32; sensitivity, 60%; specificity, 58%; correct, 60%), 48 hr APACHE II (0.649; cutoff 8; sensitivity, 53%; specificity, 69%; correct, 57%), and 48 hr APACHE III (0.652; cutoff 27; sensitivity, 52%; specificity, 72%, correct, 52%). The difference between 24 and 48 hr APACHE II and III scores AUC did not reach statistical significance.

Conclusion: Ranson’s score is superior to APACHE II and III in predicting acute pancreatitis severity. APACHE III score is no superior to APACHE II, and sequential 24 and 48 hr recording offers no advantage over 24 hr recording.

ACUTE AND CHRONIC PANCREATITIS: DISEASES ON THE INCREASE

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Aim: To investigate time trends for the numbers of hospital admissions for acute and chronic pancreatitis in England from 1989/90 to 1999/00.
Method: Data were obtained from the Hospital Episodes Statistics (HES) service from 1989/90 to 1999/00 based on ‘Finished Consultant Episodes’, excluding day cases, in England. Hospital admissions for acute and chronic pancreatitis in England from 1989/90 to 1999/00 were studied prospectively.

Results: Over the 11-year study period, admission rates for acute pancreatitis increased progressively with age whereas those for chronic pancreatitis peaked at 35–54 years of age. For both sexes, the proportions of admissions requiring surgical operations increased for acute pancreatitis but decreased for chronic pancreatitis. There was a gradual decline among both sexes in case fatality rates for acute pancreatitis.

Conclusions: There has been a steady increase in admission rates for both acute and chronic pancreatitis. The rate of increase was greater among females for acute pancreatitis, but greater among males for chronic pancreatitis. These trends are likely to reflect genuine changes in disease epidemiology rather than alterations in diagnostic and management practice. The proportions requiring operations have increased for acute pancreatitis but decreased for chronic pancreatitis.

HEREDITARY PANCREATITIS (HP) AND THE RISK OF PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)


Introduction: HP has an early age of symptom onset and is associated with a high incidence of complications, of particular importance is the reported high life time risk of PDAC. The European Consortium of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) was established in 1997 to investigate HP in Europe.

Aims: To establish the risk of PDAC in HP patients in Europe.
Method: Recruitment started in 1997, HP was diagnosed on the basis of two family members with chronic pancreatitis of unknown aetiology. PRSS1 mutation screening was undertaken for the published mutations, with sequencing in negative families. The Standardised Incidence Ratio (SIR) which is the ratio of observed PDAC to expected PDAC was calculated for histologically confirmed PDAC in families with at least three generations of HP adjusted for age, sex, nationality and surgical intervention. The cumulative lifetime incidence was calculated, and a multivariate analysis undertaken for potential confounding factors.

Results: 109 families (n=342) were recruited, 47 families (n=197; 97%) were suitable for PDAC analysis. 15 patients (BM, 7F) developed PDAC during 7648 person-years. Mean age of cancer diagnosis was 56(48–69) yrs. Expected number of cancers was 0.21 yielding an overall SIR of 7.13(53–88). The SIR in males was 7.2(49–94) and in females was 7.0(47–93). The overall lifetime risk for the development of PDAC in our cohort of patients with HP was 40% [95%CI]; (30–50%). The risk appeared to be minimal below the age of 40yrs, where after it increased sharply. Multivariate analysis showed that the risk of PDAC appeared to be independent of potential confounding variables.

Conclusion: PDAC is a real and significant independent complication of Hereditary Pancreatitis.

AUDIT OF SECHAT TESTS: WHO TO TARGET?

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Introduction and Aims: Selenium cholic acid tauroate (SeCHAT) tests are accurate in the diagnosis of bile acid malabsorption (BAM). We have audited the use of SeCHAT tests in a teaching hospital to assess if their use was appropriate, influenced patient management and to determine the prevalence of primary bile acid malabsorption (PBAM).

Method: Patients undergoing SeCHAT tests from 1994–2001 were identified and the case notes examined for the SeCHAT result (<10% being a positive test), indication, known terminal ileal pathology, previous investigations and influence on patient management.

Results: 120 patients were identified undergoing SeCHAT tests of which 51 were positive, 48 negative and 21 indeterminate (mean retention of 77% at 7 days 3.75%, 33.8% and 12.4%, respectively). The indication in all cases was diarrhoea. Of the 51 positive tests; 21 had previous surgery (16 terminal ileal [TI] resections, cholecystectomy); 21 had known TI Crohn’s disease; one had received radiotherapy involving the TI; and 2 had documented prior enteric infection. Of the negative and indeterminate tests, 4 patients had previous enteric infection, one had coeliac disease but none had known TI Crohn’s disease, previous surgery or other known predisposing factors for BAM. Prior to a positive SeCHAT test, most (90%) had

Abstract 154

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imaging of the TI compared to only 40% of those with negative tests. Of those with positive tests, 47% had a short term (3 month) response to bile acid sequestrants (BAS), but this was only sustained at 6 months in 20% of patients, the remainder being intolerant of BAS. 6 patients therefore had a diagnosis of PBAM. After 3 years of follow up, one was diagnosed with Zollinger Ellison syndrome and another with carnitine syndrome, leaving only 4 patients with PBAM (3 male, 1 female). The incidence of PBAM was therefore 6% in our group of patients with diarrhoea.

**Conclusions:** Patients presenting with diarrhoea known to have TI disease or dysfunction have a high probability of a positive SeCHAT test and therefore, can be assumed to have BAM as a contributor to their symptoms and do not require formal testing. The frequency of PBAM in our audit was 6% and BAM should be considered in these patients with a diagnosis of diarrhoea predominant irritable bowel syndrome.

**157 IS HORMONE REPLACEMENT THERAPY ASSOCIATED WITH GALLSTONE FORMATION? A PROSPECTIVE COHORT STUDY**

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**Background:** The aetiology of gallstones is unknown. High oestrogen levels whether endogenous or through a hormone replacement therapy (hrt), have been implicated. Oestrogens increase the cholesterol saturation of the bile which may precipitate stone formation. The few epidemiological studies investigating this association have given conflicting results and clarification is needed. The aim of this study was to investigate if an association existed in a prospective cohort investigation.

**Methods:** A total of 13 433 women aged 45–79 years were recruited into EPIC-Norfolk (European Prospective Investigation Into Cancer). Participants supplied information at recruitment on use of hormone replacement therapy and were followed up for the development of symptomatic gallstones. Each case was matched with four controls for age and gender.

**Results:** Fifty-eight women developed symptomatic gallstones at a median age of 64.6 years (range 43.8–79.3 yrs) after a median follow-up of 3.2 years (range 1.5–6.8 years). Use of hrt was associated with a relative risk of 2.6 (95% CI=1.4–5.0) for symptomatic gallstones. The risk increased slightly after adjusting for factors associated with stone formation, namely alcohol, parity and BMI (RR= 3.0, 95% CI =1.5–5.8). There was no association with duration of hrt use: women taking hrt for two or more years had a similar risk to those taking it for less than 2 years (RR= 3.4, 95% CI=1.5–7.6 vs RR=3.1, 95% CI=1.1–8.6).

**Conclusions:** Use of hormone replacement therapy is a risk factor for gallstone formation. Whether this is an oestrogenal relationship remains to be established, but the findings raise intriguing questions about the role of oestrogen in gallstone formation.

**158 INCIDENCE OF EMERGENCY ADMISSION WITH GALLSTONE RELATED PROBLEMS IN PATIENTS AWAITING CHOLECYSTECTOMY AND ITS COST IMPLICATIONS**

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**Introduction:** Many patients awaiting cholecystectomy are admitted as an emergency with recurrent gallstone related problems. In addition to the morbidity, significant costs are involved in treating these patients.

**Aims:** To study the incidence of emergency admission due to gallstone related problems among patients awaiting cholecystectomy, and to assess the costs of treating these patients.

**Methods:** A retrospective analysis was performed of all the patients who underwent elective cholecystectomy by 3 consultants in a district general hospital between 1999–2000. Data was collected on demographics, the specific indication for including the patient in the waiting list, the waiting time, details of emergency admissions during their waiting period and the investigations and treatment given during these episodes.

**Results:** A total number of 156 patients underwent elective cholecystectomy of which 122 were females and 34 were males. The mean duration of the waiting time for cholecystectomy was 1 year. The mean age of the patients was 54 years (range 19–82 years). Of the 156 patients, 37 patients (24%) were admitted as an emergency with gallstone related symptoms while awaiting surgery. Twenty eight patients were admitted once, 8 patients were admitted twice and 1 patient was admitted three times. Of the 47 episodes of admissions, 32 were for biliary colic, 13 were for acute cholecystitis and 2 were for acute pancreatitis. The average duration of each episode was 3 days. The cost of each episode was £ 946 and the total cost was calculated to be £44,462.

**Conclusions:** Emergency admission with gallstone related problems is common among patients awaiting cholecystectomy. By recognizing the patients prone to recurrent gallstone related problems, it is possible to offer them early surgery, thereby reducing patient morbidity and hospital costs.

**159 PLACEMENT OF BILATERAL SELF-EXPANDING METAL STENTS FOR COMPLEX HILAR OBSTRUCTION DUE TO CHOLANGIOCARCINOMA**

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**Background:** In cholangiocarcinoma, complete decompression of obstructed biliary systems is desirable to relieve symptoms, avoid secondary cholangitis and facilitate palliative chemotherapy regimes. Occlusion and migration of plastic stents limit their use. Although self-expanding metal stents (SEMS) reduce these problems, their unilateral placement for complex hilar strictures often fails to achieve adequate drainage. We report our experience of bilateral placement of SEMS for complex hilar strictures.

**Methods:** During a 32/12 period, 13 patients median age 67 years (range 50–88 years), underwent therapeutic ERCP for obstructive jaundice. All patients were found to have a cholangiocarcinoma (Bismuth stage II or higher). In these patients, following 5–10mm papillotomy, left and right intra-hepatic biliary systems were accessed with separate 035 hydrophilic guidewires. Following brushing for cytology, both strictures were balloon dilated to 6mm. SEMS (Wallstent; Boston Scientific) were deployed into both intra-hepatic systems, the most ‘angulated’, usually the left, first. In the event of failure to stent both sides at ERCP, the procedure was completed as a combined ERCP/PTC or PTC.

**Results:** In 8/13, SEMS were deployed into both left and right ducts at the time of the initial ERCP. In 6/13, after placement of the first SEM at ERCP, the second SEM was deployed during either a combined ERCP/PTC (3) or PTC (3). Double stent placement at the initial ERCP failed for several reasons: hyperacute ‘angulation’ within the stricture (4); friction between second and in situ SEM within mid CBD (1); loss of wire access to the obstructed system (1). No procedure related complications occurred in the 11 patients double stented at ERCP. In all patients good drainage was achieved (resolution of jaundice and symptoms, with no secondary cholangitis). Two patients required further ERCP and stenting for tumour ingrowth (2 months, 6 months).

**Conclusions:** Bilateral SEM placement provides good, cost-effective palliation for many patients with complex hilar malignant strictures. Modifications to the stent/delivery system design to facilitate placement across strictures with hyperacute ‘angulation’ may improve success rates.
Further experience with spiral CT

Introduction: Because of the recognised complications associated with ERCP, it is valuable to diagnose cholecdocholithiasis by non-interventional techniques. Ultrasound (US) has limited use in patients with small bile duct stones or when the common bile duct (CBD) calibre is normal. We report our experience using spiral CT cholangiography (sCTC), which has been shown to be sensitive for the detection of bile duct filling defects, in a group of patients post cholecystectomy with biliary type pain referred for ERCP.

Methods: 59 patients (43 female, 16 male, age range 24-83 years), who had had a cholecystectomy up to 20 years prior to referral, were evaluated. Details of referral, investigation and treatment were obtained by patient interview and cross-referenced with the case notes.

Results: Of 23 patients with abnormal LFTs, 16 pts on US had a CBD >/= 6mm; only one pt had a stone (10mm in size) on US. Of these patients with a "distended" CBD 6 pts had stones seen on sCTC. 2 pts had failed sCTC. 1 pt had a mild allergic reaction to i.v. biloscipin. At sCTC 15 pts had a CBD >/= 6mm and stones were detected in 13. 2 pts with normal cbd were shown to have stones at sCTC. 4 pts with normal LFTs had abnormalities detected on sCTC, 3 stones and 1 ampullary tumour. Of the 17 pts selected for ERCP in only 1 pt were sCTC findings (3 small diameter stones) not confirmed, at ERCP, though 3 months later. Stones not detected by US measured 2-3mm slices were taken every 1mm at a pitch of 1.2mm/rotation. Biloscipin was used as the contrast medium.

Conclusion: sCTC is more sensitive in detecting CBD stones than US. It should be considered in pts with biliary symptoms, where US has failed to confirm biliary pathology. This practice should reduce referral for diagnostic ERCP.

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162 EXPERIENCE OF 5-ASA NEPHROTOXICITY IN THE UNITED KINGDOM

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Nephrotoxicity is an unusual complication of 5 amino-salicylic acid (5-ASA) therapy in inflammatory bowel disease. The literature documenting its frequency, severity & recovery is limited. This study assessed the retrospective experience of all 1298 names on the British Society of Gastroenterology (BSG) register and 237 Consultant members of the Renal Association (RA).

Each was sent a detailed questionnaire asking for patient demographic details, frequency with which renal function was assessed, time to development of renal impairment, drug(s) thought to be responsible, renal function at diagnosis and recovery, renal biopsy histology & any other information.

Results: See table. 72 BSG respondents measured renal function less than once per year; 27 never measured it. Responsible agents for nephrotoxicity were: [BSG (RA)] Asacol 132(29), Colazide 1(1), <1000ug/ml; 27(6) over 1000ug/ml. Renal dysfunction occurred in 265 pts; 161 (39%) avoided. Over the eight-month period this implies ERCP usage was reduced by the use of MRCP from a possible 265 to 161 (by 39%). (4) MRCP reduced the demand for ERCP and its complications by approx 40%. (4) MRCP should be readily available in all large hospitals.

163 THE IMPACT OF NEW REFERRAL GUIDELINES ON DELAYS IN THE DIAGNOSIS OF OESOPHAGO-GASTRIC CANCER

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Background: Early diagnosis is vital to improve the outcome for patients with oesophago-gastric cancer. The aim of this study was to determine the impact of government referral guidelines on delays in the diagnosis and treatment of these cancers.

Methods: 122 patients (median age 68 (range 48-84), male to female ratio 2:1) with oesophago-gastric cancer initially referred by a general practitioner and treated within this unit from 01/08/99 to 30/09/01 were evaluated. Details of referral, investigation and treatment were obtained by patient interview and cross-referenced with the case notes.

Results: 71 patients (58%) were referred before and 51 patients (42%) after the introduction of referral guidelines. The overall median delay from the onset of symptoms to definitive treatment was 22.0
(IQR 13.0–32.2) weeks comprising patient delay in consulting a doctor (48%), delay in referral (24%), delay in diagnosis (14%), and delay in commencing treatment (14%). After the introduction of guidelines there was a significant decrease in the time from referral to endoscopy, from a median of 2.5 (IQR 2.0–5.5) to 2.0 (IQR 1.0–3.0) weeks (p=0.012). Endoscopy was carried out within 2 weeks of referral in 71% (36/51) of patients compared to only 44% (31/71) before the guidelines (p=0.06). There was a decrease in the number of patients waiting over 6 weeks for endoscopy from 23% (16/71) to 8% (4/51) (p=0.03). No significant reduction in total delay (median 24.0 (IQR 14.0–32.0) vs. 18.0 (IQR 12.0–33.0) weeks, p=0.107) or patients waiting over 6 weeks for endoscopy from 23% (16/71) to 8% (4/51) was seen in the change in the stage of disease at diagnosis identified following the introduction of the guidelines.

**Conclusion:** The introduction of guidelines has resulted in a significant decrease in the time from referral to endoscopy for patients with oesophago-gastric cancer. As the major delay occurs prior to referral this has not translated into a significant reduction in overall delay. To achieve this patient awareness must also be targeted.

**REDUCED PALLIDAL MAGNETISATION TRANSFER RATIOS ARE ASSOCIATED WITH FATIGUE IN PRE-CIRRHOTIC PATIENTS WITH PRIMARY BILIARY CIRRHOSIS**

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Fatigue is the commonest symptom in primary biliary cirrhosis (PBC), affecting individuals at all stages of the disease. We examine the hypothesis that a CNS abnormality related to cholestasis, rather than cirrhosis per se, underlies this symptom. Globus pallidus (PAL) hyper-intensity on T-weighted MRI has been reported in biliary atresia, cirrhosis, parenteral nutrition induced cholestasis and in manganese workers.

**Methods:** 18 women with PBC (I stage III [mean bilirubin 11], 4 stage III-IV [32]) and 8 age-matched healthy women underwent cerebral MRI and proton spectroscopy (1H MRS). Magnetisation transfer ratios (MTR) for white matter (WM) and 4 subcortical structures were calculated and 1H MR spectra (TE 135ms) were obtained from 8cm voxels in the basal ganglia (BG) and frontal WM. The patients completed the Fisk Fatigue Severity Score (FSSS) and a battery of neuropsychological tests.

**Results:** There were no differences between the stage III patients and controls in the WM or subcortical MTRs or in the 1H MRS. However, the PAL/WM MTR ratio was significantly reduced in the stage III PBC patients (p=0.02), with no similar changes in the thalamus, putamen or caudate. The 4 stage III-IV patients also had reduced PAL/WM ratios, although they were not statistically different from the stage III patients. When the pre-cirrhotic patients were divided into 2 equal groups on the basis of the FSSS score, the fatigued patients had a significantly lower PAL/WM than the non-fatigued patients (p=0.05). There was no similar relationship between cognitive performance and PAL/WM.

**Conclusion:** We demonstrate a highly localised abnormality in the PAL in pre-cirrhotic PBC patients, which was more pronounced in the fatigued patients. It is unlikely to be due to hepatic encephalopathy as these non-cirrhotic patients had normal MRS. We postulate that a failure of biliary excretion results in the accumulation of heavy metals in the PAL, which underlies the reported fatigue.

**ENDOSCOPIC THERAPY FOR BLEEDING PEPTIC ULCER; A RANDOMISED, CONTROLLED TRIAL COMPARING HEATER PROBE PLUS HUMAN THROMBIN INJECTION WITH HEATER PROBE PLUS PLACEBO INJECTION**

N.I. Church1, H.J. Dallal1, J. Masson3, A. Fraser2, N.A.G. Mowat1, D.A. Johnston1, G. Fullarton1, E. Radin1, M. Turner1, R. Prescott2, J. Plevris1, K.R. Palmer1, 1Western General Hospital, Edinburgh; 2Aberdeen Royal Infirmary; 3Ninewells Hospital, Dundee; 2Garvan General Hospital, Glasgow; Scottish National Blood Transfusion Service; University of Edinburgh Medical School; Royal Infirmary, Edinburgh, UK

Introduction: Ulcer haemostasis is attempted in many centres using a combination of injection and thermal application, but there is little evidence that combination therapy is better than use of a single agent. Furthermore previous studies of endoscopic therapy have not included a placebo arm. In this large multicentre, double blind, randomised, placebo controlled trial we examined the hypothesis that combined haemostatic treatment using the heater probe plus best injection (using thrombin) is superior to the heater probe plus placebo injection.

**Methods:** 247 patients presenting with major peptic ulcer bleeding were randomised to heater probe plus thrombin (group 1) or heater probe plus placebo (group 2). The two groups were well matched for all risk categories including age, endoscopic stigmata, shock and severity of comorbid diseases. Endoscopic therapy was applied using 150 joules on average of the heater probe followed by injection of 3.5ml of thrombin or placebo.

**Results:** Successful primary haemostasis was achieved in 97% of both groups. Rebleeding developed in 19 (15%) of group 1 patients and 17 (15%) of group 2 patients; surgery was necessary in 16 and 13 of these respectively. Median blood transfusion (3; range 0–32 versus 2; 0–35 units) and median duration of hospital admission (5; 2–82 versus 5; 1–120 days) were similar in both groups. Adverse events occurred in 8 group 1 patients and 4 group 2 patients. Mortality at 30 days was 8 (6%) of group 1 patients versus 14 (12%) of group 2 patients.

**Conclusion:** Combination of thrombin or placebo injection with the heater probe is a safe and effective haemostatic therapy for bleeding peptic ulcer. The combination of thrombin with the heater probe does not confer an additional benefit over heater probe and placebo, and thrombin injection can not be recommended in preference to any other injection as adjunctive endoscopic therapy for bleeding peptic ulcer in patients receiving heater probe therapy.

**ERADICATION OF H. PYLORI UNLEASHES POST PPI ACID HYPERSECRETION**

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Introduction: There is marked rebound acid hypersecretion after eradication of H.pylori -ve but not +ve subjects. Oxynic gastritis probably prevents it in the latter.

**Aim:** To determine the effect of H.pylori eradication on rebound acid hypersecretion after omeprazole.

**Methods:** 17 healthy H.pylori +ve subjects had acid secretion studies prior to commencing omeprazole 40mg/day for 8 weeks. During the last week of omeprazole, they were randomised to a 1 week course of amoxicillin/clarithromycin or placebo. Further acid secretion studies were performed at 1,2,4,6&8 weeks after treatment. A further breath test was performed at weeks 17 to determine H.pylori status after treatment.

**Results:** Marked rebound hypersecretion to physiological levels of gastrin was observed in the subjects who had their infection eradicated but not in those with persisting infection (table). A similar trend was seen with respect to supraphysiological gastrin stimulation.
TREATMENT OF CROHN’S DISEASE WITH INFliximAB

**Introduction:** Infliximab is a new treatment for refractory and fistulat- ing Crohn’s disease (CD). Clinical trials and audit data have proven efficacy on disease activity and health related quality of life although there is little data regarding cost effectiveness. Prior to the introduction of novel biological treatments hospitalisation and surgery were the major costs in CD treatment but the expense of Infliximab may change this.

**Aim:** We assessed whether Infliximab reduced hospitalisation or frequency of outpatient clinic review within 6 months of infusion.

**Methods:** We analysed 30 well-characterised CD patients who had received a single infusion of Infliximab (5mg/kg) for refractory active CD. Clinical details and initial response rates have been published. Patients were followed prospectively and out patient visits, number of hospital admissions and total number of inpatient days were collected for the 6 months prior to and following Infliximab. Data was also compiled from the hospital electronic record of all patient episodes. Only patients that were cared for exclusively at our institution were included.

**Results:** Data for the 30 patients is displayed in the table. There are no significant differences in hospital attendance or admission rates. There remains no difference in the clinic visits and admission days pre and post Infliximab if patients are stratified as to whether they had a response or not and if they are on immunosuppressive or not.

**Conclusions:** In the present study, Infliximab dose not reduce clinic visits or hospitalisation within 6 months of infusion. Although reductions may be seen with multi-dose regimes dramatic reductions in hospitalisation costs are unlikely due to Infliximab being a single dose regimen.

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**168** TREATMENT OF CROHN’S DISEASE WITH INFliximAB DOES NOT REDUCE HOSPITAL ATTENDANCE OR ADMISSION

I.D.R. Arnott, S. Ghosh. Gastrointestinal Unit, University Department of Medical Sciences, Western General Hospital, Edinburgh, UK

**Introduction:** Infliximab remains a highly effective drug for active CD but it is likely that hospital episodes are not to be expected with a single dose alone. Infliximab is administered usually as an intrave- nous or hospitalisation within 6 months of infusion. Although there were no differences between the groups in the frequency of R/G241. The control frequency of ICAM1 exon 6 K469 was 38.2%. In CD overall, it was 76.9% (p<0.001). For CD patients with ileal disease, the frequency was 10.9% and 43.3% for non-ileal colonic disease. For patients with fistulising disease, the K469 frequency was 69.2%, and 84.3% for non-fistulising disease. For patients with stenosing disease, the K469 frequency was 77.4%. For UC overall, the frequency of ICAM1 exon 6 K469 was 69.7% (p<0.001). For patients with severe disease requiring colectomy, with mild total colitis, and with proctitis, the frequencies of this polymorphism were 66.22 %, 75% and 81.1% respectively. This study suggests that the alteration in the amino acid sequences of K469 to K469 of the ICAM1 molecule may influence IBD.

**Abstract 168**

<table>
<thead>
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<th>Before Infliximab</th>
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<td>Number admitted</td>
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<tr>
<td>Total admission days</td>
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**Conclusions:** In the present study, Infliximab dose not reduce clinic visits or hospitalisation within 6 months of infusion. Although reductions may be seen with multi-dose regimes dramatic reductions in hospitalisation costs are unlikely due to Infliximab being a single dose regimen. Infliximab remains a highly effective drug for active CD but it is likely that this will have implications when drug funding is allocated.

**169** THE INTERCELLULAR ADHESION MOLECULE-1 POLYMORPHISMS IN IBD


Ulcerative colitis (UC) and Crohn’s disease (CD), both forms of inflammatory bowel disease (IBD), are complex traits. Intercellular adhesion molecule-1 (ICAM1) is expressed on vascular endothelium and plays a key role in the transendothelial migration of neutrophils and T-cell activation. The region harboring the ICAM1 gene on 19p13 is linked to CD in a Canadian genome wide scan, and a growing body of evidence indicates that ICAM1 could play a role in IBD development. Our previous work has replicated the Canadian linkage of 19p13 to CD. ICAM1 is known to contain at least two polymorphic sites, situated in codons 241 (R/G241) and 469 (K/E469). A North American study has shown an association between IBD and the R241 polymorphism (Yang et al 1995). We have examined potential associations of ICAM1 polymorphisms in 132 UC and 67 CD and ethnically matched 131 controls. CD patients include subgroups of 26 ileal disease and 31 ileo colonic disease, 26 fistulising disease and 35 non-fistulising disease, 53 stenosing disease and 8 non-stenosing disease. UC patients include 37 patients who have undergone colectomy, 22 with mild total colitis, and 37 with proctitis. Both patients and controls were genotyped by PCR-SSP for ICAM1 polymorphisms at codon R/G241 and codon K/E469. There were no differences between the groups in the frequency of R/G241. The control frequency of ICAM1 exon 6 K469 was 38.2%. In CD overall, it was 76.9% (p<0.001). For CD patients with ileal disease, the frequency was 10.9% and 43.3% for non-ileal colonic disease. For patients with fistulising disease, the K469 frequency was 69.2%, and 84.3% for non-fistulising disease. For patients with stenosing disease, the K469 frequency was 77.4%. For UC overall, the frequency of ICAM1 exon 6 K469 was 69.7% (p<0.001). For patients with severe disease requiring colectomy, with mild total colitis, and with proctitis, the frequencies of this polymorphism were 66.22 %, 75% and 81.1% respectively. This study suggests that the alteration in the amino acid sequences of K469 to K469 of the ICAM1 molecule may influence IBD.

**170** RECURRENT ORAL ULCERATION (ROU) IN INFLAMMATORY BOWEL DISEASE (IBD): THE CLINICAL HALLMARK OF A MOLECULARLY DEFINED IBD/BEHCET’S (BD) OVERLAP GROUP

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**Background:** The clinical, endoscopic and histological features of intestinal BD are similar to those of IBD. BD is rare in Northern Europe where IBD is common, whilst the prevalence is high on the ‘Silk route’ where IBD is rarely reported. This inverse relationship may reflect geographical differences in diagnostic practice. Diagnosis of BD, requires the presence of ROU. We have reported that Caucasian BD is associated with HLA-B*51 and B*57. We hypothesise that these markers might also be associated with ROU in IBD and therefore molecularly define an overlap group.

**Aims:** To determine the prevalence and genetic associations of ROU in patients with IBD.

**Methods:** History of ROU reported in questionnaires sent to 244 CD and 330 UC patients. Linkage disequilibrium mapping was carried out across 340 polymorphisms, broken down into 24 discrete gene haplotype blocks. Genetic comparisons were made between IBD and healthy controls.

**Results:** 33.2% of UC and 38.9% of CD patients reported ROU (historical prevalence in general population 10%). In UC patients with ROU, associations with alleles on two extended HLA haplotypes were observed. Peak relative risk (RR) was at DRB1*1003 on the second (12.1% ROU+ vs 3.8% ROU; P=0.003; RR=5.0) and B*57 on the second (12.1% ROU+ vs 3.8% ROU; P=0.009; RR=3.5). In CD patients with ROU a negative association was observed with B*51 (3.4% ROU+ vs 13.8% ROU; P=0.01) However 11 CD patients who carried B*51 or B*57 reported ROU. 8 of these fulfilled the diagnostic criteria for BD.

**Conclusions:** 1. Prevalence of ROU in IBD is 3x greater than in the background population. 2. ROU in UC patients is associated with B*57, a BD susceptibility allele. 3. 8/11 CD patients with ROU who possess B*51 or B*57 fulfill the criteria for diagnosis of BD. 4. In our IBD clinic 5% of patients clinically and molecularly resemble BD.

**171** LYMPhocyte TELOMerase EXPRESSION IN INFLAMMATORY BOWEL DISEASE


Background: Telomerase knockout mice develop ulceration and atrophy of the bowel. In humans colonic telomerase activity is decreased in ulcerative colitis but it is unknown whether this is restricted to the colon. The object of this study was to assess lymphocyte telomerase enzyme activity in patients with inflammatory bowel disease and to determine the role of the mRNA that encodes its catalytic sub-unit (hTERT) in the regulation of enzyme activity.

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Methods: Blood was sampled from 47 patients with ulcerative colitis (UC), 37 with Crohn’s disease (CD) and 37 controls. Lymphocytes were cultured for 72 hours with phytohaemagglutinin. Telomerase activity was measured in stimulated and unstimulated lymphocytes using the Telomerase Repeat Amplification Protocol (TRAP) assay. Lymphocyte telomerase hTERT mRNA was quantified in about 40% of samples (18 UC, 14 CD and 14 controls) by realtime PCR.

Results: Expressed as median (95 CI) in arbitrary units (stimulated lymphocytes only). Telomerase enzyme activity in controls was 5.96 (3.3 – 9.2) and was decreased significantly in UC 3.1 (3.1 – 4.1) p < 0.05) and non-significantly in CD 2.27 (1.2 – 6). There was no difference in hTERT mRNA concentration between the three groups. Telomerase activity and hTERT mRNA were generally undetectable in unstimulated lymphocytes.

Conclusion: Lymphocyte telomerase activity is decreased in unstimulated lymphocytes. This suggests that previously reported colonic telomerase deficiency in UC extends to non-colonic tissue and could represent a global defect. Factors other than hTERT mRNA expression may contribute to the regulation of telomerase activity in stimulated lymphocytes.

A COMPREHENSIVE INVESTIGATION OF D-LOOP MUTATIONS IN THE MITOCHONDRIAL DNA OF COLORECTAL TUMOURS

S. Fradley, P.D. Lewis, P. Griffiths, J.M. Parry [introduced by J. Baxter]. Human Molecular Pathology Group, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK

The human mitochondrial genome (mtDNA) contains a short hypervariable, non-coding control region known as the D-Loop. A number of recent investigations have revealed that a proportion of colorectal adenocarcinomas harbour mtDNA mutations, not present in normal surrounding mucosa and are classified as tumour-specific. Tumour specific mtDNA mutations have also been observed in many other tumours including lung and bladder and it has been suggested that these mutations may serve as diagnostic markers for cancer. The D-Loop, used commonly in population studies and the most mutable region within mtDNA, may be rapidly and cost-effectively scanned for mutations. Previous studies involving the search for tumour-specific mtDNA mutations in colorectal cancer have relied on small sample sizes or have failed to reveal mutations within the D-Loop. Using PCR-SSCP and DNA sequencing we have undertaken a comprehensive survey of the D-Loop in adenocarcinoma and normal mucosa of twenty patients. (i) To demonstrate the usefulness of the D-Loop in providing tumour-specific markers for colorectal cancer, (ii) reveal the types and distribution of mutations within the D-Loop in colorectal tumours, (iii) estimate the frequency of mutation within this region in adenocarcinomas, (iv) establish the levels of heteroplasmy in colorectal tumours. Of the twenty colorectal adenocarcinomas, 25% showed tumour specific mutations which were not normal in the normal mucosa. Sequencing revealed the mutations to be a 1-bp C→G deletion and a 1-bp C→G insertion at nucleotide position 309, two C/G:A/T transitions at nucleotide positions 61 and 52 and one T:A/A:T transversion at nucleotide position 12. The study is currently ongoing and we aim to increase the sample size by 100% and analyse adenomas and hyperplastic polyps. Our results will allow predictions to be made concerning the causative factors of mtDNA mutations in colorectal cancer and can contribute global insight into whether these mutations precede neoplasia or are a consequence of tumorigenesis.

Results: 24/40 (60%) patients were node negative in the pre tww group compared with 32/46 (70%) in the post tww group (χ²=0.21; ns). Similarly, before the introduction of the tww there were 9/40 (23%) patients regarded as being of good prognosis (T₁N₁,T₁N₂; T₂N₁; T₃N₁) compared with 13/46 (28%) in the post tww (χ²=0.29; ns). The total number at each stage pre tww (n=40) was T₁=3, T₂=8, T₃=18, T₄=11 compared with post tww (n=43) T₁ =6, T₂=7, T₃=22 and T₄=10 (χ²=0.55, ns). Irrespective of whether they were referred pre or post the tww, of all patients seen within 14 days (n=47) [median 9 & range 0–14 days], 25/47 (53%) were node negative. This compared with 38/53 (72%) of those seen greater than 14 days (n=60) [median 32 & range 15–216 days] after referral (χ²=0.01, ns). Of those seen within 14 days, 8/47 (17%) were in the good prognostic category compared with 14/53 (26%) seen after (χ²=0.19, ns). Median follow-up (days) was 513.5 (range 38–696) & 315.5 (range 12–458) for pre and post tww respectively. Overall survival (including emergency admissions) in the pre tww was 79.31% (n=59) while in the post tww (n=81) was 86.42% (p < 0.4749). Survival for elective admissions pre tww (n=47) was 91.30% compared to 91.67% (n=60) in the post tww (p=ns).

Conclusions: The two-week wait has made no impact on TNM staging for CRC at initial presentation.

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Conclusions: The two-week wait has made no impact on TNM staging for CRC at initial presentation.

CHANGES IN HCV SPECIFIC CD4+ RESPONSES DURING TREATMENT WITH PEGYLATED INTERFERON-α AND RIBAVIRIN CORRELATE WITH VIRAL RESPONSE

C.L. Brooks, E.A. Sanders, S. Hadfield, S. Green, W.M. Rosenberg.

Introduction: Hepatitis C virus (HCV) establishes a chronic infection in up to 85% of those exposed. The resultant immune mediated hepatitis leads to progressive fibrosis and cirrhosis in a significant proportion of patients. The combination of interferon-α (IFN-α) and ribavirin achieves a sustained virological response in around 40% of those treated. The addition of a Polyethylene Glycol (PEG) moiety to the IFN-α molecule significantly changes the pharmacokinetics and improves efficacy. HCV specific CD4+ T cell responses are weak or undetectable in patients with chronic hepatitis C (CHC), whilst they are brisk and multi-specific following spontaneous or acute infection. We aimed to characterise CD4+ HCV specific responses in CHC patients at the start of treatment with PEG-IFN-αa and ribavirin, and then repeat them serially throughout the course of treatment, correlating with viral response.

Methods: Peripheral blood mononuclear cells were isolated by density gradient centrifugation from 8 patients prior to starting anti-viral treatment with PEG-IFN-αa and Ribavirin. These cells were set up in culture with either recombinant HCV antigens or appropriate positive and negative controls. Cellular proliferation was assessed by incorporation of tritiated thymidine. Cellular markers of activation and cytokine secretion were assayed by fluorescence activated cell scanning. The assays were repeated at regular intervals throughout treatment and follow up. At each time point, viral load was measured by 12–45CR assay which was used to correlate with viral load.

Results: Throughout treatment, HCV specific lymphocyte proliferation increased in magnitude in 75% of patients, apparent from a median of 18 weeks. The greatest increase was seen in patients who achieved sustained vireological response, in which stronger responses were maintained. There were also changes in the CD4+ cytokine profile induced by chronic stimulation and helicase recombinants which correlated with virological response.

Discussion: There has been one study examining serial HCV specific CD4+ responses whilst on standard combination treatment [Crompy et al. 2000]. Our study has similar results but the increased magnitude of responses is later than seen on standard treatment, possibly reflecting the different pharmacokinetics. This study supports the hypothesis that successful anti-viral treatment allows tolerance to HCV to be broken.

GASTRIC EPITHELIAL CELL PROLIFERATION AND APOPTOSIS IN HELICOBACTER PYLORI INFECTED MONGOLIAN GERBILS

M. Court, M.A. Aboshkiwa, M.F. Dixon, P.A. Robinson, J.E. Crabtree. Molecular Medicine Unit, St James’s Hospital, Leeds LS9 7TF, UK

Introduction: Chronic H. pylori infection in Mongolian gerbils (MG) has been demonstrated to result in gastric cancer. The aims of this study were to assess the ability of the mouse adapted SS1 strain to...
ACID LOWERS THE THRESHOLD FOR CAPSAICIN ACTIVATION OF GASTRIC MUCOSAL NEURONS


Introduction: Many patients suffer from acid sensitive dyspepsia yet the gastric mucosa is normally anaesthetic to luminal acid. We have previously reported that the pain caused by exposure of the gastric mucosa to the neural irritant capsaicin is pH dependent. We hypothesise that acid enhances the response of gastric mucosal nerves to capsaicin in a similar way to that has been observed for somatic nerves.

Aims: To determine the response of gastric mucosal nerves to capsaicin at physiological and non-physiological pH.

Methods: To study the effects of capsaicin on the cell bodies of gastric mucosal nerves, we injected a neuronal tracer, Texas Red, into the gastric mucosa of 4 Wistar rats 2–4 weeks before removal of their dorsal root ganglia (DRG). Cultured DRG cells were placed in a perfusion chamber mounted on a fluorescence microscope where those of the gastric origin were identified by excitation of the Texas Red within them. The cells were loaded with the calcium sensitive ionophore, FURA 2-AM to detect the rise in calcium concentration accompanying cell activation and perfused with a HEPES based buffers at pH 7.4 or pH 7 containing capsaicin at a concentration of 10^-4 to 10^-6 molar to establish a dose response curve. Non Texas red containing cells were used as controls since the vast majority of these are of somatic origin.

Results: The percentage of gastric cells responding to capsaicin was less than half that of non-gastric cells but increased at lower pH (see fig 1).

Conclusion: The gastric mucosa has a lower percentage of capsaicin sensitive cells than somatic tissue but like somatic neurons responses are enhanced at reduced pH.

INCREASED PLATELET STORES OF 5-HYDROXYTRYPTAMINE (5-HT) IN FEMALE PATIENTS WITH DIARRHOEA PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS)

L.A. Haughton1, W. Atkinson1, P. Whitaker2, P.J. Whorwell1, M. Rimmer3

1Dept of Medicine, University Hospital of South Manchester; 2Dept of Chemical Pathology, University of Leicester; 3Glaxo Wellcome, Stockley Park, UK

Recent pilot data suggests that platelet depleted plasma 5-HT concentrations are undetectable under fasting conditions in both patients with irritable bowel syndrome (IBS) and healthy volunteers. However, the number of subjects studied was small (n=5 and 6, respectively) and no data was provided as to the detection limits of the methods used. We have measured fasting platelet-depleted plasma 5-HT concentrations plus platelet 5-HT concentrations in 21 female patients with diarrhoea predominant IBS (aged 19–50 yrs) and 19 healthy female volunteers (20–46 yrs). 5-HT concentration was measured by reverse-phase high performance liquid chromatography with fluorimetric detection. α-Thromboglobulin, which is a marker of platelet activation and/or leakage (and thus a marker for adequate blood collecting technique), was also measured by ELISA method.

Results: Under fasting conditions, platelet 5-HT concentration was significantly higher in the female patients with diarrhoea predominant IBS (443.96ng/10^9 platelets, adjusted geometric mean) than healthy female controls (342.86ng/10^9 platelets), ratio IBS:healthy controls (95%CI), 1.30 (1.07,1.56); p=0.008). Platelet depleted plasma 5-HT concentration however, was similar in patients (4.25ng/ml) and healthy controls (4.01ng/ml); ratio IBS:healthy controls, 1.06(0.82,1.36), p=0.65). α-Thromboglobulin concentrations were undetectable in any of the samples measured.

Conclusions: Female patients with diarrhoea predominant IBS have larger platelet stores of 5-HT than healthy women, suggesting that they may have increased exposure to 5-HT in their systemic circulation. This supports the observations of Bearcroft et al that meal ingestion is associated with a greater increase in plasma 5-HT concentration in patients with IBS compared with healthy controls.


MUC-1 IS A NOVEL LIGAND FOR GALECTIN-3 AND IS UP-REGULATED IN INVASIVE HT-29 COLORECTAL CANCER CELLS

N. Andrews, G. Yu Lu, O. Gerasimenko, J. Rhodes. Departments of Medicine and Physiology, University of Liverpool, L69 3BX, UK

Introduction: Galectins are a family of 12 to date, β-galactoside-binding lectins. It is very unclear what are the functionally important natural ligands for the galectins but galectin-3 expression is implicated in tumour invasion and metastasis. We have therefore investigated the possible ligand(s) for recombinant galectin-3 in HT-29 colon cancer cells.

Methods and Results: HT-29 cells were grown to 70% confluence, harvested, and a cytoplasmic extract prepared. The extract was then
separated by SDS-4% polyacrylamide gel electrophoresis (PAGE), electroblotted onto a nitrocellulose membrane and probed using recombinant human galecicin-3 protein followed by anti-galactin-3 antibody overlay. A major band was then identified with a molecular weight of 420KD. Since this corresponds to the mucin MUC-1, which is known to express the TF antigen (galactosyl 1,3 N-acetylglalactosaminyl), a known ligand for galecicin-3, MUC-1 immunoprecipitate was prepared and probed as before. This confirmed binding of MUC-1 by recombinant galecicin-3 protein (fig). Lane a shows three proteins identified by galactin-3 protein in HT-29 cytosolic extract, lane b shows two proteins identified by galecicin-3 protein from MUC-1 immunoprecipitate.

The two protein bands observed for MUC-1 are due to the two different alleles of MUC-1. HT-29 cells were separated into invasive and non-invasive cell types by their ability to migrate through a 0.5mm Matrigel. The technique employed was a Membrane Invasion Culture System (MIC). Immunocon focal microscopy of invasive HT-29 cells showed colocalisation of MUC-1 and galecicin-3 whereas MUC-1 expression was weak in the non-invasive cells.

**Conclusions:** The transmembrane TF expressing mucin MUC-1 is a natural ligand for galecicin-3. Its increased expression is correlated with a more invasive phenotype in colon cancer cells.

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**HFE AND TF R2 INTERACT IN SMALL- INTESTINAL CRYPT CELLS: A MECHANISM FOR IRON HOMEOSTASIS IN HEREDITARY HAEOMCHROMATOSIS**

**W.J.H. Griffiths, W.S. Sly 1, T.M. Cox. University of Cambridge Dept of Medicine, Addenbrooke’s Hospital, Cambridge; 1St Louis University School of Medicine, MO, USA**

Transferrin receptor 2 (TR2) is a recently identified homologue of the ubiquitous transferrin receptor (TR1) and is expressed in the liver and small intestine. Mutations in the HFE gene predispose to hereditary haemochromatosis and a role for HFE in the signalling of body iron status within small intestinal crypt cells has been proposed. TR2 mutations however account for rare forms of non-HFE related haemochromatosis suggesting a key role for this receptor sub-class in the control of intestinal iron absorption.

To investigate cellular interactions of HFE and TR2 a panel of rabbit and avian polyclonal antisera was generated to specific peptide sequences of the human and mouse proteins. Antibodies were first characterized by Western immunoblotting. Using laser confocal microscopy in mouse and human duodenal sections, strong staining of TR2 was observed in the crypts, where colocalisation occurred with HFE; no staining of HFE and TR2 was observed in villus enterocytes. In contrast TR expression, examined using a commercial murine antibody, was ubiquitous but did not colocalise with HFE. The localisation of HFE and TR2 was further examined in situ in human Caco-2 cells, which have a small intestinal phenotype. Using confocal microscopy TR2 stained abundantly with a vesicular pattern in undifferentiated Caco-2 cells. No colocalisation with TR was observed by dual-label fluorescence studies confirming the specificity of the TR2 antibody. HFE colocalised with TR2 in an endosomal compartment following addition of iron-saturated transferrin to the culture medium.

Identification of TR2 in small-intestinal crypt cells and the known effect of disabling mutations in the cognate gene would support a key regulatory role for this receptor in intestinal iron absorption. Colocalisation of endogenous TR2 and HFE suggests functional coupling in an endosomal transport pathway for crypt cell iron signalling.

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**BONE MINERAL DENSITY AND MINERAL STATUS OF ILEOSTOMY PATIENTS**

**D.H.L Ng, A.N.J May, S.A. Woolton, A.A. Jackson, M.A. Stroud. Institute of Human Nutrition, University of Southampton, Southampton General Hospital, Southampton, UK**

**Background/Aims:** Ileostomy patients, especially those with additional small bowel disease or resection, may have poor absorption or excess losses of calcium (Ca) and Vitamin D (Vit D) and may also be current or past users of steroid. Furthermore, they may also have magnesium (Mg) malabsorption and excessive Mg losses which could exacerbate bone demineralization (60% of total body Mg is in bone). Ileostomy patients are therefore at risk of osteoporosis but the extent of this risk has not been documented. The aims of this study were to examine bone mineral density (BMD) in ileostomy patients and its relationship with markers of Ca and Mg in those subjects along with circulating Vit D levels.

**Methods:** BMD of lumbar spine (LS) and right femoral neck (FN) were determined using DEXA in 57 unselected ileostomy patients (26–85 yr; 24F, 33M) including 13 (7F, 6M) who had had additional small bowel resection. Both plasma and 24-hour urinary excretion measures of Ca and Mg were made in all subjects along with circulating Vit D levels.

**Results:** 20 subjects (35%) had low BMDs (Z-score <1.0) at LS or FN compared to an age matched reference population. However, 28 subjects (49%) had osteopenia (-1.0<T-score<-2.5) and 7 (12%) had osteoporosis (T-score<-2.5) by WHO definition. More patients with small bowel resection had Z-scores <1.0 compared to those with colectomy alone (62% vs. 27%; p<0.05) and the mean LS BMD was also lower in this group (0.592 vs. 0.221; p<0.05). Only 3 subjects (5%) had low plasma Mg (<0.7mmol/l) but 34 (60%) had low 24-hour urinary Mg (<3.3 mmol/l) suggestive of depleted total Mg stores. The mean BMDs were lower in these subjects compared to those with normal Mg excretion (LS Z-scores -0.302 vs 0.582, p<0.05; FN Z-scores -0.273 vs. 0.495, p<0.05) whereas abnormalities in plasma Ca and Vit D and urinary Ca excretion were fewer and had no apparent relationships to BMD.

**Conclusions:** Our results suggest that 1. patients with colectomy alone are not at increased risk of low BMD but this risk may be increased by additional small bowel resection and 2. many ileostomy patients have depleted Mg stores which may adversely affect BMD. Further studies on the relationship between Mg status and bone density are needed.

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**BEDSIDE INSERTION OF NASOJEJUNAL FEEDING TUBE: BENGMARK IS BEST**

**C.W.Y. Lai, R. Barlow, M. Barnes, A.B. Hawthorne. Departments of Gastroenterology, Radiology and Nutrition Support Team, University Hospital of Wales, Heath Park, Cardiff, UK**

The success rate of unguided nasojejunal feeding tube (NJT) insertion is low, thus often requiring endoscopic or radiological assistance. The spiral end of the Bengmark NJT (spiral NJT) is supposed to aid post pyloric flow. Patients requiring nasojejunal feeding were randomised to have either Medicina (straight) or Bengmark (spiral) NJT after stratification into those with or without normal gastric emptying. NJTs were placed at bedside in a standard fashion without radiological guidance. Success rates however account for rare forms of non-HFE related haemochromatosis suggesting a key role for this receptor sub-class in the control of intestinal iron absorption.

To investigate cellular interactions of HFE and TR2 a panel of rabbit and avian polyclonal antisera was generated to specific peptide sequences of the human and mouse proteins. Antibodies were first characterized by Western immunoblotting. Using laser confocal microscopy in mouse and human duodenal sections, strong staining of TR2 was observed in the crypts, where colocalisation occurred with HFE; no staining of HFE and TR2 was observed in villus enterocytes. In contrast TR expression, examined using a commercial murine antibody, was ubiquitous but did not colocalise with HFE. The localisation of HFE and TR2 was further examined in situ in human Caco-2 cells, which have a small intestinal phenotype. Using confocal microscopy TR2 stained abundantly with a vesicular pattern in undifferentiated Caco-2 cells. No colocalisation with TR was observed by dual-label fluorescence studies confirming the specificity of the TR2 antibody. HFE colocalised with TR2 in an endosomal compartment following addition of iron-saturated transferrin to the culture medium.

Identification of TR2 in small-intestinal crypt cells and the known effect of disabling mutations in the cognate gene would support a key regulatory role for this receptor in intestinal iron absorption. Colocalisation of endogenous TR2 and HFE suggests functional coupling in an endosomal transport pathway for crypt cell iron signalling.

**Conclusion:** Bengmark spiral NJT should be used for bedside unguided post pyloric feeding.

(We are grateful to Nutricia for supplying the Bengmark tubes.)
LONG TERM FOLLOW UP OF PATIENTS WITH GASTRIC OUTLET OBSTRUCTION RELATED TO PEPTIC ULCER DISEASE (PUD) TREATED WITH ENDOCOSCOPIC BALLOON DILATATION AND DRUG THERAPY

S. Cherian, A. Cherukuri, P. Singh. Staffordshire General Hospital, Stafford, UK

Introduction: Previous studies suggest endoscopic balloon dilatation in gastric outlet obstruction from PUD does not achieve long-term remission and most patients eventually require surgery. However, these studies have not addressed the issue of altering the natural history of the underlying PUD.

Methods: We examined medical notes of 18 patients with PUD related gastric outlet obstruction treated by a single consultant gastroenterologist. In all patients, an attempt was made to establish and treat the aetiology of PUD. Where no cause was found or its removal not possible or where disease relapsed, long-term maintenance antisecretory therapy was given.

Results: Of the 18 patients, one presented with aspiration pneumonia and another with stroke and both succumbed to their illness. Of 16 available for follow up, 6 were men and 3 were smokers. Their median age was 69 years (range 43–94). Fourteen patients were treated with TTS balloon dilatation and drug therapy and 2 with drug therapy alone. The median number of dilatations was 2 (range 0–5). There were no complications from dilatation. The causes of PUD were as detailed in table 1. Nine of the 10 HP positive patients received eradication therapy. Eradication was confirmed in 5. NSAIDs were discontinued. Four patients stayed on aspirin for medical reasons. Remission was achieved in all 16 patients with a median follow-up of 30 months (range 5–54) including 2 who died from unrelated illness after being in remission for nearly 2 years. Three patients became asymptomatic without need for maintenance therapy (2 after successful HP eradication, and 1 after withdrawal of NSAID). The remaining 13 required long-term maintenance therapy for the reasons detailed in table 2.

Conclusions: PUD related gastric outlet obstruction can be kept in long-term remission by using a structured approach combining dilatation and removal of the cause of PUD and/or maintenance antisecretory therapy. TTS balloon dilatation is a simple, effective, and safe procedure.

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ENDOSCOPIC PALLIATIVE TREATMENT IN OESOPHAGEAL AND GASTRIC CANCER: EVIDENCE FROM 948 PATIENTS IN THE POPULATION BASED SCOTTISH AUDIT

A.M. Thompson, R. Stuart for the Scottish Audit of Gastric and Oesophageal Cancer.

The population based Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) accrued data over a 2 year period on 3,293 patients of whom 948, predominantly with oesophageal or junctional cancer, received endoscopic palliative treatment (EPT). Stents placement alone (506 patients) or LASER treatment alone (117 patients) were popular, but combination approaches supported by radiotherapy (188 patients) or chemotherapy (134 patients) were also administered. There was significant variation in delivery of EPT by health board of residence (chi square test, P<0.001), but not by deprivation quintile.

Complications were recorded in 221/948 patients (23%) and were associated with multiple treatments (P<0.001). Oesophageal perforation was uncommon and occurred in 23 patients post stent and 3 patients after LASER.

Stent alone was used for the relief of grade 3 or 4 dysphagia, stent and radiotherapy for grades 2,3,4 and LASER for grades 1,2,3. The majority of patients (>65%) had normal physical activity or only strenuous activity restricted before undergoing EPT. Stents were deemed by the consultant looking after the patient to have been used appropriately for 95% of patients and LASER for 83% of patients.

Survival for all the patients receiving EPT was 40% at 6 months, 17% at 12 months 10% at 18 months and 6% at 24 months, suggesting benefits from EPT intervention in patients with advanced disease.

While there may be differences between the symptoms and staging of patients receiving different types of EPT, there is evidence for regional variations in the approaches used. However, appropriate use of intervention may provide good palliation for several months.

IS IT NECESSARY TO BIOPSY ACUTELY BLEEDING GASTRIC ULCERS AT THE INITIAL ENDOSCOPY?

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Background: It is recommended that all gastric ulcers are biopsied to exclude malignancy with follow up endoscopies performed at 6–8 week intervals until healing is seen.

Aims: This prospective study aimed to identify whether these recommendations were being followed – especially at emergency endoscopy.

Methods: All patients over a 20-month period diagnosed with a gastric ulcer were identified and those with a definite ulcer (with a mucosal breach documented as >5mm) diagnosed at endoscopy were included in the study. A record of the macroscopic judgement of the ulcers as being benign, suspicious or malignant as stated by the endoscopist was made. This was correlated with the histology results.

Results: 250 patients were reportedly diagnosed with gastric ulcers. Of these 191 met the inclusion criteria. The male:female ratio was 106:85 and the mean age at diagnosis was 67 years (range 23–98). Of these 11 ulcers were diagnosed operatively, 79 were diagnosed as an emergency “bleeder” and 99 were diagnosed routinely (29% open access; 71% routine list via OP clinic). Of the “bleeders” only 55% had biopsies taken at the initial endoscopy, with the mean number of biopsies per ulcer being 2.7. This was despite only 30.4% actually requiring injection at the time of the endoscopy. Of those ulcers diagnosed routinely, biopsies were taken in 94.4%, with the mean number of biopsies being 3.5. Of the “bleeders” 6 patients required laparotomy for further bleeding of whom 1 had had a single biopsy taken at endoscopy. Overall 126 ulcers were thought to be benign, 28 to be suspicious and 17 frankly malignant. Of those ulcers diagnosed at an emergency endoscopy these figures were 60, 11 and 3 respectively. The predictive value of the macroscopic judgement can be estimated as the proportion of correct macroscopic diagnoses. The overall predictive value (PV+) of a macroscopic judgement of definite or suspicious of malignancy was 0.52 (24/46) and the overall predictive value (PV-) of a macroscopic judgement of benign was 0.96 (121/126). For the “bleeders” the PV+ were 0.43 and 0.97 respectively.

Conclusion: These results show that biopsies are often not taken at the time of an emergency endoscopy. However in this study only 2% of “benign-looking” bleeding gastric ulcers were ultimately diagnosed as malignant. Therefore the priority for benign looking bleeding gastric ulcers remains to establish haemostasis.

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CURRENT ISSUES IN THE MANAGEMENT OF COLONIC POLyps. A RETROSPECTIVE REVIEW OF 2806 CONSECUTIVE POLYPECTOMIES

J.C. Brooker, S.G. Shah, B.P. Saunders. St Mark’s Hospital, Harrow, UK.

Background: Based on current knowledge, population screening and the removal of colonic adenomas would be an effective means of reducing the incidence of colorectal cancer. However, a sound understanding of the distribution of adenomas and risks of polyectomy is a prerequisite to implementation, and will assist in the selection of the optimal screening modality and the safest and most effective methods for polypectomy. We therefore undertook polyp epidemiology and polypectomy techniques and complications in patients from a single endoscopy department.

Methods: Records of 938 patients [506 males; mean age 58.8 years [sd 14.3]; indications: symptoms 535, neoplasia surveillance 387, polyposis 55, IBD 37, not recorded 9] who had undergone 1023 consecutive colonoscopies with polypectomy during a 22-month period, were examined retrospectively. Complications were identified using a postal questionnaire.

Results: 2806 polypectomies were performed, 37.9% by hot-biopsy, 30.6% by snare and 23.3% by Argon Plasma Coagulation (APC). 44.7% were benign adenomas and 47.8% of these (excluding polyposis) were located proximal to the splenic flexure. 27% of advanced adenomas (size >1cm or villous histology) were proximal. Polypectomy failed to yield a specimen for analysis in 19.3% of snares and 5.2% of hot biopsies (p<0.0001). 67.6% patients replied to the complications questionnaire. There were no deaths, but 4 significant complications were identified, including one perforation after hot biopsy (0.16%) and three episodes of major haemorrhage (0.47%). Intra-procedural bleeding requiring endoscopic therapy was significantly associated with aspirin ingestion (p=0.02), but post-procedure bleeding was not (p=0.3). No complications were reported after polypectomy using APC.

Conclusions: These data support previous observations of a proximal shift in the distribution of colorectal adenomas, although most advanced neoplasia were still found in the left colon within reach of the flexible sigmoidoscope. The incidence of polypectomy complications compares favourably with previously reported series which may reflect improved polypectomy technique. Hot-biopsy and APC both appear to be safe for the removal of small polyps, but snare techniques, although safe, frequently fail to yield tissue for histology. No increase in secondary haemorrhage was seen in patients taking aspirin.

VIDEO-ASSESSMENT OF COLONOSCOPY WITHDRAWAL TECHNIQUE

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Background: Colonoscopy withdrawal technique has been shown to be important in the detection of adenomas. We aimed to survey current practice in a single UK endoscopy department, as well as assessing the effect of video recording on examination quality.

Method: With ethics committee approval and patient consent, consecutive routine colonoscopy extubations were video recorded using a remote, closed-circuit TV system. Endoscopists were informed that recording would take place when a “recording-light”, conspicuously placed in the endoscopy room, was illuminated. However recording took place continuously. Extubation lists were randomly assigned to "blind" or "blind" recording. The video footage was reviewed by a blinded panel of 3 experienced colonoscopists. Extubations were scored by consensus for seven segments of the colon using 5 parameters (looking behind folds, cleaning pools, adequacy of distension, time spent inspecting and quality of bowel preparation) using 50mm visual analogue scales. Patients with IBD, previous colonic resection, current colorectal-cancer or mean preparation score <30, were excluded from the analysis.

Results: 93 procedures by 16 endoscopists were included, 50 for cancer and 43 for polyps. Blind withdrawal was an effective means of cancer. 52.7% extubations attained a mean score of less than 30 (an arbitrary minimum score for acceptable quality). There was no difference in extubation scores or mean preparation time with blinded compared with open recording (see table). There was also no difference between groups in performance of retroflexion in the rectum (12% overall) of the detection of adenomas (p=0.24).

Conclusions: Over 50% of extubations were sub-optimal, and awareness of video recording made no difference to quality. We suggest that both better training in withdrawal technique and allocating more time per procedure are required to improve examination quality.

GENETIC THROMBOPHILIA AND PERI-PARTUM LIVER FAILURE

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Introduction: The aetiology of severe pregnancy-related disorders remains poorly characterised. One hypothesis is that the clinical disorders recognised - Acute Fatty Liver of Pregnancy [AFLP], HELLP syndrome and Veno-occlusive disease - represent microangiopathic disorders. Thrombotic microangiopathic disorders have previously been implicated in serious hypertensive complications of pregnancy where microangiopathy is evident. Accordingly, we tested the hypothesis that a higher incidence of genetic thrombophilia would be present in this population.

Methods: Twenty-eight patients with a history of peri-partum liver failure were tested [AFLP 22, HELLP syndrome 3, and Veno-occlusive disease 3. Median age 30 years (range 21–36). Twenty-eight patients were Caucasian and five Afro-Caribbean. All presented in the third trimester. Only one patient had a known pre-existing pro-thrombotic disorder. All patients had thrombophilia screens performed post-partum once fully recovered from their illness [factor V leiden [FVL] and prothrombin G20210A gene mutations, anticardiolipin antibody and lupus anti-coagulant, anti-thrombin III and protein C and S levels].

Results: A pro-thrombotic disorder was present in 12/28 (43%) patients. FVL heterozygosity was present in 5/23 Caucasian patients (17.5%). PT G20210A gene heterozygosity was present in 2/28 (7%). Anti-cardiolipin antibody was detected in 4/28 (14%). LUPUS anticoagulant was detected in one patient with AFLP. In the patients where a diagnosis of AFLP was made; genetic thrombophilia was present in 10/23 (42%). Protein C and S deficiency was not detected in patient.

Conclusion: The above results lend some support to the hypothesis that microvascular thrombosis may play a pathogenic role in a subgroup of patients with peri-partum liver failure. However further predisposing factors for these serious disorders require to be elucidated.

NEUROLOGICAL AND COGNITIVE DYSFUNCTION IN “NEVER-ENCEPHALOPATHIC” PATIENTS AWAITING LIVER TRANSPLANTATION

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Introduction: Patients with liver failure who are not clinically encephalopathic can show evidence of neuropsychological impairment. Inadequate treatment of previous hepatic encephalopathy is often blamed. Repeated episodes of hepatic encephalopathy may play a pathogenic role in a subgroup of patients with peri-partum liver failure. However further predisposing factors for these serious disorders require to be elucidated.
were no significant differences between baseline characteristics of patients and controls. Highly significant global impairment of cognitive function was detected, with memory and visuo-spatial problems being prominent. No abnormalities were detected with the commonly used trailmaking test. Twelve patients had an abnormal neurological examination displaying many of the physical signs associated with AHCD.

Discussion: Cognitive and neurological dysfunction occurs in patients with end stage liver failure in the absence of previous HE. It is unlikely that the progressive neurological and cognitive decline that can occur in these patients is due to repeated episodes of HE. The impairment that occurs is severe, and affects many aspects of cognitive function. This has implications for the pre-operative counseling of these patients and for obtaining informed consent. Current methods of monitoring cognitive impairment clinically, such as trailmaking tests, may be inadequate.

In this model all glucogenetic substrates studied were significantly increased whereas the end product of the pathway, glucose, is significantly decreased. This confirmed that in the model the glucogenetic capacity of the liver is lost.

A porcine model of paracetamol induced acute liver failure has been established. Thirty five kilogram large white pigs were maintained under general anaesthesia with isoflurane and nitrous oxide. Three pigs acting as controls received no paracetamol and were maintained under general anaesthesia with isoflurane and nitrous oxide. Three pigs acting as controls received no paracetamol and were maintained under general anaesthesia with isoflurane and nitrous oxide.

Materials and Methods: 51 untreated and 10 interferon-treated patients with biopsy-proven HCV liver disease were studied. Time-intensity curves of hepatic vein spectral Doppler signals and CDTs measured concentrations of lactate, pyruvate, threonine, glycine and alanine at 5-hourly intervals until the experiments were terminated. Experiments lasted for 28 hours and any surviving animals were then euthanased.

Results: In control pigs there were no significant differences in the concentrations of those substrates at any time point sampled. Animals who received paracetamol showed significant increases in the concentrations of lactate, pyruvate and the amino acids. Increase of lactate became significant at 1.5 hours and at 25 hours compared to t=0 an average increase of 405% was seen (p<0.003). Increase of pyruvate became significant at 20 hours and at 25 hours compared to t=0 an average increase of 150% was seen (p<0.018). Increase of threonine became significant at 20 hours and at 25 hours compared to t=0 an average increase of 82% was seen (p<0.048). Increase of glycine became significant at 5 hours and at 25 hours compared to t=0 an average increase of 390% was seen (p<0.005). Finally, increase of alanine became significant at 10 hours and at 25 hours compared to t=0 an average increase of 410% was seen (p<0.002).

Conclusion: In this model all glucogenetic substrates studied are significantly increased whereas the end product of the pathway, glucose, is significantly decreased. This confirmed that in the model the glucogenetic capacity of the liver is lost.

Ten interferon-treated patients were maintained under general anaesthesia with isoflurane and nitrous oxide. Three pigs acting as controls received no paracetamol and were maintained under general anaesthesia with isoflurane and nitrous oxide.

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Ten interferon-treated patients were maintained under general anaesthesia with isoflurane and nitrous oxide. Three pigs acting as controls received no paracetamol and were maintained under general anaesthesia with isoflurane and nitrous oxide.
PLASMA LEPTIN BEFORE AND AFTER CURE OF PANCREATIC STELLATE CELLS EXPRESS LOW AFFINITY PARADOXICAL DUAL EFFECT OF

Background: Decreasing H. pylori prevalence has been linked with increasing incidence of oesophageal adenocarcinoma. Increasing oesophageal reflux in CCA. Barrett’s and oesophageal adenocarcinoma is one possible route of association. H. pylori gastritis is associated with increased gastric mucosal leptin and successful cure leads to a fall in gastric mucosal leptin. However, for leptin produced by the stomach to influence appetite and cause adiposity, leptin concentration needs to be detectable.

Methods: Ten H. pylori positive healthy subjects were studied before and after cure of H. pylori. Their mean age was 36.8 years and mean Body Mass Index was 25.80. After an overnight fast they were admitted to a research ward at 8 am. Blood was sampled hourly for six hours via an indwelling IV cannula. Plasma was separated and stored at -20°C. Leptin was measured in duplicate by using the Linco Research Human Leptin Radioimmunoassay. 6 hour integrated leptin was calculated using the trapezoid rule. Paired comparison was made by the Wilcoxon rank sum test.

Results: Before H. pylori cure, median 6 hour integrated plasma leptin was 23.66 mcg/L.hr (7.33 – 128.22), and after cure it was 26.75 mcg/L.hr (7.43–72.81) p = 0.375.

Conclusions: Plasma leptin is unchanged following cure of H. pylori in healthy subjects. Decreased gastric mucosal leptin associated with cure of H. pylori does not affect plasma leptin. This study weakens the hypothesis that a fall in gastric leptin production may be responsible for increased appetite and obesity following H. pylori eradication.

EVIDENCE OF AN ENVIRONMENTAL CAUSE FOR THE RISE IN CHOLANGIOCARCINOMA

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Background and Hypothesis: Reported mortality from cholangiocarcinoma (CCA) has risen steeply in the UK and other industrialised countries over the past 20–30 years, the cause of which has not been adequately explained. DNA adducts are covalently modified bases resulting from carcinogen binding at the nucleotide level. Adduct formation is pro-mutagenic and clearly demonstrates exposure to a DNA damaging agent. It is a key step in toxin-induced carcinogenesis. We hypothesise that the increase in CCA mortality is caused by a temporally-associated rise in genotoxic environmental agent(s), causing cholangiocyte DNA damage.

Aims: To investigate and compare tumour and tumour-adjacent CCA tissue, and non-cancer control bile duct tissue, for the presence of DNA adducts as a biomarker of genotoxic exposure.

Methods: DNA from 28 CCA tissues, and in 24 cases adjacent non-tumour tissue samples from the same patients; and from bile ducts of 7 non-cancer patients (undergoing laparoscopic cholecystectomy for gallstones) were investigated for the presence of DNA adducts using the nuclease P1 method of “p-postlabelling. Relative adduct labelling values (RAL, adducts/10^8 nucleotides) quantified.

Results: No difference was found in RALs between DNA from CCA tissue (mean 14, range 1–48) and tumour-adjacent tissue DNA (mean 14, range 1–52). RALs were significantly higher in tissue from CCA patients than from non-cancer patients (mean 6, range 1–31, p=0.04, Mann-Whitney test). Different adduct patterns were also seen CCA compared to non-cancer patients.

Conclusion: Quantitative and qualitative differences in adducts between cancer and non-cancer patients support the hypothesis that genotoxins play a role in the development of CCA.

PARADOXICAL DUAL EFFECT OF HELICOBACTER PYLORI ERADICATION THERAPY ON HEARTBURN AND ACID REFLUX: THE BRISTOL HELICOBACTER PROJECT

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Helicobacter pylori eradication therapy has been reported in some studies to result in increased heartburn and acid reflux. However, other studies show either no effect on these symptoms, or even a beneficial effect. We have investigated these contradictory findings, as part of the community-based Bristol Helicobacter Project.

Methods: 10,537 people aged 20–59 years gave informed consent to take part in the Bristol Helicobacter Project, a community-based prospective randomised controlled trial of the effects of Helicobacter pylori eradication. 1634 participants had a positive 13C urea breath test, and were treated with either Helicobacter pylori eradication therapy (ranitidine bismuth citrate 400mg and clarithromycin 500mg twice daily for two weeks) or placebo. The prevalence, frequency and severity of heartburn and acid reflux were measured at baseline and two years after randomisation, using a validated questionnaire.

Results: There was an overall small benefit of active treatment, with 3.1% less heartburn and 2.5% less reflux at 2 years when compared with placebo. However, this small net benefit concealed complex differential effects. Active treatment had a more marked benefit over placebo in participants with mild or no initial symptoms - at 2 years, 6.8% fewer had heartburn and 4.3% fewer had reflux. Those with initially moderate symptoms showed little net benefit, and those with troublesome symptoms at randomisation were more likely to get worse after active treatment. Subjects with the most severe symptoms at two years after treatment were almost twice as likely to have been treated with active therapy.

Conclusions: (1) There is a small net reduction in heartburn and acid reflux after H. pylori eradication therapy, but a significant subgroup of patients get worse, particularly if they have troublesome GORD symptoms initially. (2) The contradictory results of previous studies may reflect differences in the selection of patients.

PANCREATIC STELLATE CELLS EXPRESS LOW AFFINITY NERVE GROWTH FACTOR RECEPTOR AND UNDERGO APOPTOSIS IN RESPONSE TO NERVE GROWTH FACTOR


Pancreatic Stellate Cells (PSCs) are central to pancreatic fibrosis. Our group have previously shown that recovery from liver fibrosis can occur and it is associated with apoptosis of Hepatic Stellate Cells. Nerve Growth Factor (NGF) stimulated apoptosis by activating the Low Affinity Nerve Growth Factor receptor (p75). We therefore studied the distribution of NGF and its receptors in sections of human chronic pancreatitis (CP). We further studied the effects of NGF stimulation of apoptosis in PSCs and the expression of p75 receptor.

With immunostaining techniques we examined the distribution of NGF and p75 in sections of CP and normal pancreas. Passage rat...
Biliary and pancreas posters

198 PALLIATION OF RECURRENT MALIGNANT BILIARY OBSTRUCTION: ARE TWO STENTS BETTER THAN ONE?

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Endoscopic placement of biliary stents across malignant strictures of the common bile duct is effective at palliating symptoms of obstruction. Standard practice is the initial insertion of a single plastic stent. Following this a minority of patients present with recurrent jaundice or cholangitis due to stent blockage. The decision as to which type of stent to then place can be difficult: expanding metal stents have a longer survival (mean=240 days) compared to plastic stents (mean=150 days), but are more expensive (£800 and £20 respectively). Without any clinically useful prognostic indicators for survival in these patients, a best guess approach is often used. In some patients it is possible to place a second plastic stent alongside the first. Between 1990 and 2001 we attempted 31 double-stents in 24 patients with malignant strictures of the common bile duct. All had re-presented with jaundice/cholangitis following the initial insertion of a single plastic stent. Detailed records could not be raised on 6 of these patients. Of the remaining 18 patients (7 women, mean age 81yrs, range 75–84yrs; 11 men, mean age 73.3yrs, range 61–83yrs), 19 (76%) double-stents were successfully placed, 2 (24%) attempted double placements were unsuccessful. 4 patients required more than 1 double-stenting procedure. 16 patients had pancreatic carcinoma, 2 cholangiocarcinoma. The first single stent lasted between 7 and 189 days (mean=83.3 days) before jaundice/cholangitis recurred due to stent blockage. Subsequent double-stents lasted between 26 and 312 days (mean=127.1 days). Using each patient as their own control p<0.21 (NS).

Double-stents in this series lasted 6–7 weeks longer than single stents. The double-stents are placed in more advanced malignant strictures introducing negative bias into these figures. We feel double-stenting, in patients in whom it is technically feasible, may be an alternative to repeated placements of a single stent or an expanding metal stent. This has potential benefits in terms of cost-effectiveness.

Conclusion: (1) TP gives significantly better sensitivity and it reduces the number of unsatisfactory and suspicious results (2) variability in diagnostic yield at ERBC does exist; if this difference can be overcome by improved technique the sensitivity could be further increased.

200 LAPAROSCOPIC CHOLECYSTECTOMY RATES IN IRELAND: RECENT TRENDS

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Background: Studies in other countries have suggested that the overall cholecystectomy rate increased following the introduction of the laparoscopic technique in 1985.
**Objective:** The aim of this study was to evaluate changes in rates of laparoscopic cholecystectomy (LC) in Ireland, over a 7 year period. We also performed a subset analysis in our 630 bed teaching hospital to determine characteristics of patients, imaging modalities used and indications for surgery.

**Methods:** Data for cholecystectomies performed in Ireland, in 60 Irish public hospitals, were obtained from the Hospital In Patient Enquiry (HIPE) Scheme, based at the Economic and Social Research Institute (ESRI). The information for the subset analysis in our hospital was retrieved from 139 patient chart reviews, comparing two six month periods, in 1996 and 2000.

**Results:** Overall, the rate for total cholecystectomies in Ireland (laparoscopic and open), rose by 17% over the 7 year study period. LC rates rose by 45%, with the largest increase of 15.4% observed in the 0–19 year age group, with a 121% increase in the 20–24 year age group. Of note, there was a 25% decline in LC in the 85+ age group. However, despite this overall increase in the number of operations, the total number of deaths (0.59%), remained constant. The rate of open cholecystectomy fell by 37%, with the largest fall of 55% in the 30–34 year old and 40–44 year old age group. The rates of LC also increased in the subset group by 20%, over a 5 year period (1996–2000). A review of procedures in our hospital revealed that relatively ambiguous symptomology became a more frequent indicator, rising by 11.5% over the study period. Ultrasonography, as a mode of imaging, remained constant. However, the use of preoperative MRCP increased dramatically, while oral cholecystography use continued to fall. ERCP use, both diagnostic and therapeutic, also increased.

**Conclusion:** The overall cholecystectomy rate in Ireland has continued to rise in the last 7 years. LC incidence continues to show a sustained rise 16 years after its introduction. Several factors may have contributed to this, including reduced surgical threshold, increased gallstone incidence, reduced unit cost of LC, reduced length of hospital stay and increased patient expectation.

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**203 THE GENETIC SUSCEPTIBILITY TO NON-HEREDITY CHRONIC PANCREATITIS: A CASUALTY OF XENOBIOTIC STRESS**


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Epidemiological studies have demonstrated a variety of potential environmental and cellular stress related factors that may alter susceptibility to chronic pancreatitis (CP), however a direct causal and mechanistic role has not been established. Impaired detoxification of environmental pollutants may overwhelm cellular oxidative defences leading to lipid membrane damage, protein denaturation and DNA adduct formation.

The aim of this study was to determine the relationship between functional genetic polymorphisms in the antioxidant / xenobiotic metabolising enzymes, glutathione-s transferases (GSTT-1, GSTF-1 and GSTP-1), and manganese superoxide dismutase (mitochondrial targeting sequence – MTS), and susceptibility to CP. Genetic susceptibility may in part explain not only the potential benefits of antioxidant therapy, but also the observed twenty-fold increased risk of pancreatic cancer in patients with CP.

In total 103 patients with chronic pancreatitis (71 alcohol induced, 28 IPC and 4PH), and 206 age and sex matched controls were recruited. The prevalence of the GSTT-1 null genotype was significantly under-expressed in CP (11.6 %) compared to healthy controls (24 %, p = 0.006). After stratification for ethnicity, this association remained significant in non-alcohol related disease (p<0.05). In contrast to the data with GSTT-1, no significant associations were observed between GSTF-1, GSTM-1, and MNSOD genotypes and susceptibility to CP.
The GSTT-1 functional genotype is associated with an increased susceptibility to CP, whether this is attributable to its phase-II conjugation or anti-oxidant properties remains to be determined.

**THE GENETIC PRE-DISPOSITION TO SEVERE PANCREATITIS IS ASSOCIATED WITH DISTURBANCES IN GLUTATHIONE REGULATION**


Disturbances in glutathione regulation appear central to the pathogenesis of severe acute pancreatitis (AP), by altering cellular integrity and impairing anti-oxidant defences. Individual difference in the efficiency of detoxification of the products of oxygen-derived free radicals may thus affect either by altered expression of anti-oxidant enzymes or depletion in cellular glutathione.

We investigated the prevalence of Ala/Val biallelic functional polymorphism in the mitochondrial targeting sequence (MTS) region of the manganese superoxide dismutase (MnSOD) gene in patients with AP, and examined for interactions with the previously reported polymorphism of the glutathione-S transferase (GSTT) T*1*A gene associated with severe disease (OR 4.8), and for potential influences on glutathione disturbance (glutathione and transulfuration pathway).

In total, 320 patients with AP (90 severe) and 206 matched healthy controls were recruited. Severity of AP was assessed using the Atlanta criteria, and serial venous blood samples were taken at 24-hr intervals (from pain onset) for C-reactive protein (CRP), γ-glutamyl transpeptidase (γGT), alkaline phosphatase (ALP), and alanine transferase (ALT).

A severe attack of AP was associated with an early persistent down-regulation of hepatic function (biliary aetiology) demonstrated by lower plasma γGT (p=0.001), ALT (p=0.001) and ALP (p=0.01), that inversely correlated with CRP (r=0.3, p<0.001). Although MnSOD polymorphism was not independently associated with severity of AP, among patients of the functional GSTT-1*A genotype the polymorphic MnSOD (AA) genotype was associated with a significantly greater peak CRP (p=0.02), but significantly lower systemic ALT and γGT levels (p=0.03) compared to the wild type MnSOD (VV) genotype.

Susceptibility to severe inflammatory stress may in part be mediated by differences in the ability to efficiently detoxify reactive oxygen species, through a profound depletion of cellular glutathione as a consequence of altered hepatic function.

**DISTURBANCE OF GLUTATHIONE REGULATION IN SEVERE ACUTE GALLSTONE PANCREATITIS**


Impairment in hepatocellular function often accompanies the severe systemic inflammatory response and multi-organ failure observed in acute pancreatitis (AP). These disturbances may contribute to the inability of the liver to replenish glutathione levels, the depletion of which has been demonstrated to increase cellular susceptibility to inflammatory stress. We therefore sought to determine if severe AP is associated with down-regulation of glutathione metabolism by observing the profile of ALT (transulfuration pathway) and γ-glutamyl transpeptidase (ALT), alkaline phosphatase (ALP), and bilirubin, and correlated with (1) the clinical severity (Atlanta criteria), and (2) the positive acute phase protein response (CRP). In patients with a severe attack ALT, γGT and ALP but not bilirubin, were significantly lower than those with a mild attack over the entire study period (see table). Plasma ALT demonstrated a strong correlation with γGT (24hr: r = 0.52, p < 0.001), and an inverse correlation with CRP (24hr: r = -0.34, p = 0.004).

Depletion of circulating ALT and γGT in severe disease is likely to be secondary to a down-regulation of hepatic function, and adversely contribute to the depletion of cellular glutathione.

**ANALYSIS OF SPATIAL CHANGES IN THE HISTOPATHOLOGY OF PanCREATIC TUMOURS BY IMAGE ANALYSIS**

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Objective: Pancreatic carcinoma is frequently characterised by a stromal reaction. In this paper, computer image analysis techniques were used to determine whether the histological manifestation of such a reaction can be detected for a group of patients, and for individual tumours.

**FROM GP REFERRAL TO DEFINITIVE TREATMENT: A BREAKDOWN OF DELAYS IN THE MANAGEMENT OF PATIENTS WITH PanCREATOBILIARY TUMOURS**

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The aim of this study was to assess the extent of delays at different stages in the management of patients with pancreaticobiliary tumours, from GP referral to definitive treatment at a District General Hospital (DGH) or Hepato-Pancreato-Biliary (HPB) Unit.

The notes of patients with pancreaticobiliary malignancy diagnosed at a DGH over a 2 year period (1/9/99 to 1/9/01) were reviewed. Mode of referral, presenting symptoms, investigations performed and treatment were recorded. The time taken at various stages in assessment and treatment was noted, as was delay waiting for investigations.

Of the 42 patients identified, 27 presented with jaundice. 24 were seen in the clinic, 16 were acute GP admissions and 2 were A&E referrals. 7 were referred on to the HPB Unit (see table).

Unacceptable delays occurred in those patients referred to the HPB Unit. If assessment of the majority of patients is to be carried out at HPB Units these waiting times will need to be shortened to conform to National Cancer Plan targets.


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Assessment of pancreatic exocrine function is part of the routine work-up of patients with persistent diarrhoea/suspected steatorrhoea. Indirect tests of pancreatic function such as the panreolauryl and p-aminobenzoic acid (PABA) tests are widely used but are time consuming and have a poor sensitivity. A simple ELISA kit for determination of faecal pancreatic elastase-1 (FE1) is now available and shown to have a high sensitivity. We performed a prospective study comparing the PABA test to FE1 in patients undergoing assessment of pancreatic exocrine function. All such patients had a PABA test and donated a stool sample for FE1 measurement by an ELISA method (ScheBo Biotech UK).

Results: Paired data were obtained from 44 patients. In 22 patients both tests were normal. In 3 patients with a high clinical index of suspicion for pancreatic disease both tests were low and patients improved with creon. In 14 patients the PABA test was borderline low but the FE1 normal. 9 of these patients had a low index of suspicion for pancreatic disease and did not improve on creon. In the other 5 another cause of diarrhoea was found (e.g. bacterial overgrowth). This suggests that the FE1 was correct in these 14 patients and the PABA results were in fact false lows. 3 patients had a normal PABA but low FE1. 2 of these patients improved with creon suggesting underlying pancreatic insufficiency and that the FE1 was the more accurate test. In one of these patients there was a technical problem with the PABA test giving a false high result. The third patient was diabetic with severe watery diarrhoea, which can be associated with a false low FE1.

Summary: There was concordance between the two tests in 27 patients (22 normal, 5 low). In 14 patients the PABA test was borderline low and FE1 normal, but none of these had clinical evidence of pancreatic disease. FE1 appears a more robust test of pancreatic insufficiency and is a much simpler test. In our unit it has now replaced the PABA test in the assessment of pancreatic exocrine function.

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209 FREQUENCY OF STOOL EXAMINATION: EFFECT ON REPORTED RECTAL BLEEDING

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Background: Rectal bleeding is an important symptom of colorectal cancer. However, up to 45% of people seldom examine their stools: these individuals may be less likely to report rectal bleeding. This phenomenon has not to date been studied formally.

Aims: To determine (1) the proportion of community subjects who examine their stools or toilet paper at different frequencies, (2) whether the incidence of reported rectal bleeding is related to frequency of inspection. Methods: A questionnaire was developed, validated and sent by post to subjects selected at random from patient lists of 4 general practices in south west London. Equal numbers were selected within 5 year age bands between 50 and 79 years, and between sexes. Reminders were sent to non responders after 4 and then 8 weeks.

Results: 2073 subjects were included in the study. 1633 (79%) completed the questionnaire, 162 (8%) subjects declined, and 278 (13%) did not respond. The cumulative proportion of individuals who examined their stools and toilet paper at various frequencies were: every time – 31%, 45%; more than once a week - 67%, 74%; more than once a month – 80%, 84%. 12% and 9% respectively never examine their stools or toilet paper. Men examined more frequently than women. Age had no effect. 102/439 (22%) of individuals who always examined their stools or toilet paper had noticed rectal bleeding in the past year, compared to only 4/100 (4%) of subjects who never examined either, p < 0.001. 149/429 (35%) of individuals who examined their stools or paper every time had a history of piles compared to 21/101 (21%) of individuals who never checked, p < 0.006.

Discussion: Many individuals do not examine their stool or toilet paper regularly. 9% never examine either. Infrequent examiners reported rectal bleeding less often than those who examined regularly, and this behaviour may potentially delay the presentation of colorectal cancer. It would be important to determine whether colorectal cancer patients who regularly check for bleeding present at an earlier stage than those who examine infrequently, since public education may then be a potential way of improving outcome.

210 TREATMENT OF FAECAL INCONTINENCE DUE TO SYSTEMIC SCLEROSIS WITH SACRAL NERVE STIMULATION

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Introduction: Fecal incontinence occurs in over a third of patients with systemic sclerosis. Aetiological factors include internal anal sphincter fibrosis, rectal wall fibrosis, small bowel involvement and an autonomic neuropathy. Sacral nerve stimulation is a novel treatment for faecal incontinence that is effective where other treatments have failed. Its value in systemic sclerosis has therefore been evaluated.

Patients and Methods: Five women, median age 61 years (range 30–71), with faecal incontinence secondary to scleroderma were treated with initial temporary and subsequent permanent stimulation. The median pre-operative episodes of faecal incontinence per week was 15 (7–25). The median pre-operative duration of incontinence was 5 years (5–9) and of scleroderma 13 years (4–29). All had failed traditional treatment including anti-diarrhoeal agents and behavioural therapy (biofeedback). A three-week bowel habit diary, quality of life assessment (SF36), endoanal ultrasound and anorectal physiological testing were performed.

Results: At median follow up of 24 months (range 6–60) four patients were continent, one had failed temporary stimulation. On diary the episodes of faecal incontinence per week decreased from 15, 11, 23 and 7 to 0 in all patients. Urgency and urge incontinence resolved in all patients with the median ability to defer improving from <1-minute (0–1) pre to 12.5 mins (5–15) post stimulation. Adjusted scores for the SF36 quality of life questionnaire showed an overall improvement. The internal anal sphincter was atrophic in all patients, median width 1.0 mm (0.16mm; normal range 2.4–3.4mm). Anorectal physiological testing showed an increase in resting pressure (37 (10) mm H2O (median (SD)) pre v 65 (16) post) and squeeze pressure (89 (48) pre v 105 (67) post). Rectal sensation to distension improved at threshold volume (53 (17) ml air v 33 (20)), urge volume (83 (18) v 58 (23)) and maximum tolerated volume (143 (23) v 75 (34)). There were no major complications.

Conclusion: Sacral nerve stimulation is a safe and very effective treatment for faecal incontinence in patients suffering with scleroderma when other treatments have failed.
**Methods**: New patients attending the fissure clinic were recruited prospectively into the study over a 2 month period. Patients were initially given 3 questionnaires to complete: 1) the Short-Form 36 Health Survey (SF36), 2) the Pain Coping Strategies Questionnaire and 3) a general questionnaire recording patients’ demographic details and symptoms on a visual analogue scale (VAS). Following an 8 week course of topical treatment, patients repeated the SF36 and symptoms were again recorded on a VAS. Healing of fissure was noted.

**Results**: 23 patients entered the study; 8 male, 15 female with mean age 39 years (range 17–80). Median duration of fissure was 9 months (1.5 months – 10 years). Before treatment, median VAS for pain, bleeding and irritation were 6, 1 and 5. On the SF36, patients scored below normal values for all scales except role emotional functioning and mental health. Fissure patients had more pain than age and sex matched normal population (p=0.00, Wilcoxon). Gender did not affect any of the SF 36 sub-scales. Duration of fissure positively correlated with role physical functioning and role emotional functioning (p=0.05). On follow-up, healing was complete in 15 patients (65%). Symptoms were significantly reduced in this group. Repeating the SF36 showed an improvement in role-physical functioning (p<0.05). Ignoring sensations was an adaptive pain coping strategy, being employed more often in the group responding to treatment (p<0.05).

**Conclusion**: Successful treatment of chronic anal fissure leads to symptomatic improvement and beneficiably affects role physical functioning. Patients’ coping strategies appear to have an influence on outcome, with ignoring sensations being a good predictor of response.

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**212 COLONIC DIVERTICULITIS: A DISEASE ON THE RISE?**

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**Background**: Little data exist on time trends for colonic diverticulitis.

**Materials and Methods**: Admission rates for colonic diverticulitis (ICD9: 562.1, ICD10: K57.2–57.9), excluding day cases but including diverticular abscess and perforation, operation and case fatality rates were obtained from Department of Health Hospital Episode Statistics.

**Results**: There has been a steady increase in age-standardised hospital admission rates for both sexes and in all age groups over the study period. Admission rates increased with age for both sexes. The percentage of hospital admissions with an ABS has also risen for both males and females. There has been no significant change in case fatality rates over this time for either sex (see table).

**Conclusions**: The hospital admission rates for colonic diverticulitis has increased from 1989/90 to 1999/00. As the proportion of patients who had surgical operations has also increased, while case fatality rates have remained much the same, the rise in admission rates may be due to a true increase in the incidence of colonic diverticulitis. With an ageing population, colonic diverticulitis is likely be an increasing health problem in England.
AE3 and Cam 5.2. This cell could not be identified in the level stained with pan-cytokeratin. No cytokeratin positive epithelioid cell was present in any of the other lymph nodes with all 3 antibodies. Rare to 2+ cytokeratin immunoreactive dendritic histiocytes were observed in 50% of lymph nodes with MNF 119 and in 14% with Cam 5.2. With AE1/AE3, no immunoreactive dendritic histiocytes were seen in any of the cases.

**Conclusion:** Isolated cytokeratin positive epithelioid cells are rare in benign pericolic lymph nodes. Cytokeratin positive epithelioid cells in lymph nodes draining a carcinoma could represent either tumor cells or histiocytic cells which have adsorbed cytokeratin antigen shed by tumor cells. AE1/AE3 is more specific than Cam 5.2 and pan-cytokeratin in the identification of epithelial cells in lymph nodes.

**215 INTER-EXAMINER REPRODUCIBILITY OF ANORECTAL MOTOR AND SENSORY FUNCTION TESTS**

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**Background:** Anorectal physiological tests are used to influence management of benign anorectal disorders. However their inter-examiner reproducibility has not been well established. We assessed statistical reproducibility and reproducibility with respect to clinical significance.

**Methods:** 37 consecutive patients referred for routine anorectal problems were studied by two investigators, unaware of the other’s results, in random order, 30 minutes apart. Maximum anal canal resting (MPR), squeeze (SP) and involuntary contraction pressures (CP, pressure generated on coughing) were assessed using a water perfused manometry system; anal canal (AS) and rectal mucosal sensitivity (RS) to electrical stimulation using a bipolar ring electrode. [i] Inter-examiner reproducibility was assessed using the method by Bland and Altman (Lancet 1986, 1:307–310). The difference in measurements between 2 investigators was plotted against the average measurement of both investigators for each of the described tests, after a log transformation. [ii] Reproducibility with respect to clinical result (how often result was consistently within or outside the normal range) was also assessed.

**Results:** [i] For all the measured variables the largest differences between observers were found when the means were greater, which demonstrates that the data from the two investigators were in statistical agreement, and suited to log transformation. All measured parameters, apart from CP, were significantly reproducible. (ii) The percentage of inter-examiner results showing consistency in relation to a normal or abnormal outcome (within or without 2SD of normal mean) were: MRP 92%, SP 78%, CP 62%, AS 84%, RS 95%.

**Conclusions:** All tests, apart from CP were statistically reproducible. Therefore when these tests are performed using the same standardised technique one can have confidence in the numerical accuracy of the results. These tests are also usually consistent in producing a result which is abnormal, and therefore of particular clinical significance. CP provides only a rough guide to pelvic floor contraction, but is not a precise measurement. It may be best used as present or absent above a certain level.

**216 HYPOThERapy for irritAble bowEl syndrome: improvement is long-lAStIng and reduces heAltH care cosTs**

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**Background:** We have shown that hypnotherapy (HT) improves symptoms and quality of life (QOL) in patients with irritable bowel syndrome (IBS). This is now provided as a clinical service and this study presents long-term follow-up on a large group of patients treated.

**Method:** 239 IBS patients who had undergone HT between 1 and 5 years ago were contacted and asked to complete i) a validated IBS Questionnaire rating severity of symptoms and QOL (visual analogue scales), ii) the Hospital Anxiety and Depression Scale, and iii) a Subjective Assessment Questionnaire (SAQ) assessing effects of hypnotherapy, medication use and consultation rate.

**Results:** 178 patients returned questionnaires (74% response rate).

In the SAQ, 86% of patients had improved at the end of HT (62% of whom rated symptoms as very much better). 83% of these reported that, since finishing HT, symptoms had remained the same as at the end of HT or had continued to improve, while 17% had some deterioration. In addition, 59% of patients did not require any medication and 40% of those who did took it less often than previously. 75% consulted their GP and/or a hospital consultant less often about IBS symptoms and 49% less about other symptoms. All IBS measures in the IBS Questionnaire remained significantly better at follow-up than before HT (all p<0.001), with only slight deterioration in some compared with post-HT [pre-HT v post-HT v follow-up, median (IQR): pain severity: 5.4(7.75) v 2.5(10.5) v 3.3(18.5); pain frequency: 50(30.90) v 20.5(5.50) v 20.5(18.5); bloating: 62(50.80) v 25.7(50) v 39(23.50); bowel habit dissatisfaction: 74(58.97) v 35(27.52) v 38(33.66); life interference: 75(65.89) v 33(22.60) v 39(30.65); forming an overall score: 23.2(25.87) v 156.9249) v 175(118.268). Extra-colonic symptoms, QOL and HAD scores all also remained improved (all p<0.001).

**Conclusion:** This study confirms the long-term benefit of HT. In addition, the substantial reduction of medication and consultation rates highlights the significant economic advantages of this form of treatment.

**217 A PROSPECTIVE RANDOMISED CONTROLLED TRIAL OF CONSERVATIVE MANAGEMENT VERSUS OPERATION IN PROLAPSED THROMBOSED HAEMORRHOIDS**

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**Introduction:** Conservative management has been the mainstay of treatment of prolapsed thrombosed haemorrhoids (PTH). The aim of our study was to evaluate the role of operative management for PTH in a randomised trial.

**Methods:** Fifty consecutive patients (male -43; median age - 43 years; range – 23 to 76 years) were allocated to receive either conservative management or operation by computer generated random tables. Those managed conservatively (bedrest, analgesics, ointments) who failed to respond after 5 days were offered haemorrhoidectomy. End points assessed were: pain (visual analogue scale 0–10), outcome of treatment, duration of hospital stay, urinary retention and bleeding complications.

**Results:** Median (range) pain score in those with PTH receiving conservative management was 5 (0–10) compared with a median score (range) of 5 (0–10) following haemorrhoidectomy (P >0.05, N.S.). Conservative measures were successful in 13 (52%) of twenty-five patients compared with 24 (96%) of twenty-five patients who received operation (P < 0.05 – test of proportions) for prolapsed thrombosed haemorrhoids. Duration of hospital stay (median, range) in the conservative group was 8 days (2–10) compared with 5 days (2–6) in the operative group. Urinary retention was seen in 1 in 4% in the conservative group versus 3 (12%) in the operative group (P>0.05, N.S.) whilst bleeding complicated operation in one patient (P>0.05, N.S.).

**Conclusion:** Compared with conservative treatment, operative treatment of prolapsed thrombosed haemorrhoids resulted in symptom cure in a significantly greater proportion of patients. Furthermore, duration of hospital stay was less in those receiving operation. Even though there was a tendency towards a higher rate of urinary retention and bleeding after operation it was not statistically significant. We recommend haemorrhoidectomy as the treatment of choice for prolapsed thrombosed haemorrhoids.

**218 ELECTive coLectomy for diverticuLar disease?**

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**Introduction:** Colonic diverticular disease is a common problem in the Western world. Studies about the natural history of diverticular disease and the incidence of complications after an initial attack have reported varying outcomes. This has led to a debate on the value of elective colectomy in preventing complications of diverticular disease.

**Aim:** To assess whether the complications of diverticular disease requiring emergency or urgent surgical intervention are related to previous episodes of diverticulitis and if elective colectomy might prevent such complications.

**Methods and Materials:** A retrospective analysis was performed of all the patients who were admitted with complicated diverticular disease in two adjacent district general hospitals between 1995–2000 and information was recorded on the past history of these patients with regard to previous investigations or treatment for diverticular disease.

**Results:** A total number of 108 patients (42 males and 66 females) were admitted with complicated diverticular disease. Ninety eight
patients (91%) were emergency admissions and 10 patients (9%) were urgent admissions. Ninety eight patients (91%) underwent a Hartmann’s procedure. Two patients had a subtotal colectomy and 4 patients had a sigmoid colectomy with primary anastomosis. Four patients were not operated on due to their poor general condition. Out of the 108 patients, only 28 patients (26%) were previously diagnosed to have diverticular disease, either by barium enema or endoscopy. Eight of the twenty eight patients had required previous admissions for acute exacerbation of their symptoms, 3 having been admitted twice. Only 3 patients (2.7%) had needed treatment for acute diverticulitis with intravenous fluids and antibiotics. 

Conclusions: Our study has shown that elective colectomy after an attack of diverticulitis would not have a significant impact on the incidence of complications as most of them occur de novo in patients with no previous history of the disease. Further prospective studies are needed to be carried out with known diverticular disease to identify any further risk factors for development of future complications. This would help to identify a group of patients who may benefit from elective colectomy.

219 GASTROINTESTINAL SYMPTOMS AFTER RADIOTHERAPY FOR PELVIC CANCER

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Introduction: About 13,000 patients undergo pelvic radiotherapy annually in the UK. The incidence of severe GI toxicity (fistulation, bowel obstruction, transfusion dependent bleeding or secondary cancer) is not known but probably occurs in 4-8% at 5 years. More common are symptoms such as incontinence or diarrhoea which may significantly impair quality of life in >50% of long term survivors. Aim: To describe symptoms and outcomes of patients following pelvic radiotherapy referred to a specialist gastroenterology/GI oncology clinic during its first year.

Methods: Oncologists were offered direct flexible sigmoidoscopy for any patient with bright rectal bleeding without other symptoms, irrespective of proctoscopic findings. Other patients were reviewed in clinic. Data were recorded prospectively.

Results: Over 12 months, 60 patients were referred: 37 men, 23 women with a median age 64 years (range 38-80). Primary tumours sites included prostate (n=33), cervix (n=12), endometrium (n=7), bladder (n=3), large bowel (n=2), and anus, vagina and ovary (n=1 each). Radiotherapy was used a median 2 (range 0.5-21) years previously except in 3 patients referred to exclude inflammatory bowel disease before starting treatment. Major symptoms included rectal bleeding (n=27), frequency (n=22), faecal incontinence (n=19), diarrhoea (n=14), pain (n=8), steatorrhoea (n=5), subacute obstruction (n=4) and tenesmus (n=3). Eight patients described significantly abnormal bowel habit before starting radiotherapy. Of patients with bleeding alone (n=19), 1 had no radiation proctitis but was bleeding from mucosal prolapse, 3 had unsuspected advanced adenomas and 2 had squamous polyps. Sulfasalazine was always effective in reducing bleeding in those with radiation proctitis. All patients with tenesmus or incontinence alone or were cured with medical therapy including 2 patients with marked anal sphincter changes on endoanal ultrasound. Steatorrhoea was multifactorial, (2, bacterial overgrowth, 2 pancreatic insufficiency, 2 fatty acid malabsorption). Pain was associated with relapse in 50%. Two patients with obstruction required surgery.

Conclusions: Chronic GI symptoms after radiotherapy are often highly debilitating and complex to assess, but may respond dramatically to simple combination therapies. Patients with new onset rectal bleeding following radiotherapy should be offered at least a flexible sigmoidoscopy. Patients appear to benefit from being seen in a specialist setting.

220 TIMING OF OPERATION AFTER RADIOTHERAPY FOR RECTAL CANCER

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Aim: Preoperative adjuvant radiotherapy for rectal cancer has two problems, radio sensitivity and timing of operation. We have examined the effect of radiation and its timing on the relationship between apoptotic cell index (AI) and proliferative activity index (PI).

Methods: Patients were given one of three alternative modalities, standard radiotherapy (SD) [40Gy, 4 fraction of 4-8weeks, n=23], short-course radiotherapy (SC) [25Gy, 1-2weeks, n=11], or chemoradiotherapy (CR) [45Gy, 6-9weeks, n=7]. AI and PI were estimated in paired sections of biopsies and post-irradiated resected tumours. The reduction ratio was histologically estimated and radiosensitive was judged in cases in which over 2/3 of tumour tissue was destroyed.

Results: Radiosensitive ratio and median reduction ratio were 43.5% and 45% in SD, 27.3% and 25% in SC, 26.8% and 45% in CR, respectively. In SD, the AI was significantly higher (5.9 v.s 2.7; p= 0.001) and the PI was significantly lower (33.9 v.s 50.0; p=0.028) than in the pretherapy biopsies. In SD, the PI in the radio sensitive subgroup was lower than in the radiosensitive one [25.9 v.s 46; p=0.005]. However, the AI of radiosensitive subgroup was lower than that of resistant one [2.4 v.s 4.2; p=0.005]. Plotting each AI according to time course from finishing radiotherapy to operation in SD showed that the slope in the radiosensitive subgroup was steeper than in the radioresistant one and extrapolation back to the time of radiotherapy (day 0), suggests that in the radiosensitive subgroup would have a high AI. The difference between two slopes means that in radiosensitive subgroups, the apoptotic response was significantly more than that of resistant one (2.4 v.s 4.2; p=0.005). Plotting each AI against radiotherapy ratio revealed that the AI was proportional to the size of the residual tumour volume (low in the radiosensitive).

Conclusions: Apoptosis may be a time- limited and volume- dependent phenomenon; radiosensitive tumours should be surgically resected earlier than the more resistant ones.

221 RANDOMISED CONTROLLED TRIAL OF BIOFEEDBACK FOR FAECAL INCONTINENCE

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Background: Behavioural treatment (biofeedback) has been reported to improve symptoms in a majority of patients with faecal incontinence, but there are no trials comparing biofeedback with placebo or standard medical care.

Methods: 171 consecutive patients with faecal incontinence to solid or liquid stool were assessed by anal ultrasound and then stratified to structurally intact or disrupted anal sphincter muscles. Within each of these two groups they were then randomised to one of four groups: (1) standard medical/nursing care [advice] (2) advice plus verbal instruction on sphincter exercises (3) hospital based computer-assisted sphincter pressure biofeedback (4) hospital biofeedback plus use of a home EMG biofeedback device. Outcome measures immediately and at one year included diary, symptom questionnaire, continence score, patient’s rating of change, quality of life (SF36 and disease specific), psychological status (HAD), and anal manometry.

Results: Improvement or cure occurred in groups 1 to 4 respectively: 80%, 83%, 81%, and 76% (p=NS). Overall, 75% of patients had symptomatic improvement and 5% were “cured”. Major benefit was more likely if patients had structurally intact sphincters. Benefit was maintained for all groups at one year. Episodes of incontinence decreased from median 2 to 0 per week (p<0.001). Continence score (worst = 20) decreased from median 11 to 8 (p<0.001). Disease specific quality of life, SF36 (vitality, social functioning and mental health), and HAD (anxiety and depression) all significantly improved. Patients demonstrated improved resting, squeeze and sustained squeeze pressures (all AI against reduction ratio revealed that the AI was proportional to the size of the residual tumour volume [low in the radiosensitive]).

Conclusions: Conservative therapy for faecal incontinence improves continence, quality of life, psychological well being, and sphincter function. Benefit is maintained in the medium term. The pretherapeuter interaction and improved coping strategies appear to be most important, rather than physiological feedback of sphincter function (biofeedback).

222 FAECAL CALPROTECTIN: NORMAL LEVELS IN A LATE MIDDLE-AGED POPULATION, EFFECTS OF LIFESTYLE FACTORS AND RELATION TO BOWEL SYMPTOMS

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Background: Faecal calprotectin is more sensitive but less specific than faecal occult blood (FOB) in the detection of colonic neoplasms (Tibble et al, Gut 2001). Little is known about levels in a late middle aged population, which would be the target for screening, and factors...
that determine levels. Furthermore it is unknown whether elevated levels are associated with symptoms, diarrhoea in particular.

Aims: To assess levels of faecal calprotectin and the factors that could effect them in a healthy late middle aged population and to assess the association with symptoms.

Methods: 230 asymptomatic subjects (115 male, 75 female) aged between 50 and 70 were recruited randomly from GP lists in South London. Subjects with IBD or a history of colorectal cancer (CRC) were excluded. A previously validated lifestyle questionnaire was completed and a stool sample analysed for calprotectin by ELISA.

Results: Faecal calprotectin was bi-modally distributed, with 46/230 (20%) of subjects having levels above the reference range (10mg/l). There was no association between NSAID use, units of alcohol consumed in the previous week, being a current smoker, daily bowel frequency, or presence of abdominal pain or constipation in the previous week and faecal calprotectin. Males had higher calprotectin levels than females (median 1.9 IQR 7.6 v 0.5, 2.8 p=0.0001). 65% of subjects in the 3rd calprotectin tertile (C.T.) were past smokers v 45% of subjects in 1st C.T. (p=0.06). Mean cigarette pack years of smoking increased through each C.T. 9.8, 10.5, 17.9 (p=0.009). 20% of subjects in the 3rd C.T. had suffered an episode of diarrhoea in the previous week v 12% in the 1st C.T. (p=0.05). Mean age increased in each C.T. 58.9, 60.5, 60.8 (p=0.03).

Conclusion: Smoking history, diarrhoea in the previous week, increase in age and male sex are all associated with an increasing faecal calprotectin. Adjustment of values for the above variables may increase faecal calprotectins specificity as a screening marker for CRC.

223 IS CONSTIPATION A CONSEQUENCE OF GROWING OLDER?

Background: The number of GP visits for constipation increases markedly among people over 60. Nevertheless, there is no good evidence that ageing per se affects colonic function. The association between age and constipation may be confounded by factors such as institutionalisation, inactivity and chronic disease.

Aim: To assess the prevalence of functional constipation according to the Rome II diagnostic criteria and institutionalisation, physical activity and chronic disease.

Methods: Ethical approval was obtained from South Bank University Ethics Committee. 50 FL subjects (mean age 74 years, range (65–97), 42% male) and 42 INS subjects (mean age 84 years, range (69–101) 36% male) were recruited. Bowel habit was recorded using a 7-day bowel habit diary. Subjects were classified as constipated according to Rome II diagnostic criteria, if they experienced at least 2 of the following: less than 3 defecations per week, straining on more than 25% of occasions, feelings of incomplete evacuation on more than 25% of occasions. Statistical analyses were performed using the Ttest and Chi-square, as appropriate.

Results: Since the INS group was significantly older than the FL group, the mean ages of constipated and non-constipated subjects were assessed in each group separately. There were no significant differences in age between constipated and non-constipated subjects. Constipation was associated with institutionalisation (χ²=9.9, p=0.003) and inactivity (χ²=12.2, p=0.001). Although 65% of constipated subjects suffered from more than one chronic disease, this association was not statistically significant.

Conclusions: This study suggests that the prevalence of functional constipation is associated to factors related to ageing such as institutionalisation and inactivity. However, no association was found with chronic diseases.

224 K-RAS MUTATIONS IN COLORECTAL POLYPS: SITE, HISTOLOGY AND SIZE DO MATTER
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Introduction: Mutation of the oncogene Kras is thought to be important in the early progression of colorectal carcinogenesis. Kras is involved in the cell signalling pathway and its mutation causes uncontrolled cell proliferation. The aim of our study was to assess the relationship between K-ras mutations and various characteristics of colorectal polyps such as: site, size and histology.

Results: K-ras mutations were found in 21% of 55 polyps; none of the controls had mutations. Of the 15 rectal polyps 33% had a mutation; whereas only 18% of the 40 colonic polyps had a mutated Kras. 36 polyps were <1cm (mutation rate 8%) and 19 polyps were >1cm. These larger polyps had a higher K-ras mutation rate of 47%. Histological type was also analysed; revealing that 39% of the tubulovillus/villous polyps had a mutation, compared to much lower levels of mutations in tubular (9%) and metastatic polyps (0). No difference in mutation rate was found in varying grades of dysplasia in our study.

Discussion: This small study reveals that K-ras mutations in our population tended to be associated with polyps having a rectal location, a larger size and villous histology. Further studies are needed to understand the role of this important oncogene in adenoma growth and progression to carcinoma.

225 DO CYTOKINE LEVELS PREDICT PROGNOSIS IN COLORECTAL CANCER?
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Suppression of the immune system and cytokine production, as an essential function of the immune response, in patients with colorectal cancer has been extensively investigated. The aim of this study was to determine the predictive prognostic value of cytokine levels before & after treatment in patients with colorectal cancer.

Methods: Heparinized venous blood samples were taken from thirty-three patients (14M & 19F) with primary colorectal cancer before and at least 10 weeks after operation. Patients who had preoperative radiotherapy had blood samples taken before radiation therapy. Interferon (IFN) γ, Interleukin (IL) 10 and Tumour necrosis factor (TNF) α levels were measured by lipopolysaccharide stimulated blood cultures. The patients were followed up in a Colorectal Cancer Clinic for evidence of local recurrence, distant metastases and survival.

Results: Patients with high preoperative levels of IFN γ developed distant metastases later than those with lower levels. (Correlation coeff=0.812 at P=0.05) Similarly, those with high postoperative IFN γ levels developed local recurrence later than those with lower levels. (Correlation coeff=1 at P=0.01) IL 10 & TNF α levels did not show a similar correlation. Higher levels of postoperative IL 10 levels were associated with development of metastatic disease. (Correlation coeff=0.853 at P=0.002) Higher TNF α levels before preoperative radiotherapy were associated with a longer survival in patients with rectal cancer. (Correlation coeff=0.829 at P=0.04) Similar TNF α levels without preoperative radiotherapy did not appear to confer the same survival advantage.

Conclusions: Higher levels of pro-inflammatory cytokines (TNF α, IFN γ) were associated with a better outcome in terms of time to local recurrence, distant metastases and survival. Higher levels of immuno-suppressive cytokine (IL 10) were related to the development of distant disease. Those with lower levels of pro-inflammatory cytokines before treatment, and those with higher postoperative levels of immuno-suppressive cytokines need close surveillance for the development of loco-regional or systemic relapse.

226 SUCCESS OF A SIMPLE “TICK BOX” GP REFERRAL FORM FOR COLORECTAL CARCINOMA AND ITS IMPACT ON ACHIEVING THE “2 WEEK WAIT” TARGET
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Introduction: In June 2000 the UK government introduced the target that a hospital specialist should see all patients with suspected GI cancer within 2 weeks of GP referral. With unlimited resources, all patients with any symptoms could be seen and immediately investigated, but in the UK methods to stratify patients in terms of risk of serious pathology are needed to ensure urgent investigation of patients at the highest risk.

Methods: We introduced a simple 10-question tick-box GP form for referral of all patients with rectal bleeding and change of bowel habit, which could be e-mailed or faxed directly to the endoscopy
Management of Peptic Ulcer Disease in Primary Care: Implications and Success of the Two-Week Referral Criteria

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Aim: Eradication of H. pylori infection in patients with peptic ulcer disease patients reduces the need for long term acid suppression therapy and the risk of complications such as bleeding and perforation. Patients with this diagnosis therefore can continue to be treated with acid suppression therapy in primary care. We aimed to assess the extent to which these patients had been investigated for H. pylori infection and identify a population who might benefit from H. pylori testing and eradication.

Methods: From 11,149 patients who had received acid suppression therapy in primary care, we undertook case note review and identified 3071 (27.5%) patients who had previously diagnosed peptic ulcer disease (77.2% DU, 13.1% GU, 6.1% both, 3.5% unspecified ulcer type). 2063 patients were receiving maintenance therapy (defined as ≥3 prescriptions/year). Of these, 1275 who had no contraindication to H. pylori eradication were invited to nurse led clinics for H. pylori testing: 705 attended and underwent 13C urea breath testing to establish H. pylori status.

Results: Only 36.4% of patients identified with known peptic ulcer disease had previously received eradication therapy. 26.9% were taking NSAIDs concomitantly (53.6% aspirin, 37.7% other NSAIDs). Of these, 60% had never had documented eradication therapy and, although lower if patients had prior eradication therapy, 23.0% of previously treated ulcer patients remained infected at the time of testing.

Conclusions: A substantial proportion of ulcer patients receiving acid suppression therapy in general practice have never received H. pylori eradication and almost a quarter of those previously treated remain infected with the organism. There is considerable potential for improvement in the management of this easily identifiable patient group but post treatment testing is important to establish eradication of infection.

228 SERVICE IMPLICATIONS AND SUCCESS OF THE IMPLEMENTATION OF THE TWO-WEEK REFERRAL CRITERIA FOR UPPER GASTROINTESTINAL CANCERS IN A DISTRICT GENERAL HOSPITAL

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Introduction: The introduction of 2-week criteria in July 2000 has added a significant burden to the provision of gastroenterology services. The targets are not proven to improve outcomes for patients found to have cancer and it is unclear how effectively they are applied by primary care physicians. This study addresses the appropriateness of referrals, the success in meeting the criteria and the pickup rate for upper GI tumours.

Methods: Data were collected prospectively by a specialist nurse. Patients referred from primary care within ‘2 week criteria’ and those who were thought to meet the criteria but were not referred through that route were included. Time to first consultation (clinic or gastroscopy) was recorded. The final diagnosis and outcomes when available are also recorded.

Results: 149 patients are included in the study. Their average age (range) is 67(19–92). 79 were referred by ‘two week criteria’ and the others were reprioritised by the consultant reading the referral. Gastroscopy was performed in all cases. This was achieved in an average of 9 days (range 1–14) for those referred by 2-week criteria and 15 (range 7–35) days in those thought to meet the criteria but not referred by that route. There were 25 extra cases per month when the system was established. 14 malignancies were identified (9.4%). 12 cases were identified correctly by GP application of 2-week criteria (15.2%). 2/70 further malignancies were identified by consultant interpretation of routine referrals (2.9%).

Conclusion: The application of the 2-week criteria for upper GI cancers has led to an additional 25 procedures/month. Primary care physicians achieved a cancer pickup rate of 15.2%. Additional case finding by assessment of other referrals seems to have little additional benefit.

229 RABEPRAZOLE 20 MG COMPARED WITH ESOPEMPRAZOLE 40 MG IN THE CONTROL OF INTRAGASTRIC PH IN HEALTHY VOLUNTEERS

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Purpose: To compare the effects of single doses of rabeprazole (RAB) 20 mg and esomeprazole (ESO) 40 mg on intragastric pH in healthy H. pylori-negative volunteers.

Methods: 27 H. pylori-negative subjects underwent two 24-hour treatment periods, washout by 14 days, with a 2-way, single-dose study comparing RAB 20 mg with ESO 40 mg. Intragastric pH was recorded over 24 h on Days 0 and 1 of each period. Percentage of time that intragastric pH >3 and >4 during each 24 h interval, and area under the intragastric pH-time curve (AUC<sub>pH>3</sub>, AUC<sub>pH>4</sub>) were calculated, and compared using ANOVA.

Results: There were no statistically significant differences in mean AUC<sub>pH>3</sub>, mean percent time pH >4 and mean percent time pH >3 between RAB and ESO treatments on Day 0 (pre-dose) or Day 1. On Day 1, mean percent time pH >4 after RAB 20 mg was 43.1 (SD=18.3) and after ESO 40 mg was 45.2 (SD=17.1); mean percent time pH >3 after RAB 20 mg was 54.8 (SD=18.3) and after ESO 40 mg was 54.9 (SD=15.1). For intragastric pH control during the nighttime hours (14–24h post dose), mean percent time pH >3 and >4 was significantly higher on RAB 20 mg than ESO 40 mg (pH >3: 42.1%, SD=23.5 and 22.1%, SD=21.3; pH >4: 32.4%, SD=24.1 and 17.0%, SD=14.9, respectively; p=0.001). During daytime hours, mean percent time pH >3 and >4 was significantly higher on ESO 40 mg than RAB 20 mg (pH >3: 76.2%, SD=15.7 and 63.8%, SD=20.7, respectively; pH >4: 64.5%, SD=21.5 and 50.7%, SD=21.3, respectively; p=0.02).

Conclusion: Over a 24 h period, there was no difference between RAB 20 mg and ESO 40 mg with respect to effects on intragastric pH. In the morning, the effects of ESO were greater than those of RAB, whilst during the nighttime hours, the effects of RAB were greater than those of ESO. These results concur with published data on the effects of RAB and ESO on intragastric pH. This research was supported by Eisa Ltd, London, UK.

230 "TEST AND TREAT" A PILOT STUDY OF A COMMUNITY BASED C<sup>13</sup> UREA BREATH TEST SERVICE (C<sup>13</sup>UBT)

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H pylori (HP) "test and treat" strategies have been shown to be effective and safe in the management of uncomplicated dyspepsia in under 45 year olds and may reduce endoscopy demands. Non-invasive HP tests include serology, breath tests and recently a faecal antigen test. Near patient tests have been shown to be unreliable, serology does not allow early follow up assessment. UBT allow non-invasive pre and post treatment assessment of HP. C<sup>13</sup> based tests cannot easily be used in the community.

Aims: To assess the practicability, accessibility, appropriate use and effectiveness of a C<sup>13</sup>UBT service in the community of North Cumbria.
Methods: Two practices were recruited to act as local C13 UBT sites and clinics led by a single nurse specialist for 6 months. Criteria for referral; age >18, <45, new onset uncomplicated dyspepsia, no NSAID, no PPI. After a 4 hour fast, CO2 samples were taken at baseline and 30 minutes post ingestion of C13 labelled urea with orange juice. CO2 samples were analysed (Cumberland Infirmary, Carlisle, PDZ Europa C13 analyser) and result returned to GP within 24 hours. Subsequent management and outcome was monitored and nurse recorded any problems encountered during the process from referral to treatment.

Results: 55 referrals (34F, 21M), 17 HP +ve, 38 –ve. 78.2% were tested within 1 week of referral (10 deferred at patient request) 6 tests deferred because not fasted, 3 taken medication. 2 patients were >45, 36 patients had had symptoms for >6 months, 2 previous eradication failures. Control ECs significantly proliferated at 48, 72, and 96 hrs. An MTT proliferation assay quantified EC proliferation, ECs were exposed individually to the two NSAIDs for 24, 48, 72, and 96 hours.

Conclusion: Rapid HP testing was achieved with a low endoscopy rate. Changes to information sheets avoided further problems with pre-test preparation. Central booking would allow patient choice of test site. These figures translate to ∼1850 C13 UBT but only 166 endoscopies per year for this age group if extended to the whole of North Cumbria.

### Abstract 232

**ALOE VERA GEL STIMULATES PGE2 PRODUCTION AND COX2 EXPRESSION IN GASTRIC CARCINOMA CELL LINES**

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**Background:** Aloe vera gel (AV) is the mucilaginous aqueous extract from the leaf of Aloe barbadensis Miller. It is a widely used herbal remedy for inflammatory conditions and digestive disorders. It is claimed to have anti-ulcer effects. Gastric epithelial cells produce COX2 and prostaglandins in response to ulceration as part of mucosal healing.

**Aims:** To determine the effects of AV on production of PGE2 and expression of COX2 by gastric epithelial cells in culture.

**Methods:** MKN7 and MKN 45 gastric cell lines were cultured in vitro in RPMI medium containing increasing concentrations of AV gel for 24 hrs. PGE2 production was measured in the culture supernatant by EUSA. Western blotting was used to detect COX2 expression by cells. Results were corrected for cell numbers estimated by MIT assay.

**Results:** Incubation of both MKN7 and MKN 45 cell cultures with AV gel at 1:10 dilution produced significant increases in PGE2 production compared with control incubations. Higher dilutions of AV had no effect. Control experiments showed the effects of AV were not mediated solely by its low pH (6.8 at 1:10 dilution). PGE2 concentrations (pg/ml, median and range, n=5) for each cell line (*p<0.005 versus controls) are shown in the table.

**Conclusion:** The stimulatory effect of aloe vera gel (in a concentration likely to be to found in the stomach after an oral dose) on PGE2 production and COX2 expression by gastric cell lines suggest that this herbal remedy is worth assessing for the treatment and prevention of peptic and NSAID-induced gastroduodenal ulceration.

### Abstract 233

**PEPTIC ULCER IN GENERAL PRACTICE IN ENGLAND AND WALES 1994–1998: A DISEASE IN DECLINE**

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**Background:** While hospital admission rates in England and Wales for complicated peptic ulcer has increased among older people, little is known about its prevalence in the community.

**Aims:** To analyse recent time trends in England and Wales in the prevalence of peptic ulcer, based on the proportion of the population who had been seen either by the general practitioner or a hospital doctor, during each one-year period. The drug treatment for peptic ulcer was also studied.

**Methods:** For each year between 1994–98, information on the age, sex and drug treatment for patients with peptic ulcer was extracted from the General Practice Research Database. Age-sex specific prevalence and treatment rates were then calculated.

**Results:** See table. The decline in age-standardised prevalence was more evident among people aged less than 65 (60% for males,

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**Table 1:**

<table>
<thead>
<tr>
<th>Prevalence/ 1000 persons</th>
<th>1994</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Female</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Age standardised prevalence</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Prevalence &lt;65 years</td>
<td>3.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Prevalence &gt;65 years</td>
<td>5.9</td>
<td>3.9</td>
</tr>
<tr>
<td>% prescribed PPI</td>
<td>53.1</td>
<td>51.6</td>
</tr>
<tr>
<td>% prescribed H2 antagonist</td>
<td>72.3</td>
<td>70.8</td>
</tr>
<tr>
<td>% prescribed COX2 antagonist</td>
<td>41.2</td>
<td>44.7</td>
</tr>
</tbody>
</table>
234 A PROSPECTIVE STUDY OF GASTROENTEROLOGY CONSULTATIONS IN AN URBAN TEACHING HOSPITAL

S. Bohra, M.F. Byrne, D. Manning, C. Smyth, S.E. Patchett, F.E. Murray. Dept of Gastroenterology, Beaumont Hospital, Dublin, Ireland

Consultation between individual specialities is common and little studied. Gastroenterology consultations account for a substantial workload for the GI team. The aim of this study was to prospectively analyse the referral patterns and outcome for Gastroenterology in-patient consultations in a teaching hospital over a five month period.

242 consecutive in-patients consultation to the GI service were analysed. All patients were initially evaluated by a GI registrar prior to being seen by one of the two consultants. The patients were referred by 32 consultants from various specialities. Average delay before consultation was less than the working day. The referral sources were predominantly from medicine, surgery, nephrology and neurosciences. The commonest reasons for referral were abdominal pain (15.8%), PEG tube insertion (13.6%), diarrhoea (12.8%), and normal abdominal blood tests (10%). Ongoing care for previous problems was less than one working day. The referral reasons were predominantly from medicine, surgery, nephrology and neurosciences. The commonest reasons for referral were abdominal pain (15.8%), PEG tube insertion (13.6%), diarrhoea (12.8%), and normal abdominal blood tests (10%). Ongoing care for previous problems was less than one working day.

The provision of the GI inpatient consultation services constitutes a significant and increasing proportion of the workload in Gastroenterology. Major problems assessed were dealt with satisfactorily in a consultation setting, with only a minority requiring transfer to a Gastroenterology team during inpatient stay but a significant percentage required endoscopic procedures and follow up at a GI clinic after discharge. Consultations for PEG tube insertion was especially worthwhile.

235 GASTRODUODENAL MUCOSAL DAMAGE IN MAJOR BURNS: HOW SIGNIFICANT IS IT?

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Introduction: Acute gastro-duodenal mucosal injury has been known to be associated with major burns. The aim of this study was to assess the incidence and rationale of giving prophylactic acid suppression treatment to all patients with major burn injury.

Patients and Methods: 18 patients (13 females, median age 23 years, range 14-42) with major burn injury (Burn surface area >20%) admitted over 20 months were analysed. The aetiology was flame burns (10), hot water burns (5), and acid burns (3). All patients were received within 6 hours of injury. Initial fluid resuscitation was performed according to the Parkland regime. Non-stereoidal anti-inflammatories and acid suppression were not employed. All patients were subjected to upper gastrointestinal endoscopy (UGE) between 24-72 hours after admission and antral mucosal biopsy was obtained. UGE was repeated a week later. Histology samples were evaluated by a single blinded pathologist.

Results:
1. 2(11.1%) Patients had mild upper abdominal pain.
2. 2(11.1%) Patients had abnormal UGE findings during the first endoscopy: (1) superficial gastritis, 1 (erosive gastritis). 3(16.7%) Patients had abnormal endoscopic findings during subsequent endoscopy: (2) superficial gastritis, 1 (erosive gastritis).
3. No Peptic ulcers were detected in any of the patients.
4. 8(44.4%) Patients had mild histological changes (7-mild acute inflammatory changes, 1-chronic inflammatory changes).

Conclusion: This study shows that there was no endoscopic evidence of serious gastro-duodenal mucosal injury in patients with major burns. Furthermore, antral mucosal histology revealed only mild inflammatory changes. The use of prophylactic acid suppression in major burns may be questioned. Further studies are required to evaluate the incidence of major burns.

236 NSAID AND PEPTIC ULCER DISEASE: A RANDOMISED TRIAL OF OMEPRAZOLE 20 MG VERSUS 10 MG FOR MAINTENANCE OF REMISSION AFTER PEPTIC ULCER HEALING AND HELICOBACTER PYLORI ERADICATION

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Background: The role of H. pylori eradication in NSAID users with peptic ulcer disease is controversial especially in countries with a high prevalence of the infection. Also, the value of low dose Omeprazole for maintenance of remission is not yet known.

Patients and methods: 138 symptomatic outpatients receiving continuous Cox 1 NSAID therapy, were treated with Omeprazole 40mg/day upon endoscopic confirmation of gastroduodenal ulceration or erosions while those infected with H. pylori received in addition Clarithromycin 500 mg and Amoxicillin 1000 mg twice daily during the first week of treatment. After endoscopic confirmation of healing at the end of week 5 (n=116), the patients were randomised to receive Omeprazole 10 mg (n=50) or 20 mg once daily (n=64) and endoscopy repeated after 20 weeks. No patients discontinued treatment because of adverse effects of the drugs and efficacy results are for patients completing the trial protocol.

Results: The overall healing rates at five weeks (n=130) was 89.1% (95% confidence limits 84.7–93.5) while in 86.3% (81.2–89.1) eradication was successful. The healing rate for the H. pylori eradicated patients (n=65) was 89.2%, for those who failed eradication (n=11) it was 72.7% (NS). While for patients not infected with H. pylori (n=44) it was 96.1% (NS). After 20 weeks of Omeprazole prophylaxis with the 10mg dose (n=45), 91.1% (86.1–95.8%) had maintained healing while for the 20mg dose (n=60) a similar figure was observed (96.7%, 91.1–99.9%; NS). Of the nine patients who had persistent H. pylori infection, two were not captured before the endoscopy.

Conclusion: In a Middle Eastern population with NSAID induced gastro-duodenal lesions, H. pylori eradication and high dose Omeprazole treatment were not associated with impaired ulcer healing. After eradication, Omeprazole 10 or 20 mg per day were highly and equally effective for maintenance of gastrroduodenal mucosal integrity during continued NSAID use.

237 WARFARIN ANTI-COAGULATION CONTROL IN PATIENTS TAKING PROPON TUM INHIBITORS

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Background: There is evidence that proton pump inhibitor (PPI) use can increase the prothrombin time in healthy volunteers taking warfarin. However, no studies have been carried out to investigate the effect of PPIs on anti-coagulation (AC) control in patients requiring warfarin therapy. Therefore we tested the hypothesis that PPI therapy worsens AC control in patients attending an AC Clinic.

Methods: The Leeds AC Clinic database was analysed retrospectively. We collected data on patient age, indication for and duration of AC, PPI use and warfarin dose. We also obtained all the INR values for each patient. INR control was expressed as the percentage of INR values above, within or below the target range for each individual.

Results: 14.8% (n=503) of patients were taking a PPI (omeprazole, n=310 [61.7%]; lansoprazole, n=167 [33.2%]; pantoprazole, n=15 [3%]; rabeprazole, n=8 [1.6%] and esomeprazole, n=3 [0.6%]). There were 2885 (85.2%) patients not taking a PPI (non-PPI). The proportion of patients in each group who were receiving AC for AF or venous thrombo-embolic disease was similar (PPI 75.7% vs non-PPI 74.4%). For all patients, the mean percentage of INR values above the target range was 19.8%, in the target range 49.6% and below the target range 30.6%. Comparative values for non-PPI patients were 17.6% (p<0.001; Student’s t test) 52.6% (p<0.001) and 29.8% (p=0.32). However there was no significant difference in mean INR value, warfarin dose or duration of therapy between the two groups. The two groups did differ with respect to age (PPI, mean 72.4 yrs vs non-PPI, 70.8 yrs; p=0.005) and frequency of INR testing (PPI, every 53 days vs non-PPI, 47 days; p=0.017). Logistic regression analysis confirmed that percentage of INR values in the target range, patient age and test rate were all significantly different between PPI and non-PPI patients (all p<0.01).
Aim: To assess the clinical practice of hospital doctors across United Kingdom in eradication of Helicobacter pylori.

Methods: The study was carried out between October 2000 and May 2001 during which time a questionnaire was sent to 130 gastroenterologists and 130 general and upper G.I surgeons across United Kingdom inquiring the following: (1) The pathological conditions in which they chose to eradicate the organism - Gastric atrophic/reflux disease (GORD), gastritis, gastric ulcer, gastric erosions, duodenal ulcer, duodenitis, non-ulcer dyspepsia (NUD), a combination of some of the conditions and (2) the type of regimen used.

Results: 61.5% gastroenterologists and sixty-two (47.5%) surgeons replied to the questionnaire. The over all response rate was 55%. Almost all gastroenterologists and surgeons recommended treatment for eradication in duodenal and gastric ulcer disease. However, there were wide variations in recommending eradication therapy for patients with NUD and GORD. Fifty gastroenterologists (62.5%) and thirty-two (51.6%) surgeons did not recommend eradication therapy for patients with GORD while 47.5% of gastroenterologists and 53% of surgeons did recommend eradication in patients with NUD. 24% of gastroenterologists and 18% of surgeons had not considered eradication at all in gastritis while in patients with duodenitis, 17.5% of gastroenterologists and 11.3% of surgeons did not favour eradication of the organism. Majority of surgeons and gastroenterologists favoured triple therapy using combination of proton pump inhibitor, clarithromycin and amoxicillin.

Conclusions: In this study, we have noted wide variations in the practice of gastroenterologists and surgeons across United Kingdom in advising eradication therapy for H. pylori positive patients in various upper GI conditions. While there is a general consensus in the mode of therapy offered, there seems to be varied practice in eradication of the organism in conditions such as NUD and GORD.

A 5-YEAR, DOUBLE-BLIND, RANDOMISED COMPARISON OF RABEPRAZOLE AND OMEPRAZOLE IN GORD MAINTENANCE TREATMENT: GASTRIC BIOPSY RESULTS

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Background: Although long-term treatment with proton-pump inhibitors is generally considered safe, there is still little evidence from prospective studies about the effect of such treatment on the gastric mucosa.

Objectives: The primary objective was to assess efficacy in preventing GORD relapse. The secondary objective reported here was to assess the effect of 5 years' treatment with rabeprazole or omeprazole on the gastric mucosa.

Methods: 243 patients were randomised to double-blind treatment with rabeprazole (10 mg or 20 mg) or omeprazole (20 mg) once daily for up to 5 years. Biopsy samples were taken from the corpus and antrum after 13, 26, and 52 weeks, and annually thereafter.

Results: The percentage of patients with H pylori infection fell substantially during the study in all groups, but only in the 10 mg rabeprazole group in the corpus. Inflammation, activity of inflammation, and atrophy in the corpus, which generally improved during the study, except inflammation in the corpus, which improved only in the 10 mg rabeprazole group and clinical and little in the other groups, and atrophy in the corpus, which became more marked in all groups. Argyrophil ECL cell hyperplasia was generally mild, with no dysplasia or neoplasia observed in any patient. However, it became less marked during the study in the rabeprazole groups, but tended to increase in the omeprazole group.

Conclusions: Treatment with 10 or 20 mg rabeprazole or 20 mg omeprazole once daily for 5 years is largely free of deleterious effects on the gastric mucosa. Features of the gastric mucosa were more affected by H pylori status than by treatment, few differences being observed among the treatments.
60±2.1, range 18–96). Ten patients were on non-aspirin NSAIDs (four men, mean age 52±8, 18–96) of whom three were on lower-risk formulations. None of these ten patients were co-prescribed gastro-protective drugs, one patient each was on aspirin and corticosteroids in addition to the NSAID. Eight patients on NSAID had significant co-morbid disease, five of whom were aged over 65 years. No patient on NSAID had a history of PUD. Twenty-three patients (17 aged ≥65, 2 with PU history) were taking aspirin. Only one was co-prescribed a gastro-protective drug.

Summary: Patients who presented with an upper GI bleed while on NSAIDs were not prescribed NSAIDs in accordance with locally agreed guidelines. NSAID-associated ulcer complications could be reduced by better prescribing.

**Immunology/Infection/Inflammation posters 242–257**

**242 IDENTIFICATION OF POSSIBLE GUT HOMING DENDRITIC CELLS IN PERIPHERAL BLOOD BY EXPRESSION OF β7 INTEGRIN**
R.J. Rigby1, A.L. Hart1,2, E. D. A. Westcott3, M. A. Kammi, A. Windsor, S. C. Knight, A.J. Stagg1. 1Antigen Presentation Research Group, Imperial College at Northwick Park, 2St Mark’s Hospital, London, UK

Dendritic cells (DC) are amongst the earliest cells to recognise enteric antigens and shape T cell responses. At least in part, DC in the tissues are derived from immature circulating DC populations. Gut DC may be functionally different from DC at other sites and contribute to the special features of intestinal immune responses. Given that there are markers on peripheral blood DC precursors that identify skin homing cells (CD1c and CLA), this study aimed to identify peripheral blood DC destined to home to the gut. We examined DC expression of β7, an integrin associated with mucosal homing of lymphocyte populations.

**Methods:** DC were identified by multi-colour flow cytometry as an HLA-DR-lineage (CD3, CD14, CD16, CD19, CD34, CD56) population in peripheral blood and in mononuclear cells extracted from the lamina propria of the colon or small intestine. Co-expression of β7 with CD11c, CD1c and CLA was assessed.

**Results:** Gut DC from both the small and large intestine expressed β7 integrin. In blood, most DC expressed β7 but they were heterogeneous for the level of expression and for co-expression of the molecules associated with skin homing. Both myeloid and plasmacytoid DC were studied. All CD11c+‘myeloid’ DC were β7++, with some also expressing skin-homing molecules. CD11c+‘plasmacytoid’ DC, which are thought to migrate directly into lymphoid tissue, comprised two subpopulations, β7− and β7+. Neither of these populations expressed the skin homing markers CLA or CD1c.

**Conclusions:** It appears that DC with markers associated with homing to the gut mucosa can be identified in the peripheral blood. A population of DC, β7hi CD11c+, that may migrate directly into lymph nodes draining the gut, has been identified. Circulating precursors of gut DC that are functionally committed to specialised roles in the intestine may provide an early target for manipulating mucosal immune responses.

**243 NEUTROPHIL RESPIRATORY BURST AND TISSUE PENETRATION ARE NORMAL IN CD DURING G-CSF ADMINISTRATION**
M. Harbord1, R. Day1, A. Hankin1, S. Bloom1, A. Forbes1, A.W. Segal1. 1Department of Medicine, University College, London; 2St Mark's Hospital & Academic Institute, Imperial College, London, UK

**Background:** Neutrophil migration into the tissues is defective in Crohn’s disease (CD). Granulocyte Colony Stimulating Factor (G-CSF) has been used to treat CD. The effects of G-CSF in CD on venous neutrophil respiratory burst (B) and neutrophil tissue penetration (P) are unknown.

**Aim:** To measure B&P in CD and matched control subjects.

**Method:** 16 outpatients were entered (CD n=8, 4518 years, 3 male; control: n=8, 4217 years, 7 male). Subcutaneous G-CSF (Lenograstim) 5ug/Kg was administered at 24 & 48 hours. Venous neutrophils were purified at 24 & 72 hours by Hypaque-Ficoll gradient centrifugation after erythrocyte osmotic lysis. Oxygen consumption of 1x10⁶ neutrophils was measured in an oxygen electrode after stimulation with autologously opsonised human fetal flora (1x10⁵) or with PMA (1ug). Duplicate skin blisters were induced at 0 & 48 hours by applying 0.1% contractin in 25% acetic acid to 0.8cm² paper discs on the forearm, which were covered with parafilm and an adhesive dressing. At 24 and 72 hours the blister fluid was removed. The cellular composition was counted microscopically. Flow cytometry using anti-CD11b and anti-CD14 antibody labelling together with light scatter properties were used to quantitate neutrophils and monocytes/macrophages respectively.

**Results:** Increase in venous monocyte concentration was reduced in CD subjects at 72 hours (1.2±0.11 x 10⁶/μl; P<0.03). B & P were normal in CD. However in all subjects, B was significantly reduced after G-CSF (flora challenge from 87.1±8.5 to 44.2±6.9 [n.mol.O₂/10⁶neutrophils/min] (p=0.008); PMA challenge from 64.8±8.0 to 26.8±3.4 (p=0.002). P was markedly lower than initial venous neutrophil concentration (CD 21±10% and controls 14±5%). P increased with G-CSF (CD from 0.72±0.68 to 3.42±2.51 [10⁶CD16+/ml] (p=0.02); controls from 0.52±0.43 to 3.70±2.68 (p=0.02)) but proportionally less than the increase in venous neutrophil number (CD 12±5% and controls 15±6%).

**Conclusion:** Efficacy of G-CSF in CD will be affected by the reduction in B. The increase in P during G-CSF does not parallel the increase in venous neutrophil concentration.

**244 STREPTOCOCCUS FAECIUM, A POSSIBLE PROBIOTIC BACTERIUM, BUT NOT LACTOBACILLUS ACIDOPHILUS OR ESCHERICHIA COLI (NISSEL), DECREASES PROINFLAMMATORY CYTOKINE PRODUCTION (IFN-γ) BY AN IL-10 DEPENDENT MECHANISM**
A.L. Hart1, A.J. Stagg1, R. Rigby1, A. Jones1, L. Lammer3, F. Rizzello1, P. Gionchetti1, M. Campieri1, S.C. Knight1, M.A. Kamm1, 1APRG, Imperial College, 2St Mark’s Hospital, London, UK; 3University of Bologna, Bologna, Italy

**Introduction:** Probiotics are effective in the treatment of some inflammatory bowel diseases, but their mechanism of action is unclear.

**Methods:** A whole blood assay was developed to assess the effect of probiotic bacteria on gamma-interferon (IFNγ) production by polyclonally activated T-cells. Cell wall and soluble fractions of Lactobacillus acidophilus, Streptococcus faecium (S. faecium) and Escherichia coli (Nissel strain) at the equivalent of 10⁶ colony forming units per millilitre were cultured with blood overnight. A neutralising anti-interleukin 10 (IL-10) antibody (20μg/ml) was added to some cultures. Subsequently, production of IFNγ by CD8+ and CD8− T-cell populations was determined by intracellular labelling and flow cytometry after 4-hour activation with phorbol-myristate-acetate and ionomycin in the presence of monensin. The production of IL-10 in whole blood cultures was determined by ELISA.

**Results:** Cell wall, but not soluble components, of S. faecium decreased the proportion and number of IFNγ producing CD8+ and CD8− T-cells. IFNγ production was not altered by the other probiotics. Cell activation assessed by CD69 expression was not affected. The inhibition of IFNγ production by S. faecium was partly dependent on IL-10. However, all three bacteria stimulated IL-11 production in whole blood suggesting that IL-10 is required but not sufficient for the inhibitory effect.

**Conclusions:** The data indicate that a cell wall component of S. faecium, a gut commensal and putative probiotic, down-regulates T-cell IFNγ production by a mechanism that involves IL-10. This may be a direct effect of the bacteria on the T-cell or may act via additional cell-cell interactions.

**245 ASCA AND ANCA IN THE DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE AND OTHER DIARRHOEAL ILLNESSES**
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**Background:** Several studies have examined the utility of ASCA and ANCA either alone or in combination for aiding the diagnosis of inflammatory bowel disease (IBD). ASCA and ANCA in combination are said to be more specific than either alone. ANCA-ASCAs is the
result expected in Crohn’s and ANCA-ASCAs in UC. We have tested the utility of ASCAs or ANCA alone or in combination in distinguishing between IBD and other diarrhoeal illnesses.

Methods: 150 sera from patients attending a gastroenterology clinic with diarrhoeal disease were screened for ASCA by EUISA using the GENESIS IgA and IgG ASCA kits, and for ANCA by indirect immunofluorescence on ethanol fixed neutrophils. Patients were classified as Crohn’s, UC or other diarrhoeal illness, independently of the ANCA/ASCAs results, according to standard criteria.

Results: IgA ASCA alone has a sensitivity of 0.44 and specificity of 0.94 for Crohn’s disease [0.44/0.94]. Increases in sensitivity are accompanied by reduction in specificity when IgG ASCA [0.58/0.85] or IgG ASCA/ANCA [0.52/0.90] in combination are added. ANCA alone has a sensitivity of 0.54 and specificity of 0.85 for the diagnosis of UC. The addition of ASCA does not affect sensitivity or specificity [0.5/0.86].

Conclusions: [1] The high specificity of IgA ASCA for Crohn’s suggests that the presence of this antibody should trigger appropriate further investigation. However, its low sensitivity means that a negative result does not exclude Crohn’s. For this reason, the small loss of specificity resulting from adding IgG ASCA or ANCA will result in a loss of utility, despite the increase in sensitivity. [2] The low sensitivity and specificity of these assays for UC suggests that their utility in this setting is low. [3] While IgA ASCA screening may have value in diagnosing Crohn’s, IgG ASCA and ANCA are not useful in routine diagnosis of patients with diarrhoeal disease.

INCREASED EXPRESSION OF ß-DEFENSINS WITH INCREASING SEVERITY OF TROPICAL ENTEROPATHY

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Background: Tropical enteropathy is a term used to describe a different villous and crypt architecture to that seen in temperate climates. Its consistent with the hypothesis that tropical enteropathy is an adaptive response to microbial challenge.

Methods: Biopsies (n=84 in the first year, n=44 second year and n= 36 third year) were obtained from a longitudinal study of patients with diarrhoeal disease.

Results: Peptide and mRNA expression were only seen in the Paneth cell compartment. Mucosal architecture and defensin mRNA expression shared considerable variation in the 84 biopsies analysed at baseline. In cross-sectional analysis, HD5 mRNA and villous height (VH) were inversely correlated (Spearman’s ρ = -0.50, p = 0.002). Over one year, change in HD5 and change in VH showed a similar correlation (ρ = 0.50, p = 0.002). VH varied with time of year and this seasonality was seen in HD5 mRNA expression levels, in a reciprocal relationship to VH. A similar pattern was seen for HD6. Isoform expression of these defensins did not vary with the severity of enteropathy.

Conclusions: Increased severity of tropical enteropathy correlated with increased quantity of ß-defensin mRNA in jejunal biopsies, consistent with the hypothesis that tropical enteropathy is an adaptive response to microbial challenge.

THE CLINICAL SPECTRUM OF GASTROINTESTINAL INVOLVEMENT IN PATIENTS WITH PRIMARY HUMORAL IMMUNODEFICIENCY: A CLINICAL SURVEY OF PATIENTS FROM IRANIAN PRIMARY IMMUNODEFICIENCY REGISTRY

Aghahosseini, Asghar, Moein Mastafa, Farhoudi Abolhasan, Pourpak Zahra, Rezaei Nima, Abolmaleki Kamran, Movahedi Masoud, Gharagouzloo Mohammad, Mahmoodi Maryam, Hojjati Ashrafi Tahera. Department of Immunology, Allergy and Asthma, Children Medical Center Hospital, Tehran University of Medical Sciences

Background: Primary Humoral Immunodeficiencies (PHID) are currently increasingly recognized, thanks to novel advances in the immunology and its laboratory techniques. Gastrointestinal involvement, together with respiratory infections, account for most of the complications and the main cause of hospitalizations in such patients.

Objectives: To determine the clinical spectrum of gastrointestinal involvement in patients with PHID.

Method: We have reviewed the data from the clinical files of patients with PHID, diagnosed according to WHO criteria, who were enrolled in Iranian Primary Immunodeficiency Registry.

Results: We analyzed 125 patients (84 males), with the diagnoses of primary antibody deficiency including common-variable immunodeficiency (64 pts), x-linked agammaglobulinemia (29 pts), IgA deficiency (20 pts), IgG subclass deficiency (8 pts), and hyper-IgM syndrome (4 pts). The mean age of the patients at the time of study was 11 years. In the evolution of their disease, 78 cases (62.4%) have had involvement. Diarrhea, being the most common type of involvement was seen in 70 patients (56%). Seventeen of these (24.2%) have progressed to chronic diarrhea. Giardiasis and hepatitis were seen in 12 (9.6%) and 7 (5.6%), respectively. Also, we had 5 cases of chronic active hepatitis and 3 cases of ulcerative colitis. Among nonspecific symptoms, hepatomegaly was seen in 32 patients and splenomegaly in 28 patients. Celiac disease was seen in 2 cases with the diagnosis of selective IgA deficiency.

THE RESPONSE TO PROTON PUMP INHIBITOR THERAPY IS GENETICALLY DETERMINED

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Aim: The metabolism of PPIs by the CYP2C19 enzyme is genetically determined with considerable inter-individual variation. The aim of this study was to establish the relative frequencies of fast, medium and slow metabolisers, and to examine PPI dose with respect to metabolic capacity.

Methods: 535 patients with benign acid disorders on acid suppression therapy, and 106 patients with gastro-oesophageal cancer were genotyped by PCR and restriction enzyme digest to determine their capacity to metabolise PPIs. The benign group was further subdivided according to H. pylori status and presence of peptic ulcer.

Results: The frequency of each metabolic group was similar in the benign and cancer patients. Rapid Extensive (fast) metabolisers had 5 cases of chronic active hepatitis and 3 cases of ulcerative colitis. The mean age of the patients at the time of study was 11 years. In the evolution of their disease, 78 cases (62.4%) have had involvement. Diarrhea, being the most common type of involvement was seen in 70 patients (56%). Seventeen of these (24.2%) have progressed to chronic diarrhea. Giardiasis and hepatitis were seen in 12 (9.6%) and 7 (5.6%), respectively. Also, we had 5 cases of chronic active hepatitis and 3 cases of ulcerative colitis. Among nonspecific symptoms, hepatomegaly was seen in 32 patients and splenomegaly in 28 patients. Celiac disease was seen in 2 cases with the diagnosis of selective IgA deficiency.

Abbreviations: PPI = proton pump inhibitor, PCR = polymerase chain reaction.

HELICOBACTER PYLORI INFECTION IN CHILDHOOD REDUCES THE RISK OF ATOPIC DISORDERS IN ADULT LIFE: THE BRISTOL HELICOBACTER PROJECT

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Background: The prevalence of atopic disorders including asthma has increased dramatically over the last 20 years. Exposure to early childhood infections, including gastrointestinal infestations, may influence the developing immune system in such a way as to reduce the risk of later development of asthma, eczema and similar atopic diseases.
**Probiotic Bacteria Stimulate Natural Killer (NK) Cell Activation and Cytokine Production, An Early Step in Innate Immunity**

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**Introduction:** Probiotics are effective in the treatment of inflammatory bowel diseases, but their mechanism of action is unclear. Given that NK cells have a central regulatory role in host defence against bacteria, we have explored the role of IFN-γ in the activation and stimulating cytokine production by NK cells.

**Methods:** Whole blood and mononuclear cells from colonic biopsies were cultured overnight with Lactobacillus acidophilus bacteria on NK cell activation and cytokine production.

**Results:** Those individuals found to be HP positive were less likely to be taking a medication for asthma, eczema or allergic rhinitis (OR 0.48, 95% CI 0.24 to 0.96). Those individuals found to be HP negative were more likely to have a high baseline expression of CD69 by NK cells, indicating a high level of baseline natural killer (NK) cell activity.

**Conclusions:** Childhood infection with Helicobacter pylori is associated with a reduced risk of atopic disorders in adult life.

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**Dyspepsia is More Common in Elderly Women**

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**Background:** Dyspepsia is said to be a common symptom in the general population. This has not previously been formally studied in the elderly population, despite them having a higher prevalence of Helicobacter pylori (HP) infection.

**Aims:** To conduct a questionnaire survey of the general population of 60 years in the London Borough of Croydon in order to document the prevalence of, and risk factors for dyspeptic symptoms.

**Method:** A total of 1860 individuals over the age of 60 years were chosen at random from the lists of general practitioners across the London Borough of Croydon. They were sent a single sheet questionnaire.

**Results:** In total 1116 subjects (60%) returned both the questionnaire and a usable sample. Of these 616 (55%) had had symptoms of dyspepsia more than once in the previous month, and 370 (33%) specifically reported reflux related symptoms (waterbrash / heartburn). HP infection was detected in 25% of both these groups. The prevalence of dyspeptic symptoms was not related to HP seropositivity, age, smoking, social class, BMI nor NSAID use. It was more common in women (51 vs 39%, p<0.0001). In particular women had more symptoms of bloating (25 vs 13%, p<0.0001) and nausea (11 vs 5%, p<0.015). These differences remained significant even after subjects on occasional or regular medication for dyspepsia were excluded from the analysis.

**Conclusion:** The prevalence of self reported dyspepsia in older individuals is high, and is more common in women. It is not related to NSAID use, smoking or HP infection, and deserves further investigation.

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**Cholera Toxin (CT), Escherichia coli Heat Labile (LT) and Heat Stable Toxin (STA) Have an Indirect Effect on Distal Intestinal Fluid Transport in the Rat Small Intestine**

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**Background:** CT, LT and STA induce intestinal secretion directly via cyclic AMP and cyclic GMP dependent pathways respectively. Increasing evidence exists that these enterotoxins may mediate intestinal secretion through a local intramural neural reflex arc. To investigate this neural enterotoxin-induced intestinal secretion, we measured the effects of CT, LT and STA on intestinal fluid and electrolyte transport in distal non-contiguous and transected intestinal segments separately.

**Methods:** A model of distal aboral secretion was created in anaesthetised 200g male Whistar rats. CT (50 μg/ml), LT (50 μg/ml), STA (25 μg/ml) and saline (control) were placed independently in a proximal intestinal loop (an isolated 15cm jejunal loop) separated from a distal intestinal loop (a 15cm ileal loop) by tissue glue (Ginder); the luminally placed glue maintained neurological and vascular but not luminal continuity. The distal loop was perfused with a plasma electrolyte solution containing 14C-polyethylene glycol as a non-absorbable marker to measure changes in fluid and electrolyte transport. The experiment was repeated with the distal loop transected, for each enterotoxin.
Results: In controls, absorption in the distal loop ranged between 75 and 112 µl/min/g. Following application of CT, LT and STa to the proximal loop, distal loop absorption was reduced by 28%, 55% and 20% respectively (p<0.05). Following transection of the distal loop, the application of CT, LT and STa had no significant effect compared to control, on distal intestinal fluid or electrolyte transport.

Conclusions: These observations support a non-direct mechanism of CT, LT and STa-induced intestinal secretion. This mechanism is likely to be caused by an intrinsic or extrinsic nerves. Transection of the intestinal wall abolished the distal effect on intestinal transport by CT, LT and STa supporting the hypothesis that intrinsic intramural neurones play a key role in enterotoxin-induced intestinal secretion. Further work is required to define the circuitry of these intrinsic neural pathways.

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<td>(±11)</td>
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*p<0.03.

Methods: Monolayers of T84 cells were pre-exposed to purified C. difficile toxin A for 3 h and cytokine release was assessed after subsequent culture for 24 h. TGF-β and IL-8 levels were determined using specific bioassay and ELISA respectively. Barrier function was assessed by measurement of transepithelial electrical resistance.

Results: See table for TGF-β and IL-8 conc. in culture supernatants, mean (±SEM). TGF-β1 was the predominant isoform released. Within 24 h of pre-exposure to ≥10 ng/ml toxin A, there was complete and irreversible loss of electrical resistance across T84 monolayers. At conc. <10ng/ml of toxin A, loss of monolayer resistance was followed by recovery that was dependent upon the conc. of toxin originally applied. This recovery of epithelial barrier was significantly enhanced in the presence of 1 ng/ml recombinant TGF-β1 (maximal % increase in resistance, 0.01 ng/ml toxin A: 179%; 0.1 ng/ml toxin A: 156%; 1 ng/ml toxin A: 232%. All p<0.04).

Conclusions: In intestinal epithelial cells, (i) exposure to low concentrations of toxin A induces the release of TGF-β, which facilitates recovery of barrier function (ii) exposure to high concentrations of toxin A induces the expression of the neutrophil chemoattractant IL-8 and rapid, irreversible loss of barrier function. Thus the level of exposure of epithelial intestinal cells to C. difficile toxins may determine the development and severity of colitis.

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NITRIC OXIDE (NO) RELEASED BY GLYCO-SNAP-1 SIGNIFICANTLY INHIBITS THE LPS STIMULATED PRODUCTION OF IL-1β BUT NOT TNFα BY HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCs)

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Introduction: NO donating anti-inflammatory drugs such as NON-SAIDS and Nitropridinolamine are currently being evaluated for enhanced anti-inflammatory properties believed to be related to NO release. PBMC’s are routinely used for sites of inflammation in conditions such as ulcerative colitis or Crohn’s disease. We therefore investigated the effect of NO release on these cells by measuring the production of pro-inflammatory cytokines IL-1β and TNFα after stimulation with LPS.

Methods: Human PBMC’s were purified using Histopaque. The isolated cells were re-suspended in RPMI to a final concentration of 1x10⁶ per ml. The cells were then pre-incubated with the NO donor (G-SNAP-1) over a concentration range of 0 to 1 mM for 30mins prior to the addition of LPS (1µg/ml). After overnight incubation (37°C, 5% CO₂), the cells were centrifuged and the supernatant IL-1β and TNFα concentrations measured by ELISA (R&D DuoSet).

Results: There was a dramatic and highly significant inhibition of IL-1β but not TNFα release in a concentration related response (P<0.001). One Way ANOVA analysis, IL-1β IC50 = 61.7µM, SEM 0.04 (see fig).

Conclusion: NO released from G-SNAP-1 is a potent inhibitor of pro-inflammatory mediator IL-1β production by human PBMC’s but not TNFα.
**Diagnostic Yield of Stool Analysis and Endoscopy in HIV Population Presenting with Diarrhoea**

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**Background:** HIV patients commonly attend with history of diarrhoea. The use of highly active antiretroviral therapy (HAART) has led to a change in the epidemiology of diarrhoea in HIV patients. The patients with negative stool studies are frequently referred for endoscopic evaluation. We aimed to determine the diagnostic yield of stool analysis and endoscopy in HIV patients presenting with diarrhoea.

**Methods:** We retrospectively reviewed 525 HIV positive patients who presented with diarrhoea from January 1, 2000 to August 31, 2001 at Chelsea & Westminster hospital. Patients were divided into 3 groups: Group 1 (CD4 count ≤200), Group 2 (CD4 >200 - <350) and Group 3 (CD4 >350). Patients who had 2 or more stool examinations were included. We also reviewed the endoscopy and biopsy findings of the patients who had negative stool studies.

**Results:** Of 86 patients with CD4 count ≤200 (Group 1) the stool examination was diagnostic in 30 patients (34.8%) - the commonest diagnosis being cryptosporidiosis (10 patients - 11.6%), other causes were E histolytica, giardiasis, campylobacter, salmonella, C difficile, toxoplasmosis, isospora, ratatoves. Of 30 patients, 12 patients (40%) were on HAART, however only 2 patients (20%) presenting with cryptosporidiosis were on HAART. In group 2 (CD4 >200 - <350) and group 3 (CD4 >350), diagnostic yield of stool examination was in 37 patients (24.34%) and 74 patients (25.78%) respectively. The cause most frequently found in group 2 and group 3 was giardiasis (14 patients - 9.2%) and campylobacter (20 patients - 6.96%) respectively. 64 patients (16.6%) with negative stool studies were referred for endoscopy. Upper GI endoscopy and lower GI endoscopy with biopsies was diagnostic in 12 (30%) and 19 (50%) patients respectively.

**Conclusion:** In our population stool analysis in HIV patients with higher CD4 count has a low diagnostic yield. With the advent of HAART the infectious causes of diarrhoea are probably less important. Our study also showed that upper and lower GI endoscopies with biopsies are useful diagnostic investigations in patients with chronic diarrhoea.

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**Does the Initial Health Perception of IBS Patients, Recorded at the Time of Diagnosis, Change Over the Following Two Months, and How Valuable is This Health Perception in Predicting Outcome? A Pilot Study**

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**Introduction:** Irritable Bowel Syndrome (IBS) is a common condition affecting up to 30% of the population. The determinants relating to the uptake of primary and secondary medical care are unclear although IBS patients referred to secondary care have been found to have greater severity of symptoms, greater psychiatric-comorbidity and more negative health beliefs about their illness such as death phobia and catastrophizing. It is unclear whether these health beliefs are pre-existing or develop in response to the symptoms or perhaps in response to having negative test results. This study analyses the health perception (Leventhal et al. 1980; 1984) of IBS patients at the time of diagnosis and again two months later.

**Methods:** Thirty-five patients with IBS were recruited from the out-patient clinic of the Gastroenterology Department of the Kent and Canterbury Hospital, Kent. Each patient was recruited on their first visit to the gastroenterologist and completed a brief demographic questionnaire. A diagnosis of IBS was determined after taking a complete history of the patient, and receiving clear test results from barium enema or colonoscopy and from bloods. Patients completed the illness perception questionnaire within the first couple of weeks of receiving their IBS diagnosis. Two months later, these patients were contacted again and asked to complete the illness perception questionnaire, the hospital anxiety and depression scale and questions relating to their perceived quality of life and satisfaction with health.

**Results:** The individual components of the health perception: psychological cause, external control, the possibility for cure / control did not change significantly over the two time points, suggesting that the initial health beliefs regarding their abdominal and bowel symptoms remain fairly steady in the early months after diagnosis. The most predictive component of the health perception is serious consequences. Reporting that IBS has many serious consequences was strongly associated with poor outcome: poor quality of life, dissatisfaction with health and higher scores on the anxiety and depression scales.

**Conclusion:** This pilot study has shown that the initial health perception of IBS patients remains stable during the first couple of months of the diagnosis and also that serious consequence beliefs are predictive of poor outcome and may remain so if left unchallenged. Future researchers should consider the role of these consequences beliefs as a potential predictor of refractory IBS patients.

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**Cigarette Smoking and Crohn’s Disease: Effect on Disease Localisation**

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**Introduction:** Smoking is an established risk factor for the development of Crohn’s disease (CD). Continued cigarette consumption has an adverse effect upon the clinical course of CD. More severe disease, recurrence post-surgical resection and an increase in frequency of relapse are reported. Studies investigating anatomical disease localisation in CD with regards to smoking status have however, proved inconclusive.

**Aims:** To evaluate the relationship between smoking status and anatomical site of disease in a single centre cohort of CD patients.

**Subjects and Methods:** All patients with a diagnosis of CD were identified from the Inflammatory Bowel Disease database. Smoking status was determined by postal questionnaire, direct interview and case note review. Anatomical extent was classified as isolated small bowel disease (SBD), terminal ileal/ileo-caecal, colonic or mixed. Patients with indeterminate or ulcerative colitis were excluded. Analysis by way of 2×2 contingency table of smoking status compared to patient subgroups was performed.

**Results:** N=511, 202 male (39.5%), mean age at presentation=31 years. See table. Patients with isolated colonic disease were less likely to be smokers at presentation than those with mixed small/large bowel disease (p<0.0001, OR=2.45, 95%CI: 1.66–3.63). Significance remains, comparing isolated colonic with ileo-caecal/SBD (p<0.0001, OR=3.71, 95% CI: 1.77–4.14).

**Conclusion:** Patients with isolated colonic CD are less likely to be smokers at diagnosis in comparison to patients with mixed small/large bowel disease and those with ileo-caecal/SBD. Smoking at diagnosis is a risk factor for small bowel Crohn’s disease.

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**Outcome of Enteral Feeding for Newly Diagnosed Crohn’s Disease**

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**Introduction:** Induction of remission in Crohn’s disease can be achieved with exclusive enteral nutrition (EN) or oral steroids. It has been suggested that EN only delays the inevitable use of steroids.
this study we have followed up the outcome of children newly diagnosed in our unit with Crohn's disease.

Methods: The case notes of patients newly diagnosed with Crohn's disease during 1999 and 2000 were reviewed in August 2001.

Results: Patients: 36 patients new patients were diagnosed with a median age of 12.9 years (range 6.67–15.0). 22 had small bowel and colon affected, 7 had small bowel alone and 2 had colonic disease alone. 31/36 had disease severity requiring treatment with EN or steroids. The remaining 5 had localised oral/perianal disease not requiring EN or steroids. Initial treatment: Exclusive polymeric EN (Modulin, Nestle, UK) was started in 30/31 patients, one refused and was treated with steroids. 24/30 (80%) went on to remission. 6/30 required steroids to induce remission. 3 were early failures within 2 days (i.e. could not drink the feed or tolerate a naso-gastric tube) and 3 were late failures due to lack of response. Follow up data: The median time of follow-up was 1.25 years. Of 24 children successfully treated with EN, 1 has been lost to follow up, 42% (10/24) remain in remission and 54% (13/24) have relapsed. Of the 13 children who relapsed 54% (7/13) have been successfully treated with EN, 15% (2) failed to respond to EN and started steroids and 23% (3) were treated with AZA. 2/7 children who required steroids at presentation remain in remission, 5/7 had relapses, one of which was treated with EN.

Conclusions: These data confirm that EN is a very effective treatment for newly diagnosed Crohn's disease and can be used successfully for the majority of patients. During the period (1985/1990) (58% [18/31]) have exclusively been treated for active disease using EN and have not required steroids. More prolonged follow up will establish the proportion of children who can be repeatedly treated with EN for relapses of their Crohn's disease.

LOW DOSE ORAL METHOTREXATE FOR THE MEDICAL TREATMENT OF STEROID DEPENDANT/RESISTANT CROHN'S DISEASE: EXPERIENCE IN A SINGLE LARGE IBD CLINIC

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Introduction and Aim: Methotrexate (MTX) is a considered option for medical treatment of steroid dependent Crohn's disease (CD) or those intolerant or resistant to azathioprine (AZA). Few studies involving MTX use have been published. We report the experience of MTX use for CD in a large inflammatory bowel disease clinic.

Methods: MTX use was initiated in 42 patients with CD at a dose of 15–25mg/week orally. Indication for treatment was steroid dependent or resistant CD (n = 35) or fistula (n = 7). Efficacy was assessed by steroid withdrawal, abbreviated Harvey Bradshaw index or fistula closure. Adverse effects were recorded at each visit.

Results: Mean duration of treatment: median 25.5 and range 1–91 wks. Total MXT dose: mean 693 mgs, median 420 mgs and range 15–2330 mgs. Ten patients withdrew because of adverse effects: nausea (7), transaminitis-ALT rise (1), headaches (1) and multiple side effects (1). In two patients neutropenia occurred (1 severe and complicated by fungal sepsis), both patients were folate deficient. Haematronics were normal in all other cases. On an intention to treat basis 19 of the 42 patients achieved remission (42%). 16 of the 35 tolerating treatment withdrew steroids (46%), 3 out 7 achieved fistula closure (43%). In 16 of the 42 patients AZA was continued as concur rent treatment (mean dose 0.75mg/kg). Whilst both cases of neutro penia were receiving AZA, overall adverse events were not associated with its concurrent use.

Conclusion: In practice success rates of treating CD with MXT are similar to other reports in the literature. The majority of patients can be treated successfully with MTX and are able to discontinue or reduce their corticosteroid use.

APHTHOUS ULCERATION IN THE COLON AFTER SODIUM PHOSPHATE BOWEL PREPARATION FOR COLONOSCOPY

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Introduction: It appears to be little known that sodium phosphate, a laxative used in bowel preparation for colonoscopy, may potentially damage the colonic mucosa. A 51 year old man undergoing colonoscopy for chronic diarrhoea was found to have severe aphthous ulceration of the sigmoid and histology suggested Crohn's disease. No treatment was prescribed, but three weeks later a second examination, after a phosphate enema rather than sodium phosphate, was both endoscopically and histologically normal. We suspected that the ulcers were caused by the bowel preparation and we therefore reviewed the presence of aphthous ulceration, in a series of reports of colonoscopies where either sodium phosphate (Fleet) or sodium picosulphate (Picolax) had been used for bowel preparation.

Methods: 175 consecutive colonoscopies were retrospectively reviewed for the amount of sodium phosphate or sodium picosulphate used. The incidence of ulcers was reviewed with respect to age, sex, indication for the examination and the presence of ulceration.

Results: Sodium picosulphate was used in 124 colonoscopies and sodium phosphate in 51. The groups were evenly matched for age and sex. Aphthous ulceration was documented in 4/124 (3.2%) after sodium picosulphate but 7/51 (13.7%) after sodium phosphate (p=0.015; Fisher's Exact Test). The incidence of ulceration in patients known to have inflammatory bowel disease was only 3/27 and the incidence of ulcers was only significantly increased in the group whose indication for the exam was altered bowel habit (1/24 [4.2%]; 6/23 [26.1%] (p=0.048; Chi squared test).

Conclusion: It has been shown previously that sodium picosul phate can cause colonic ulceration. Our series confirms this finding which might potentially lead to an increased need for colonoscopy in this patient group. There is no evidence to suggest that sodium phosphate preparation is causative of colonic ulceration but further studies are needed to confirm this.
Background: The identification of NOD2 emphasises the role of the innate immune system in the pathogenesis of Crohn’s disease (CD). CD14 and PPARγ are positional and functional candidate genes for IBD. Bacterial LPS binds to CD14 and its co-receptor the toll-like receptor 4 leading to NFκB activation. A CD14 promoter SNP is associated with increased protein expression. The peroxisome proliferator-activated receptor-γ (PPARγ) gene is located at 1p23, a CD locus (LOD score 4.9) (Duer et al., AGA 2001). PPARγ agonists antagonize monocyte function through inhibition of activated protein 1 and NFκB. Tregllatizone (a PPARγ agonist) ameliorates the features of animal models of colitis. A common PPARγ SNP (Pro12Ala) is associated with type 2 diabetes.

Aims: To test for association between Pro12Ala and the CD14 promoter SNP and IBD.

Methods: The transmission disequilibrium test (TDT) was performed on 457 families containing 294 CD and 254 UC trios. Genotyping was by PCR-RFLP.

Results: No association was seen between the 3q13 risk haplotype and ulcerative colitis (TDT Transmitted/Untransmitted: 105/124, P=0.24). Association was confirmed with Crohn’s disease (162/114, P=0.006), specifically in CD patients not carrying NOD2 mutations [110/67, P=0.003] (CD NOD2 carriers: 32/47, P=0.3). In the UK population the haplotype plays a lesser role in CD susceptibility than in the Canadian population (T/U CD all 1.4 or CD NOD2 neg 1.6 versus CD 2.5; an estimate of genotype relative risk using a multiplicative model).

Conclusions: The 3q13 cytokine cluster risk haplotype does not influence susceptibility to ulcerative colitis and plays a lesser role in genetic susceptibility to Crohn’s disease in the UK than in the Canadian population. In addition, these data provide experimental evidence for genetic heterogeneity in Crohn’s disease.

CD14 and PPARγ Polymorphisms: Candidate Genes for IBD?

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Summary:

The identification of NOD2 emphasises the role of the innate immune system in the pathogenesis of Crohn’s disease (CD). CD14 and PPARγ are positional and functional candidate genes for IBD. Bacterial LPS binds to CD14 and its co-receptor the toll-like receptor 4 leading to NFκB activation. A CD14 promoter SNP is associated with increased protein expression. The peroxisome proliferator-activated receptor-γ (PPARγ) gene is located at 1p23, a CD locus (LOD score 4.9) (Duer et al., AGA 2001). PPARγ agonists antagonize monocyte function through inhibition of activated protein 1 and NFκB. Tregllatizone (a PPARγ agonist) ameliorates the features of animal models of colitis. A common PPARγ SNP (Pro12Ala) is associated with type 2 diabetes.

Aims: To test for association between Pro12Ala and the CD14 promoter SNP and IBD.

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Conclusions: The 3q13 cytokine cluster risk haplotype does not influence susceptibility to ulcerative colitis and plays a lesser role in genetic susceptibility to Crohn’s disease in the UK than in the Canadian population. In addition, these data provide experimental evidence for genetic heterogeneity in Crohn’s disease.
IBD associated arthritis, rheumatoid arthritis, erythema nodosum and uveitis were compared in the two populations to establish whether there were phenotypic differences. The groups were compared using 2x2 contingency tables and Fisher’s exact test.

**Results:** The prevalence of EIM’s in the 2 groups is shown in the table.

### Abstract 267

<table>
<thead>
<tr>
<th>EIM</th>
<th>PSC Colitis</th>
<th>UC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>4 (6%)</td>
<td>9 (1%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Perinuclear arthritis</td>
<td>0 (0%)</td>
<td>59 (6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>AS</td>
<td>1 (1%)</td>
<td>10 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (8%)</td>
<td>52 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>EN</td>
<td>0 (0%)</td>
<td>10 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1 (1%)</td>
<td>27 (3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Conclusions:** Typical IBD associated arthritis is not seen in PSC colitis, and this is significant even when compared to a subgroup of 232 patients with total UC (p=0.009). In contrast rheumatoid arthritis is more common in PSC colitis than UC. These findings support the concept that PSC colitis and UC are different phenotypic entities.

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### Abstract 268

**A NEW ORAL INHIBITOR OF TUMOUR NECROSIS FACTOR EFFECTIVELY TREATS PRIMATE MODELS OF COLITIS**

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**Introduction:** RDP-58 is a D-isomeric decapeptide that inhibits TNFα production in both murine DSS and TNBS colitis. The effect of RDP58 on spontaneous colitis in non-human primates has been evaluated.

**Methods:** Rhesus (mean age 9.3 years, weight 4.9 Kg) and cynomolgus monkeys (7.1 years, 3.9 Kg) with spontaneous colitis (>4 months, infection excluded, housed in accordance with US Federal regulations) were given oral or intravenous RDP-58. Stool quality was scored (1-normal, 2- loose, 3-liquid, 4-bloody) twice daily and colonoscopy performed. Response was defined as a reduction in stool score 0-none; 1-minor; >2-good). Duration of response after treatment was recorded.

**Results:** See table. All responses occurred with 1 day of dosing. No effects on full blood count or metabolic profile were observed. Four animals were colonoscoped and macroscopic resolution of colitis was observed.

### Abstract 269

**CIRCULATING MUCOSAL HOMING (β7+) MEMORY T CELLS ARE DECREASED IN NUMBER AND DISPLAY ALTERED CYTOKINE PRODUCTION IN CROHN’S DISEASE**

A.L. Hart1,2, R. Rigby1, A. Jones1, M.A. Kamm2, S.C. Knight1, A.J. Stagg1. 1Antigen Presentation Research Group, Imperial College, 2St Mark’s Hospital, Harrow, London, UK

**Introduction:** Circulating mucosal homing (β7+) memory T cells may be primed in intestinal lymphoid tissue and home selectively to the gut. Monoclonal antibodies to cd4(β7+) ameliorate gut inflammation, supporting the functional significance of this population. Analysis of β7+ memory T cells in blood may allow sampling of mucosally relevant cells from an accessible site. We have characterised quantitative and functional changes in β7+ memory T cells in Crohn’s disease.

**Methods:** Whole blood labelling and flow cytometry was used to identify β7+ (β7+ and β7- ) and β7- populations within CD3+CD45RA- leukocytes from 7 Crohn’s disease patients (CD3+>220) and 10 healthy controls. Production of cytokines (IFNγ, TNFα, IL-10, TGFβ, and IL-2) was determined by intracellular labelling following activation with phorbol-myristate-acetate and ionomycin in the presence of monensin.

**Results:** The number of T cells was the same in both groups but a greater proportion were memory T cells in Crohn’s disease, suggesting a re-distribution to the memory pool as a result of chronic inflammation. The ratio of β7+β7- memory cells was significantly reduced in Crohn’s disease (p<0.05) in Crohn’s disease. Absolute number analysis demonstrated both a fall in the number of β7+ cells and a smaller increase in β7- cells, ruling out a dilution effect of naive cells and indicating that the disappearance of β7 expressing cells cannot be accounted for by loss of the marker alone. In healthy controls, production of all cytokines increased with β7 expression. Compared with healthy samples, fewer β7+ cells from Crohn’s disease patients produced IL-10 but more produced TGFβ.

**Conclusions:** Recruitment to inflamed tissue probably contributes to the observed loss of blood β7+ memory cells in Crohn’s disease. Alterations in cytokine production suggest selective recruitment of functionally distinct populations. These perturbations in β7+ populations support the development of therapeutic strategies that target these cells.

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**CONTRIBUTORS TO COLITIS-ASSOCIATED ARTHRITIS IN PATIENTS WITH ULCERATIVE COLITIS who have not required surgery.**

A.L. Hart1, 2, R. Rigby1, A. Jones1, M.A. Kamm2, S.C. Knight1, A.J. Stagg1. 1Antigen Presentation Research Group, Imperial College, 2St Mark’s Hospital, Harrow, London, UK

**Introduction:** The prevalence of EIM’s in the 2 groups is shown in the table.

**Results:** The number of T cells was the same in both groups but a greater proportion were memory T cells in Crohn’s disease, suggesting a re-distribution to the memory pool as a result of chronic inflammation. The ratio of β7+β7- memory cells was significantly reduced in Crohn’s disease (p<0.05) in Crohn’s disease. Absolute number analysis demonstrated both a fall in the number of β7+ cells and a smaller increase in β7- cells, ruling out a dilution effect of naive cells and indicating that the disappearance of β7 expressing cells cannot be accounted for by loss of the marker alone. In healthy controls, production of all cytokines increased with β7 expression. Compared with healthy samples, fewer β7+ cells from Crohn’s disease patients produced IL-10 but more produced TGFβ.

**Conclusions:** Recruitment to inflamed tissue probably contributes to the observed loss of blood β7+ memory cells in Crohn’s disease. Alterations in cytokine production suggest selective recruitment of functionally distinct populations. These perturbations in β7+ populations support the development of therapeutic strategies that target these cells.

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**CYTOCHROME P450 AND MULTIDRUG-RESISTANCE GENE POLYMORPHISMS: PREDICTORS OF THE NEED FOR COLECTOMY IN ULCERATIVE COLITIS?**

D.P.V. McGovern, D.A. van Heel, T. Ahmad, N. Lench, D.P. Jewell. Wellcome Trust Centre for Human Genetics and Gastroenterology Unit, University of Oxford, UK

**Background:** Cytochrome P450 enzymes convert many chemicals (including cyclosporin and endogenous corticosteroids) into more water soluble products thereby facilitating their elimination from the body. CYP3A is the most abundantly expressed P450 in the liver. Up to 90% of the inter-individual variation in CYP3A activity is genetic in origin. CYP3A activity is the sum activity of the family of CYP3A genes, including CYP3A4, SNPs in CYP3A5*3 cause alternative splicing and protein truncation resulting in the absence of CYP3A5 in tissues. Cyclosporin and corticosteroids are also substrates of the efflux pump P-glycoprotein 170 (Pgp-170) encoded for by the MDR-1 gene. Patients with IBD poorly responsive to medical therapy have increased MDR-1 expression. Recently homozygosity for a polymorphism in exon 26 of MDR-1 has been associated with lower duodenal MDR-1 expression and elevated serum substrate (digoxin) levels.

**Aims:** To evaluate whether carriage of the CYP3A5*3 SNP and the MDR-1 exon 26 polymorphism predict the need for colectomy in patients with ulcerative colitis.

**Methods:** Allele counts were compared between 135 patients with UC who needed colectomy and 182 patients with pan-ulcerative colitis who have not required surgery.

**Results:** CYP3A5*3: Allele frequency was not significantly different between the two groups: colectomy 8.5%, non-colectomy 5.6% (p = 0.33).

MDR-1 exon 26: Homozygosity was not significantly different between the 2 groups: colectomy 21.0%, non-colectomy 25.2% (p = 0.47). Allele frequency was not significantly different between the 2 groups: colectomy 47.6%, non-colectomy 51.6% (p = 0.32).

**Conclusions:** These polymorphisms do not predict the need for colectomy in UC. Future studies should examine the role of other polymorphisms within genes involved in drug metabolism.
Impaired linear growth is a major complication of Crohn’s disease in young patients. Both undernutrition and direct effects of the inflammatory process contribute to the growth deficit. In the trinitrobenzene (TNBS)-induced colitis model, immunoneutralisation of interleukin-6 increases serum concentrations of insulin-like growth factor (IGF-I) and linear growth. Immunoneutralisation of tumour necrosis factor alpha (TNF-α) also increases growth but has no effect on IGF-I and thus the mechanisms of growth suppression by TNF-α are unexplained. The purpose of this study was to explore the hypothesis that TNF-α has direct effects on growth plate chondrocytes.

Methods: Growth plate chondrocytes were isolated by collagenase digestion from prepubertal rat tibia and maintained in monolayer culture. After 3 days, varying concentrations of TNF-α or IL-6 were added and cultures maintained for a further 4 days. At the end of the experimental period, cell proliferation and alkaline phosphatase (as a marker of chondrocyte maturation) was measured.

Results: TNF-α inhibited maturation of growth plate chondrocytes in a dose dependent manner (P<0.01, figure). TNF-α had no effect on chondrocyte proliferation. In contrast, IL-6 had no effect on either chondrocyte maturation or proliferation.

Conclusion: The inhibitory effects of TNF-α on linear growth are mediated by inhibition of growth plate chondrocyte maturation. In clinical practice, anti-TNF antibodies may directly increase linear growth by inhibition of TNF-α at the chondrocyte.

**Abstract 272**

**CROHN’S DISEASE AND ULCERATIVE COLITIS: DIVERGENT TRENDS IN HOSPITAL ADMISSION RATES**

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1St George’s Hospital, London; 2Office for National Statistics, London; 3University College, London

**Aim:** To investigate time trends in hospital admissions for Crohn’s disease and ulcerative colitis in England from 1989/90 to 1999/00.

**Methods:** Data were obtained from the Hospital Episodes Statistics (HES) service from 1989/90 to 1999/00 based on records of ‘Finished Consultant Episodes’ in England. Hospital admissions were selected by primary diagnosis (ICD 9: 555 and ICD 10: K50 for Crohn’s disease; ICD 9: 556 and ICD 10: K51 for ulcerative colitis) and admissions where a surgical operation, excluding endoscopic procedures, was performed were identified. Day case admissions were excluded. Age standardised hospital admission rates were calculated by comparison with the European standard population.

**Results:** Over the initial 12 months 18 patients were referred to the service. Nine patients did not make contact. Of the 9 patients who did make contact, 5 have successfully stopped smoking, 1 has been lost to follow up and the other 3 stopped but have relapsed. This represents a success rate of 35% of those making contact with the service.

**Conclusion:** Referral of Crohn’s patients to a smoking cessation service allows patients who are motivated to have appropriate and effective help with smoking cessation. All smokers with Crohn’s disease should be encouraged to contact a smoking cessation service.

**Abstract 273**

**SMOKING CESSATION IN CROHN’S DISEASE: WORTHWHILE RESULTS ARE POSSIBLE**

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**Background:** Smoking cessation is known to be a key therapeutic event in Crohn’s disease, decreasing subsequent relapse rates by up to 50%. Doctors often feel that little can be done to influence a patient’s smoking habit and that raising the issue may be a waste of clinic time or even detrimental to good doctor patient relations.

**Aim:** This study aimed to evaluate a smoking cessation service in Crohn’s disease patients.

**Methods:** Patients with Crohn’s disease who were habitual smokers were referred to the smoking cessation service. Information was sent followed by the patient to make contact with the service to take the referral forward. Counselling, nicotine patches and Zyban were available to the smoking cessation service. Success was determined by measurement of carbon monoxide levels to confirm cessation status.

**Results:** Over the initial 12 months 18 patients were referred to the service. Nine patients did not make contact. Of the 9 patients who did make contact, 5 have successfully stopped smoking, 1 has been lost to follow up and the other 3 stopped but have relapsed. This represents a success rate of 35% of those making contact with the service.

**Conclusion:** Referral of Crohn’s patients to a smoking cessation service allows patients who are motivated to have appropriate and effective help with smoking cessation. All smokers with Crohn’s disease should be encouraged to contact a smoking cessation service.

**Abstract 274**

**ORAL IRON THERAPY DOES NOT EXACERBATE INFLAMMATORY BOWEL DISEASE**

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**Background:** We have prospectively tested the suggestion that oral iron therapy increases disease activity in patients with IBD, and that this effect is mediated by pro-inflammatory mechanisms.

**Methods:** 6 iron-deficient patients with ulcerative colitis (UC) (2 active) and 8 with Crohn’s disease (CD) (6 active) were given oral ferrous sulphate 200mg tds for 4 weeks. Iron intolerance and disease activity were monitored with symptom diaries and inflammatory markers. Serum antioxidant capacity (AOC) was used to assess systemic oxidative activity.

**Results:** 3/14 (21%) patients, 2 with active CD, 1 with inactive UC, did not tolerate and discontinued oral iron after 3, 15 and 21 days; these patients showed no consistent rise in platelet count, ESR or CRP. In the 11 patients completing 4 weeks of iron, mean Hb rose from 10.6 ± 1.6 g/dl (SD) before, to 11.9 ± 1.1 after treatment (p<0.05), and ferritin from 9 mcg/l ± 9 to 23 ± 10 (p<0.05); there were no significant changes in platelet count (367 ± 4t o4 1 ± 1.3), CRP (11.3 mg/l ± 7 to 13 ± 13), albumin (41 ± 4 to 41 ± 5), Harvey-Bradshaw Index (for CD patients) (3 ± 2 to 3 ± 1.9), Simple Clinical Colitis Activity Index (for UC patients) (3 ± 1.4 to 4 ± 1.3) or AOC (shown as % reduction from background) (25 ± 35 to 29 ± 30). ESR fell following treatment from 40 mm/hr ± 23 to 25 ± 19 (p<0.05). Diagnosis and disease activity prior to therapy had no clear effect on the response to oral iron.
Conclusions: While a minority of patients do not tolerate it, oral azathioprine has no detectable adverse effect on disease activity or serum antioxidant capacity in IBD. Most patients show a good haematological response to oral azathioprine therapy.

275 AZATHIOPRINE METABOLITES IN INFLAMMATORY BOWEL DISEASE AND INCIDENCE OF NON-COMPLIANCE

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Introduction: The immunosuppressive drug azathioprine is well established in the treatment of inflammatory bowel disease (IBD). Myelosuppression occurs in 2 to 5% of IBD patients. Thioguanine nucleotides (TGNs) are active azathioprine metabolites, elevated TGNs are associated with myelosuppression. Aim: To investigate steady-state TGN metabolite concentrations in a large cohort of IBD patients.

Methods: IBD patients who had been taking azathioprine for at least 1 year were studied. Blood samples (10mL) were taken for the monitoring of blood counts and measurement of red cell TGN metabolite concentrations at each clinic visit.

Results: 133 patients were recruited into the study. 114 patients had repeat metabolite assays taken over 1 year. 89 of these patients were at TGN steady-state (metabolite assays varied by <50%). The remaining 25 patients had wide variations in TGN concentrations (>2 fold), 10 had dosage adjustments but 15 did not. 11 of these 15 patients had TGN levels below the level of detection, indicating non-compliance. Steady-state TGN concentrations ranged from 59 to 566 pmol/8x10^11 red cells and the azathioprine dosage from 0.3 to 2.8 mg/kg (median 1.6) in the n=89 cohort. Within this group there was no difference in TNF α or azathioprine dosage for patients on monotherapy (n=20), azathioprine and steroids (n=15) or azathioprine and 5-aminosalicylic acids (n=42). There was no significant difference in TGN metabolite concentrations between patients in remission (n=80, median TGN 176 pmol) compared to the small number with active disease (n=9, median TGN 153 pmol).

Conclusion: There was a 9 fold range in steady state TGN concentrations between IBD patients in remission. This range was not influenced by concurrent steroid or 5-aminosalicylate therapy. In addition, these metabolites can be used as indicators of compliance with oral azathioprine therapy. 10% of patients were non-compliant.

276 INFlixIMAB FOR CROHN’S DISEASE: ONE UNIT’S EXPERIENCE

P. Kennedy, J. Andreyev, B. Gazzard, J. Fell, I. Murray-Lyon, P. Vlavianos, D. Westaby, R. Zeegen. Chelsea & Westminster Hospital & Imperial College School of Medicine, London, UK

Background: The limitations of corticosteroids in the treatment of Crohn’s Disease (CD) are well recognised. About half the patients with CD who initially respond to medical therapy relapse within one year or become dependent on steroids with their associated risk of toxicity. One fifth of patients are unresponsive to steroids and many continue to have refractory disease despite combination therapy with immunomodulatory drugs. Fultulating CD rarely heals with conventional medical therapy. This underlines the need for an alternative agent in the treatment of active CD. Intestinal mucosal production of TNF-α is increased in CD and has a key role in the initiation and propagation of intestinal inflammation. Infliximab (lgG1 chimeric monoclonal antibody) binds soluble and membrane bound TNF-α and so acts to neutralise its effect.

Methods: We undertook a retrospective analysis of patients treated with Infliximab for refractory CD in our unit. The clinical indications, treatment protocol and outcome of these patients were reviewed. Clinical records, haematological and biochemical indices and where available, available endoscopic and histological findings pre and post treatment were evaluated to assess efficacy and tolerability.

Results: Between 2000-2001, 19 patients with CD were treated with Infliximab after 2 consultant gastroenterologists agreed they had failed medical therapy. Clinical indications for Infliximab therapy were fistulating CD (n=5) and refractory luminal CD (n=14). 11/19 had undergone previous GI surgery. 18/19 were unresponsive to and intolerant of steroids. 13/19 had failed to respond to at least 1 immuno-modulatory drug. Infliximab (5mg/kg) was administered by infusion over 2 hours with intravenous steroid and antihista-mine cover. 12/19 were treated as out-patients. A repeat course was administered in 13 patients (median interval 8 weeks, range 2-30 weeks), 7 patients had 3 or more infusions. Five patients had a complete response (median 8 weeks, range 2-36 weeks), 12 had a partial response (median 6 weeks, range 4-28 weeks) and 2 did not respond. Two of the 5 patients with fistulising CD, closed their fistulae. Patients requiring surgery (n=4) following therapy had all undergone surgery for their CD previously. No side effects were reported in 15/17 patients. Two patients developed severe headache, precluding further treatment and requiring hospital admission with CT scan and lumbar puncture in one patient.

Conclusions: Our data confirm the previously reported benefit of Infliximab therapy in achieving rapid responses in patients failing other medical therapies. However, our findings suggest that responses are short-lived and patients with steroid resistant CD tended to relapse, questioning the benefit of Infliximab in that group. Patients unresponsive to initial treatment with Infliximab failed to respond to subsequent infusions. Perhaps Infliximab therapy should be considered primarily as a first-line alternative to corticosteroids in the treatment of moderate to severe CD.

278 DRB1*15 MOLECULAR SUBTYPING CONFIRMS THAT CAUSACIAN ULCERATIVE COLITIS (UC) IS ASSOCIATED WITH DRB1*1502 AND NOT DRB1*1501

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Background: A replicated association between UC and the serotype DR2 has been reported in the Japanese. Studies in caucasian populations however have produced more conflicting results. Modern molecular typing has shown that the Japanese association is attributable to DRB1*1502, an allele common in this ethnic group but rare in caucasians. This allele differs from DRB1*1501 by a single amino acid (position 86 of exon 2), located within pocket 1, which may alter peptide binding. DRB1*15 molecular subtyping has been carried out in 5 previous studies of Caucasian patients. Only one (Trachtenberg et al Hum. Immunol. 2000; 61:326) reported an association from DRB1*1502.

Aims: To determine whether DRB1*15 molecular subtypes or linked polymorphisms in nearby genes confer susceptibility to caucasian UC in a large cohort of accurately phenotyped patients.

Methods: 340 polymorphisms across 24 genes were carried out using PCR-SSP. Extended HLA haplotypes based upon DRB1*1501 and *1502 were constructed from these data. Disease associations were evaluated at each allele on these extended haplotypes. 331 accurately phenotyped caucasian UC patients and 354 healthy control subjects were studied.

Results: DRB1*1502 was associated with disease susceptibility (4.2% vs. 0.8%; P=0.004; RR 4.59; CI 1.31-16.11). A rare extended haplotype A*3002-Cw*1202-B*5201-MICA*00901-MICB*0102-1C7H3-DRB5*0101-DRB1*1502-DGB1*00601 was constructed. None of these alleles carried a relative risk of disease greater than DRB1*1502. This allele was not associated with disease phenotype (extent or severity). DRB1*1501 was not associated with disease susceptibility or phenotype.

Conclusion: Although rare in Caucasian UC patients, DRB1*1502 appears to be associated with UC in all ethnic groups. This unique trans-racial concordance suggests that this allele or a closely linked allele determines disease susceptibility.

279 TUMOUR NECROSIS FACTOR ALPHA (TNFα) PROMOTER POLYMORPHISMS AND COLITIS ASSOCIATED COLORECTAL NEOPLASIA (CACRN)

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Persistent colonic inflammation in ulcerative (UC) and Crohn’s colitis (CD) confers increased colorectal cancer risk. Tumour necrosis factor alpha (TNFα) mediates inflammation in colitis. TNFα promoter polymorphisms associated with variable TNFα production. This study tests the hypothesis that TNFα promoter polymorphisms confer cancer risk, in colitis.
Methods: Genotyping for TNFα -863CA and -308GA promoter polymorphisms were carried out by RFLP analysis in 194 colitis patients (127 UC, 62 CD, 5 indeterminate colitis), 31 colitis patients with CACRN (24 carcinomas, 7 high grade dysplasia) and 167 healthy controls.

Results: Linkage disequilibrium was found between TNFα -863A and -308A (p<0.05). TNFα -308A allele frequency was increased in CACRN (38.3% CACRN vs 21.2% control; p=0.01) but was not increased in colitis alone (22.1%). The homozygous TNFα -308AA genotype was enriched in CACRN (16.7%) vs control (3.1%) p=0.01. TNFα -863A was increased in colitis vs controls (TNFα -863A 21.2% vs 12.6% control; p<0.005) but was not associated with CACRN.

Conclusions: In this study, TNFα -863A associated with colitis but not neoplastic change. The rare TNFα -308AA genotype was enriched in CACRN and may be useful as a risk marker in cancer surveillance.

**280 DIFFERENCES IN MICRO-VASCULAR BLOOD FLOW AT SITES OF SKIN BLISTERING MAY ACCOUNT FOR REDUCED LEUKOCYTE TRAFFICKING IN CROHN’S DISEASE**

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Background and Aims: Previous studies have demonstrated a reduction in the number of neutrophils migrating into skin windows in patients with Crohn’s disease (CD). This effect may result from an impaired microvascular response preventing leukocytes from entering skin windows. This study examines blood flow in microvasculature at sites of skin windows using laser Doppler imaging, a well-established technique for assessing microvascular blood flow.

Methods: A novel skin window technique using cantharidin induced skin blisters was used to assess the acute inflammatory response. Blisters were created on the forearms of 7 subjects with inactive CD (male n=5) and 5 healthy controls (male n=5). Activity was assessed using a modified Crohn’s Disease Activity Index. Tissue blood flow at the site of blistering was assessed at 8 h and 24 h. The blisters were harvested at 24 h and the number of cells quantified.

Results: At 8 h blister formation was not visible, but blisters were evident in all subjects at 24 h. The number of cells that had migrated into the blister at 24 h was lower than in the control group (mean ± SEM: CD 4.23±10^5 ± 1.644 cells/ml; controls 5.68±10^6 ± 1.630 cells/ml). Microvascular blood flow was significantly increased at 8 h but reduced at 24 h in CD patients compared with controls. Net mean flux values (relative units) for each group are shown in the table (values shown are mean (SEM); unpaired t-test).

Conclusions: Reduced neutrophil migration into CD skin windows may be caused by inappropriate changes to microvascular blood flow. This could result from either a leukocyte or endothelial cell defect leading to impaired diapedesis of cells from the vascular lumen into the surrounding tissue. A defect in innate immunity such as this could account for some cases of inflammatory bowel disease.

**281 DELAYED PUBERTY AND RESPONSE TO TESTOSTERONE IN EXPERIMENTAL COLITIS**

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Delayed puberty is common in young patients with Crohn’s disease. In rats with trinitrobenzene (TNBS)-induced colitis, puberty is also delayed and related to both undernutrition and a direct effect of inflammation. In this model serum concentrations of gonadotrophins and sex steroids are similar to controls and we have speculated that delay in puberty results from end-organ resistance to androgens. The purpose of this study was to test this hypothesis.

Methods: Colitis was induced in 14 prepubertal Wistar rats (age 32 days) by intrarectal administration of trinitrobenzene in ethanol. Half of the colitic group were treated with testosterone (T; colitic, 0.225mg/100g body weight/day s.c.) and the remainder received only vehicle (control/colitic). The control group was healthy free-feeding rats. Food intake and body weight were measured daily and weight of the testicles, seminal vesicles (SV) and prostate determined at sacrifice (46 days). Intestinal inflammation was measured by macroscopic assessment.

Results: TNBS induced distal colitis with macroscopic inflammation (colitic 5.6±2; T/colitic, 6.2±3), hypophagia and reduced weight gain (68±23 vs 85±23g) compared to HC (114±8g, P<0.001). Administration of testosterone had no effect on the severity of colitis. Organ weights (SV, prostate) of control/colitic groups were reduced compared to HC, demonstrating the detrimental effect of intestinal inflammation on puberty. These effects were completely or partly overcome by testosterone suggesting that there is not complete end-organ resistance to sex steroids (table).

**282 PHOSPHOINOSITIDE SIGNALLING IN INFLAMMATORY BOWEL DISEASE AND COLORECTAL NEOPLASIA**

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Introduction: Patients with inflammatory bowel disease (IBD) have a 30% lifetime risk of developing colorectal cancer (CRC). Tumourigenesis in IBD does not follow the stepwise genetic process characteristic of adenomatous polyp progression, hence an alternative molecular pathway is thought to exist. Activation of phosphoinositide-3-kinase (PI(3)K), develop ulcerative colitis and adenocarcinoma. The PTEN tumour suppressor gene opposes the action of PI(3)K and mice deficient in PTEN develop tumours and autoimmune phenomena. We therefore hypothesised that abnormal PI(3)K signalling may contribute to the development of CRC in patients with IBD.

Method: Expression of PI(3)Kγ and PTEN was investigated in paraffin embedded human tissue sections of approximately 30 normal colon, active colitis, sporadic CRC and IBD associated CRC by indirect immunohistochemistry. Both positive (anti-CD45 antibody) and negative controls (secondary antibody only) were used.

Results: Approximately 66 percent of tumours arising in patients with IBD lacked PI(3)Kγ expression and in 40 percent PTEN protein expression was absent. Both results were statistically significant when compared with normal tissue. There was no statistical difference in expression of PI(3)Kγ or PTEN in sporadic CRC when compared with normal tissue.

Conclusion: Loss of expression of PI(3)Kγ and PTEN proteins is seen at higher frequency in IBD associated CRC than sporadic CRC. We conclude that aberrant signalling through this pathway may occur...
ADENOMATOUS POLyps ARE RARE IN ULCERATIVE COLITIS

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Colon cancer in ulcerative colitis (UC) does not follow the adenoma-carcinoma sequence of non-UC colorectal neoplasia. Polyps with dysplasia do occur in UC, and there is debate whether they should always be managed as dysplasia associated lesion/masses (DALMs) requiring colectomy, or whether some can be managed as sporadic adenomas by polypectomy. There are few data on the prevalence of non-inflammatory polyps in UC; this study aimed to see if adenomatous polyps occur as often in UC as in patients without inflammatory bowel disease (IBD).

The clinical, endoscopy and histology records of 150 patients with UC undergoing colonoscopy were scrutinised for any history of polyps. The control group was 205 patients having colonoscopy for altered bowel habit. Patients with rectal bleeding, anaemia, abnormal barium enema, a personal or family history of colorectal cancer/polyps, or those who were adopted as controls, as those who were in whom cancer or IBD was found at endoscopy.

The mean (SD) age of UC patients, 48.8 (13.8) years, was not different to that of controls, 51.9 (15.5) years. Sex distribution of 79/71 in UC, 90/115 in controls was similar. In UC, the median (range) duration was 10 (0–48) years, and the median number of colonoscopies was 2 (1–10). The most proximally recorded UC extent was pancolitis in 85 (57%) patients, to the hepatic flexure in 16 (11%), to the splenic flexure in 19 (13%), proctosigmoiditis in 28 (18%), proctitis in 12 (8%).

Only 6 UC patients had ever had dysplastic polyps. 2 had a single adenomatous polyp proximal to the colitis segment. 4 patients had dysplastic polyps within the colitis segment. In 2 of these the polyps were treated endoscopically as sporadic adenomatous polyps (1 patient having 2 polyps). In the other 2, the lesions were considered to be DALMs and colectomy advised. In contrast, 24 controls had at 1 least adenomatous polyp, \( \chi^2 = 6.7, p<0.01 \). Metaplastic polyps were found in 4 UC patients (within colitis in 3, proximal to colitis in 1) and in 24 control patients, \( \chi^2 = 9.7, p<0.01 \). 38 UC patients had inflammatory pseudopolyps. Adenomatous and metaplastic polyps occur less frequently in patients with UC than in patients without IBD. Despite the increased cancer risk in longstanding UC, the colitic mucosa (or possibly drug treatment of UC) seems to protect against the formation of sporadic adenomas.

MAGNETIC RESONANCE IMAGING (MRI) IN PATIENTS WITH ACUTE COLITIS: A PILOT STUDY

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Aim: To evaluate the potential of MRI in patients with acute colitis.

Methods: Consecutive patients admitted with acute colitis were studied. All had AXR on admission and MRI of the colon. Axial (T1/ T2) and sagittal T1 images were performed according to a predetermined protocol using a Siemens 1.5 Tesla Vision Scanner. The following parameters on AXR were recorded: disease extent, bowel dilatation and wall thickness. At MRI, disease extent, bowel dilatation, wall thickness, changes in peri-colic fat and the presence or absence of free fluid were noted.

Results: To date eleven patients with acute colitis have been included. One male and ten females, mean age 40.7 (range 22–71) were analysed. Six out of eleven patients with Powell Tuck score ranging between 8–13 had no or minimal changes on AXR. MRI showed disease extent and established bowel wall thickening in all six cases. Three patients required colectomy and in two of these cases MRI showed free fluid and changes in peri-colic fat.

Conclusions: (1) MRI is more informative than a plain abdominal film in assessing the severity and extent of disease in patients admitted with acute colitis. (2) Features like presence of free fluid and changes in the peri-colic fat may be important prognostic factors.
THE ROLE OF DIET IN THE AETIOLOGY OF ULCERATIVE COLITIS: A PILOT STUDY IN A EUROPEAN PROSPECTIVE COHORT STUDY

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Background: The causes of ulcerative colitis are unknown, although it is plausible that dietary factors are involved. To address this hypothesis a prospective cohort study is needed to eliminate the biases associated with the previous case-control studies of diet and IBD.

Aims: To conduct a pilot study to determine whether it was feasible to identify subjects who developed ulcerative colitis who are participating in a large European cohort study and to conduct a provisional analysis of the dietary data.

Methods: 25623 men and women aged 45–74 years in Norfolk, UK (4345 men and women aged 25–64 years in Potsdam, Germany) were recruited to the EPIC Study (European Prospective Investigation Into Cancer & Nutrition). These subjects completed information on diet at recruitment and are being followed up for the development of ulcerative colitis. Each case was matched with four controls and an analysis performed for food groups, adjusted for cigarette smoking.

Results: 20 incident patients with ulcerative colitis (7 women, 13 men) were identified, which is the expected number over the follow-up period. Analysis showed a non-significant positive association with carbohydrate, sugar and fat consumption (for lower vs upper tertiles of consumption: carbohydrate OR=2.8 (95% CI=0.7–11.1), sugar OR=1.8 (95% CI=0.5–7.3), fat OR=1.6 (95% CI=0.5–5.6). A higher fish consumption appeared to protect against the development of ulcerative colitis (lower vs middle tertile OR=0.6 (95% CI=0.1–2.1) & lower vs upper tertile OR=0.8 (95% CI=0.2–3.2)).

Conclusions: A prospective cohort study of diet and ulcerative colitis is feasible. Other European centres participating in EPIC now need to be included to increase the number of participants studied so that the role of diet in the aetiology of ulcerative colitis can be accurately defined.

COMPLIANCE WITH MAINTENANCE MESALAZINE IN INFLAMMATORY BOWEL DISEASE

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Background: Most patients with inflammatory bowel disease are prescribed regular medications to reduce the risk of disease relapse. Non-compliance with such treatments may increase the risk of relapse and some have suggested an increased risk of colorectal cancer. We have therefore conducted a survey of outpatients with IBD to determine the prevalence of non-compliance with maintenance mesalazine therapy, and to identify possible risk factors.

Methods: Outpatients with quiescent IBD receiving maintenance therapy with delayed-release mesalazine (Asacol) were recruited to the study. Patients underwent a structured interview including assessment of regular compliance and medication use. Anxiety and depression, quality of life, and measures of the doctor-patient relationship were also assessed using validated questionnaires. Poor compliance was defined as taking <80% of the prescribed dose.

Results: 98 patients were studied. 51 were male and ages ranged from 17–85 years. 63% had ulcerative colitis, 27% Crohn’s disease and 10% indeterminate colitis. Disease duration was 8.6 (0.2–53) years and patients had taken mesalazine 2.4 (0.4–3.6) g/day for 4.3 (0.2–13) years. 64% of patients were prescribed mesalazine three times daily. 43% of patients reported regular non-compliance. Non-compliance was associated with a younger age, full-time employment, three-times daily dosing, education beyond the age of 16 and the patient’s perception of treatment efficacy. Logistic regression revealed the only independent predictors of non-compliance to be three-times daily dosing (OR=3.1 (95% CI 1.8–8.4)) and full time employment (OR=2.7 (95%CI 1.1–6.9)).

Conclusions: Non-compliance with maintenance mesalazine is a common problem in patients with inflammatory bowel disease. Three-times daily dosing and full-time employment are the main predictors of non-compliance. These factors should be considered when selecting and advising on maintenance drug regimens.

RELATIONSHIP OF THIOPURINE METHYLTRANSFERASE (TPMT) ACTIVITY TO MEAN CORPUSCULAR VOLUME (MCV) IN INFLAMMATORY BOWEL DISEASE (IBD) PATIENTS MAINTAINED ON AZATHIOPRINE

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Introduction: TPMT is a cytosolic enzyme that catalyses the S-methylation of aromatic and heterocyclic sulphhydril compounds including 6-mercaptopurine and azathioprine (AZA). AZA induces TPMT activity variably and unpredictably. We have recently reported that IBD patients with TPMT activity > 20 nmol/hr/ml of RBC relapse more often if AZA is prescribed at doses > 2 mg/kg/day. MCV is increased in patients on AZA, but the implications of this increase in guiding AZA therapy is unclear. We investigated the relationship between TPMT activity and MCV in IBD patients and AZA maintained on AZA.

Patients and Methods: We recruited a cohort of 84 IBD (45M, 39F) patients (38 Ulcerative Colitis, 46 Crohn’s disease) who were maintained on AZA. TPMT activity was determined from blood samples by a radiochemical assay on haemolysed red blood cells (RBC) as previously reported and MCV was obtained on the same day. Relapse rates per year of follow up and time to first relapse were related to respective TPMT activity and MCV.

Results: The MCV did not correlate with TPMT activity (r=0.025; p=0.8). The mean MCV was 91.45 fl (SD 7.38) in patients with TPMT > 20 nmol/hour/ml of RBC compared with MCV of 92.19 fl (SD 5.77) in patients with TPMT > 20 nmol/hour/ml of RBC (p=NS). A Kaplan-Meier survival curve was constructed based on time to first relapse for patients with MCV < 98 fl compared with MCV > 98 fl and the difference was not significant by log rank analysis.

Conclusions: In IBD patients on AZA, MCV does not correlate with TPMT activity. MCV in IBD is influenced by a number of conflicting factors such as iron or folate deficiency, and cannot be used to determine AZA effect or outcome of therapy.

PRE-POUCH ILEITIS: A DISEASE OF THE ILEUM IN UC

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Introduction: Inflammation of the ileum occurs in UC patients. In addition to “backwash ileitis”, pouchitis and pre-stomal ileitis we have observed inflammation proximal to the pouch in the neo-terminal ileum (NTI) and sought to ascertain the characteristics of this “pre-pouch ileitis” (PPI).

Methods: Retrospective notes review of those with ileal abnormalities amongst the 661 consecutive cases undergoing restorative proctocolectomy for UC at a single centre to 1998. Histological slides were reviewed. Staining for colonic metaplasia was undertaken.

Results: 19 cases were found. 3 had Crohn’s Disease (CD), 1 had a discrete NSAID stricture. These 4 are termed alternative group (AG). The remaining 15 had characteristic diffuse disease from the NTI-pouch junction proximally for varying distances (PPI group). The disease became milder more proximally in PPI and CD cases. In 3/15 disease was limited to the pouch-NTI junction. 2 of the other 12 had stricture disease and 1/12 had fistulating PPI. The majority presented with frequent and pain. Extra-intestinal manifestations were seen in 4/15 PPI but 0/4 AG. Smoking was unusual. In the PPI group half had pouchitis but few had backwash ileitis pre-operatively. A significant distal stricture was present in only 1/15 PPI and 1/4 AG. The pathology was discovered by contrast studies in 8/19, endoscopy in 7/19 and at surgery in 3/19. Roughly a quarter responded to each of antibiotics, IBD therapy or resection with spontaneous remission in the remainder. Histological appearances of resection specimens and biopsies revealed nothing characteristically to distinguish PPI from pouchitis.

Conclusion: 15 cases of pre-pouch ileitis were found in patients with confirmed UC and otherwise normal BAFT with no histological evidence of Crohn’s. This disease may have a distinct pathogenesis from Crohn’s.
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Osteoporosis in Crohn’s disease is not determined by NOD2 genotype

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Background: Osteoporosis is a common and 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 NOD2 gene mutations.

Methods: 80 patients had their bone density assessed by DEXA scanning at the lumbar spine, hip and femoral neck. Osteoporosis was defined by WHO criteria as a T(30) score worse than –2.5 at any site, osteopenia as a T(30) between –1 and –2.5. DNA was genotyped for the 3 NOD2 mutations previously shown to be associated with Crohn’s disease (SNP 8, 12 and 13).

Results: There are no significant differences (see table10).

Conclusions: NOD2 mutations associated with Crohn’s disease do not appear to contribute to the incidence of osteoporosis in this condition.

Abstract 292

The genetic prediction of the clinical response to infliximab in Crohn’s disease (CD): A role for polymorphisms in the TNFA and LTA genes?

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Background: The monoclonal anti TNFa antibody, Infliximab offers an alternative to current medical therapy in CD with two thirds of CD patients responding. Stage 1: 43 Caucasian patients recruited from two UK centres. Polymorphisms were genotyped by PCR-SSP in two patient cohorts. SNPs at positions –1031, –863, –857 and –308 have been associated with increased transcription and production of TNF alpha and may therefore influence response to this agent.

Aims: To determine whether polymorphisms in the TNFA and lymphotxin alpha (LTA) genes can predict response to Infliximab

Methods: 3 LTA (+A720C, +C365G and +G249A) and 7 TNFa (-T1031C, -C863A, -C857A, -G380A, -G308A, -G238A, +G488) polymorphisms were genotyped by PCR-SSP in two patient cohorts. Stage 1: 43 Caucasian patients recruited from two UK centres. Response was assessed retrospectively by two blinded physicians and by patient’s own assessment of response. Stage 2: Replication of positive findings sought in 154 patients recruited from a single Belgian centre (positive response defined as fall in CDAI >70 / remission a CDAI of <150).

Results: Stage 1: 29/43 (67%) patients responded to Infliximab. Doctor and patient assessment of response was concordant in 43/43 (100%) patients. TNF-1031C was associated with a positive response (P=0.03 positive predictive value 82%). All 5 Patients homozygous for TNF-1031C responded. Stage 2: 29/1031C and the linked polymorphism TNF-863A were genotyped. No association with clinical response to Infliximab was found.

Conclusions: The polymorphisms studied in the TNFA and LTA genes do not predict response to Infliximab. The association with TNF-1031C observed in Stage 1 is likely to represent a Type I error. Alternatively the failure to replicate this genetic association may due to clinical differences between centres in the selection of patients offered Infliximab.

Abstract 293

Polymorphisms of the vitamin D receptor gene and inflammatory bowel disease

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Background: The vitamin D receptor (VDR) maps to chromosome 12q, which has been identified as a region of interest in inflammatory bowel disease (IBD). VDR is the cellular receptor for 1,25(OH)2 vitamin D, which has antiproliferative properties. VDR polymorphisms may confer increased risk of Crohn’s Disease (CD). This study tests the hypothesis that the Taq1, Fok1 and Apa I VDR polymorphisms associate with incidence and extent of ulcerative colitis (UC) and CD.

Methods: 141 patients with UC, 71 with CD and 178 healthy controls were genotyped for Taq1, Fok1 and Apa I nuleotide polymorphisms in VDR using allele specific PCR. Clinical risk factors including age of onset, disease extent and duration were recorded.

Results: Homozygotes for the Taq1 polymorphism ‘ff’ were increased in CD patients (31%) vs control (12%), p=0.001. The Fok1 ‘ff’ allele was not associated with extensive colitis in both UC and CD.

Conclusions: The Taq1 ‘ff’ genotype is associated with CD. The Fok1 ‘ff’ genotype is associated with extensive IBD.

Abstract 294

The prevalence of gut translocation and septic morbidity in surgical patients with inflammatory bowel disease

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Introduction: Postoperative sepsis is common in patients with inflammatory bowel disease (IBD). There is increasing evidence to suggest that the passage of bacteria across the gut barrier to sterile extra-intestinal sites is the cause of this septic morbidity. The aim of this study was to document the rate of bacterial translocation (BT) in patients with Ulcerative Colitis (UC) and Crohn’s Disease (CD) and relate this to the development of postoperative septic morbidity.

Methods: All patients with IBD who underwent abdominal surgery were entered into this prospective study. Bacterial translocation was assessed through the microbiological culture of a mesenteric lymph node and serosal biopsy, obtained at the start of laparotomy. Septic morbidity was defined as any positive culture in the postoperative period.

Results: Sixty-four patients were recruited into the study, 28 with UC (M:F 18:10, Age 51 years) and 36 with CD (M:F 14:22, 44 years). The overall prevalence of bacterial translocation was 19% (12/64 patients). The most commonly isolated organism from nodes and serosa was Escherichia Coli (42%). Twelve patients (19%) developed 14 septic complications. Enteric organisms were responsible in 86%. Patients with microbiological evidence of BT had a higher incidence of postoperative sepsis (4/12, 33% vs 8/52, 15%, P=0.15).

Conclusions: Bacterial translocation occurs in patients with IBD and may promote the development of septic morbidity. Our data supports the gut origin of sepsis hypothesis.
**TGF-β1 EXPRESSION IS UPREGULATED IN CROHN’S DISEASE (CD) BUT NOT IN ULCERATIVE COLITIS (UC) MUCOSA AFTER INCUBATION WITH ELEMENTAL DIET-WHEY ENRICHED WITH TGF-β1 (EWT) AND ELEMENTAL DIET-COLOSTRUM (ECO)**

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**Introduction:** Chronic intestinal inflammation in IBD is caused by inappropriate immune response to luminal antigens, inadequately downregulated by mucosal counter-regulatory mechanisms. TGF-β1 is a potent negative regulator of mucosal inflammation. In CD, elemental diet (ED) heals mucosal ulceration and down regulates the pro-inflammatory response. We aimed to demonstrate if enrichment of ED with TGF-β1 results in upregulation of mucosal expression of TGF-β1 in IBD tissues compared with ED alone.

**Method:** Three liquid formulae were used: (1) ED (EO28, SHS Ltd, Liverpool) with addition of bovine colostrum rich in TGF-β1 (0.9mg TGF-β1 per 100gm colostrum) (ECO); (2) ED with addition of whey enriched with TGF-β1 (300mg TGF-β1 per 1gm whey) (EWT); (3) ED alone. Colonoscopy biopsies from patients with CD (n=23), UC (n=13) and non-inflamed controls (n=19) were incubated for 24h in Waymouth medium diluted 1:20; 1:10 and 1:5 with ECO, EWT and ED medium alone as control. Tissue viability in organ culture was determined by BrdU uptake. Immunohistochemical staining was performed for TGF-β1 with a polyclonal rabbit anti TGF-β1 (Santa Cruz Biotechnology, sc-146, UK) diluted 1/50 in 20% Normal sheep serum (diluted in 0.05 moltral TBS, pH 7.6). Crypts and epithelial surface staining was quantified with a Video-Image-Analyzer Q500MC (Leica Cambridge, UK) examined under a calibrated x 10 objective. Results are expressed as % of staining expression per mm2 of tissue (mean ± SEM) and compared with one-way ANOVA.

In CD, ECO incubation resulted in a significant increase in TGF-β1 expression in all 3 dilutions 1:20 (43.87±3.19, p<0.0001), 1:10 (27.35±7.13, p<0.0001), 1:5 (29.4±14.0, p=0.09) compared with control medium alone (3.57±0.6). EWT incubation resulted in a similar increase in TGF-β1 expression 1:20 (32.87±5.78, p<0.0001), 1:10 (28±11.4, p<0.01), 1:5 (33.1±18.8, p<0.0001) compared with medium alone (3.57±0.6). ED incubation resulted in a modest increase in TGF-β1 expression reaching statistical significance only in 1:10 (17.72±5.23 Vs 3.57±0.6, p=0.03). In UC and control tissues, no significant increase in TGF-β1 expression was observed after incubation with ECO and EWT.

**Conclusion:** Incubation of CD tissue with ED alone only modestly upregulated TGF-β1 expression, but much more marked up-regulation was observed after incubation with EWO and EWT. The effect of these diets on UC and control tissue regarding TGF-β1 expression was not significant. Clinical trials of ECO and EWT in active CD are warranted.

**INCREASED SERUM LEVELS OF YKL-40 IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE**

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**Background:** Initiation of a fibrotic process has been suggested as part of the intestinal response to chronic inflammation in inflammatory bowel disease. YKL-40 has been proposed as a new serum marker of fibrosis. We studied therefore the serum levels of YKL-40 in patients with ulcerative colitis (UC) and Crohn’s disease (CD) in comparison to healthy controls.

**Methods:** YKL-40 serum levels were measured in 106 IBD patients (55 UC and 51 CD) and in 50 matched healthy controls using a commercially available enzyme-linked immunosorbent assay (Metra Biosystems, Inc., CA USA). YKL-40 levels were correlated with disease activity, type and localization. UC and CD diagnosis was based on inflammation to increased bone turnover in a model of colitis.

**Results:** Mean serum YKL-40 levels were 91.1 ± 52.1 ng/ml in UC patients and 94.9 ± 80.3 ng/ml in CD patients, significantly higher compared to healthy controls (66.2± 22.7 ng/ml) (p=0.015). Concerning the disease activity the mean serum YKL-40 levels were higher in the active compared to inactive phase of both diseases. Moreover, a strong correlation between serum YKL-40 and disease activity score and CRP levels was found (Spearman Rank correlation coefficient r=0.30, P= 0.02). Patients with stenotic CD had mean YKL-40 levels (99.5 ng/ml) not significantly different compared to non stenotic disease (93.8 ng/ml). By contrast, current smokers had significantly lower values of YKL-40 than non or ex-smokers (69.9 vs 103.6 & 102.9 ng/ml respectively).

**Conclusions:** Serum levels of YKL-40 are increased in patients with inflammatory bowel disease and this is associated with the inflammatory process rather than with the degree of fibrosis.

**DETECTION OF CHROMIUM MICROPARTICLES IN INFLAMMATORY BOWEL DISEASE (IBD) TISSUES BY ENERGY DISPERSIVE ANALYSIS OF X-RAYS**

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**Introduction:** Inorganic microparticles as compounds of titanium (Ti), silicon (Si), and aluminium (Al) have been implicated in pathogenesis of chronic inflammatory bowel disease such as Crohn’s disease (CD) and benefit of reducing intake of such microparticles has been demonstrated in humans. The pro-inflammatory roles of Al, Si and Ti are unclear. Other elements such as chromium are more strongly granulogenic.

We investigated the distribution and composition of inorganic microparticles in resected intestine from IBD patients and controls by light microscopy, confocal microscopy and energy dispersive analysis of X-rays (EDAX) with special reference to chromium.

**Methods:** Resected human intestines were immunolabelled with CD68 and number of macrophages with inorganic microparticles were quantitated by automated image analysis. Specimens were also prepared for EDAX and analysed in conjunction with a transmission electron microscopy. Selected intestinal tissues were from Crohn’s disease, UC and controls [proximal end of cancer bowel].

**Results:** Immunolabelled, CD68+ ve [macrophages] were significantly greater in CD and UC compared to controls. EDAX revealed compounds of Al, Si and Ti within the macrophages of the inflamed mucosa. The percentage of inorganic microparticle-laden macrophages were [means±SE]: 70.4±5.9 vs 50±5.6 ±1±3 in Crohn’s, UC and controls. The area [%±SE] of mucosa occupied by macrophages were: 6.3±0.3 vs 4.±0.2 vs 2±0.1 in CD, UC and controls.

**Conclusion:** We have confirmed the presence of Ti, Al and Si in intestinal tissues. For the first time we report the presence of chromium microparticles within the IBD tissues. Inorganic microparticles particularly chromium have been reported to be granulogenic in skin, lung and joint tissues. Whether chromium microparticles perpetuate chronic inflammation in IBD, especially CD, requires further investigation.
Results: Administration of TNBS produced distal colitis with a 7-fold elevation in MPO, hypophagia and weight loss. At 5 days body weight of the colitis group was 73% of healthy controls (P<0.001). Weight was similar in colitic and PF groups. There was a 45% reduction in bone formation (osteocalcin), 51% increase in bone resorption (PYD) and a 13% reduction in BMD in the colitic group. Values were similar to those in PF rats. See table.

Conclusions: There are early and marked changes in bone formation and BMD in intestinal inflammation. Undernutrition is the major determinant. The inflammatory process itself, although severe, does not play a significant role.

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Abstract 298

CO-EXISTENT FUNCTIONAL DYSPEPSIA (FD) IN PATIENTS WITH IRritable BOWEl SYNDROME (IBS) WORSENS EXTRA-INTESTINAL SYMPTOMATOLOGY AND QUALITY OF LIFE

E.L. Calvert, L.A. Houghton, P.J. Whorwell. Dept of Medicine, University Hospital of South Manchester, UK

Extra-intestinal (EI) symptomatology and poor quality of life (QOL) are frequently reported by patients with functional gastrointestinal disorders (FGID), such as IBS and FD. Given that these two conditions often co-exist, it was the aim of this study to assess (i) the frequency of occurrence of FD in patients presenting with IBS and vice versa; (ii) EI symptomatology and QOL in these sub-groups; and (iii) the relationship between FGID symptom severity, EI symptomatology and QOL. A questionnaire addressing FD, IBS (Rome II) and EI symptomatology, and QOL (visual analogue scales) was therefore completed by 80 patients presenting at the out-patients clinic with IBS (20–77 yrs; 64 female) and 77 patients presenting with FD (18–74 yrs; 46 female).

Methods: 52 (65%) of patients with IBS had co-existent FD (IBS FD), whilst 45 (58%) of patients with FD had co-existent IBS (FDIBS). Patients with IBSFD reported a greater number of EI symptoms [20(19,22)] than those with FDIBS [17(14,19)] or those with FD only [15(13,19); p=0.06]. IBS only [13(10,16); p<0.001] or FD only [17(14,19); p=0.08]. In addition, patients with IBSFD had a poorer QOL [28(27,30)] than those with FDIBS [31(30,33)] or those with FD only [33(31,36)]. Interestingly, poor QOL correlated with the number of EI symptoms reported in all patient sub-groups [IBSFD r=0.562, FDIBS r=0.582, IBS r=0.568, FD r=0.469; p<0.01]. Furthermore, FGID symptom severity correlated with both the number of EI symptoms and poor QOL in patients with IBSFD [r=0.573, p<0.001; r=0.333, p=0.017, respectively]. FDIBS [r=0.309, p=0.039; r=0.352, p=0.019] and IBS [r=0.392, p=0.035; r=0.339, p=0.08] but not those with FD [r=0.095, p=0.6; r=0.018, p=0.9].

Conclusions: IBS patients with co-existent FD have more extra-intestinal symptomatology and poorer quality of life than patients with IBS only or FD patients with and without co-existent IBS. The occurrence of co-existent FGIDs and extra-intestinal symptomatology could influence treatment choice and outcome.

Abstract 300

USE OF OVER THE COUNTER MEDICATIONS AND ALTERNATIVE THERAPIES IN COMMUNITY BASED IBS “VOLUNTEERS”

G.D. Smith, I.D. Penman. Gastrointestinal Unit, Western General Hospital, Edinburgh, UK

Introduction: Although the majority of irritable bowel syndrome (IBS) patients are managed in primary care, relatively little is known about the natural history of this condition especially treatment efficacy and the use of non-prescription medications and alternative therapies.

Aim: To gather prospective data about the natural history of IBS in a community based group of “healthy volunteers” and to examine their utilization of over the counter (OTC) medications and alternative therapies.

Method: Five hundred and three volunteers (419 females, median 42.1 years) with a confirmed diagnosis of IBS using Rome II criteria were recruited and assessed as previously described*. A majority of IBS volunteers had consulted a hospital specialist at some stage (n = 318, 69%). One hundred and thirty-eight (27%) volunteers had consulted their General Practitioner (GP) within 4 weeks and 346 (69%) were taking prescribed medication. OTC preparations were being taken in nearly one third of IBS (see table12). Alternative therapies were employed by 15 % of patients (hypnotherapy, homeopathy, aromatherapy) and 140 volunteers employed relaxation therapies to counter their symptoms. Dietary adjustments had been made by 80% of the study group.

Conclusion: Despite the high demand the management of IBS places upon health service resources in both primary and secondary care settings many IBS patients self-medicate on a regular basis and utilise alternative therapies to treat their symptoms.

Abstract 300 Prescribed vs. OTC medications in IBS “healthy volunteers”

<table>
<thead>
<tr>
<th>Drug taken</th>
<th>Prescribed (n=346)</th>
<th>OTC (n=146)</th>
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<tr>
<td>Anti-spasmodics</td>
<td>135</td>
<td>24</td>
</tr>
<tr>
<td>Alter gut motility</td>
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<td>Bulk laxatives</td>
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<tr>
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<td>Herbal remedies</td>
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<tr>
<td>Others</td>
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</tr>
</tbody>
</table>

Financial support for this study was given by Glaxo Smith Kline. *Smith, G.D & Penman, I.D, Gut (2001); 48 (suppl II): A45.

Abstract 301

IS LACTOSE INTOLERANCE IMPLICATED IN THE DEVELOPMENT OF POST INFECTIOUS BOWEL SYMPTOMS IN PREVIOUSLY ASYMPTOMATIC PEOPLE?

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Introduction: Studies looking at lactose intolerance in post-infectious IBS patients are scanty and the relationship between lactose development of symptoms is considered diagnostic of lactose intoler-

Aims: We wished to see if lactose intolerance was evident in a cohort of subjects with a recent diagnosis of stool culture positive gastro-enteritis.

Methods: 42 subjects with recent enteric infection underwent the combined lactose tolerance test 3 to 6 months after their gastro-enteritis. To reduce false positive and negative results, subjects had fasted, refrained from smoking on the day and denied recent anti-biotic use. Using the self-complete Rome II modular questionnaire, 24 were diagnosed with post-infectious IBS (16) or functional diarrhoea (8) and 18 were not (controls). Lactose intolerance was diagnosed by a test of absorption (lactose tolerance test) and malabsorption (lactose breath hydrogen test) according to accepted protocol. An increase in plasma glucose by less than 1.1mmol/L together with a rise in the breath hydrogen value over 20ppm from baseline together with the development of symptoms is considered diagnostic of lactose intoler-

Conclusions: IBS patients with co-existent FD have more extra-intestinal symptomatology and poorer quality of life than patients with IBS only or FD patients with and without co-existent IBS. The occurrence of co-existent FGIDs and extra-intestinal symptomatology could influence treatment choice and outcome.

Results: In the subjects who had developed functional diarrhoea or IBS, none had evidence of lactose intolerance. Although there were four tests where the plasma glucose failed to increase by more than 1.1 mmol/L, the breath test was not confirmatory and all the subjects were asymptomatic post test. In the control subjects, there was only one positive combined test. Since this was in a subject who was currently asymptomatic, lactose intolerance could not be excluded. In addition, there were six other subjects in the asymptomatic group where the plasma glucose failed to increase by more than 1.1 mmol/L but the breath test was not confirmatory and again, no subject complained of symptoms post test.

Conclusions: Infectious diarrhoea does not cause persistent lactose intolerance. Lactose intolerance does not appear to be implicated in the aetiology of post-infectious IBS or functional diarrhoea. Advice to avoid dairy products in patients presenting with post-infectious bowel symptoms on the basis they may have lactose intolerance is unfounded.

302 5-HYDROXYTRYPTAMINE (5-HT) CONCENTRATIONS IN THE GASTROINTESTINAL TRACT OF FED AND STARVED RATS

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Introduction: There is evidence to suggest that the differing clinical presentation and response to therapy of men and women with functional gastrointestinal disorders may be related to differences in the processing of 5-HT. There is also evidence that 5-HT levels increase in the circulation following a meal in irritable bowel syndrome patients and that this may be related to postprandial increase in symptoms.

Methods: Eight patients (4 DD, 4 controls) following anterior resections for rectal tumours. Isotonic organ bath experiments were used to examine muscarinic sensitivities to exogenous acetylcholine.

Results: Circular muscle in DD showed a reduction in ChAT activity (DD: range 10–100%, median 45. Controls: 45–100%, median 95%), an up-regulation of M3 receptors (DD: 5–27, median 16. Controls: 1–5, median 3) and increased sensitivity to exogenous acetylcholine (DD: EC50 range 0.15–12µmol, median 4.0. Controls: 0.4–55, median 17). Longitudinal muscle showed a reduction in ChAT activity (DD: range 90, median 45. Controls:30–100%, median 95), an up-regulation of M3 receptors (DD: 2–32, median 10. Controls: 1–5, median 2) and increased sensitivity to exogenous acetylcholine (DD: EC50 range 0.3–9.5µmol, median 4.0. Controls: 0.5–100, median 10). All p-values <0.02.

Conclusions: Our results show cholinergic denervation hypersensitivity in DD, a recognised phenomenon in skeletal muscle, but one not previously reported in association with smooth muscle.

304 ACUPUNCTURE FOR IRRITABLE BOWEL SYNDROME: A BLINDED PLACEBO-CONTROLLED TRIAL

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Irritable bowel syndrome is common and many patients currently fail to find adequate relief from their symptoms. It is claimed that acupuncture is effective for a majority of these patients but there are few data to support this.

Sixty patients with well-established irritable bowel syndrome were recruited to a controlled trial of traditional Chinese acupuncture. The blinded comparator was sham acupuncture administered by the second of 2 therapists who alone was aware of the randomisation, and who otherwise followed the prescription of the first. The primary end-point was a defined fall in the symptom score at 13 weeks (by intention to treat). The prior expectation was a 30% placebo response, and a response rate of about 70% from acupuncture, for which the study was adequately powered.

Patients in treated and sham groups improved significantly during the study - mean improvement in scores being equal (minus 1.9) and significant for both (p<0.05; 1-tailed t test). There was a small numeric but non-significant difference between the response rate in patients receiving acupuncture (40.7%) and sham treatment (31.2%). Some of the secondary end-points marginally favoured active treatment, but an improved symptom score of any degree of magnitude occurred more often with sham therapy (65.6% vs 59.2%). For no criterion was statistical significance approached.

Traditional Chinese acupuncture is relatively ineffective in irritable bowel syndrome, and the magnitude of any effect appears insufficient to warrant investment in acupuncture services for this group of patients.

305 COMMUNITY BASED “VOLUNTEERS” WITH IRRITABLE BOWEL SYNDROME: SYMPTOM PATTERNS, HEALTH RELATED QUALITY OF LIFE AND USE OF HEALTH CARE RESOURCES

G.D. Smith, I.D. Penman. Gastrointestinal Unit, Western General Hospital, Edinburgh, UK

Introduction: Irritable bowel syndrome (IBS) has a substantial impact upon patients’ quality of life and medical resources among those attending hospital clinics.

Aim: To examine the symptom patterns, health related quality of life and use of health care resources in a group of community based, “healthy volunteers” with IBS.

Patients and Methods: Five hundred and three volunteers (419 females, median 42.1 years) with a confirmed diagnosis of IBS using Rome II criteria were recruited via a national newspaper advertising campaign as previously described*. Abdominal pain / discomfort was reported to be the predominant symptom in 62% of volunteers, whereas 31% reported altered bowel habit as most bothersome. Health related quality of life was measured with EuroQol EQ-5D questionnaire.

Results: A majority of volunteers reported a history of IBS symptoms for over a year, with more than half reporting symptoms for more than five years. A half of all volunteers (n = 254) had received their diagnosis from their General Practitioner (GP) and 138 (27%) had consulted their GP within the previous month. 318 (63%) had attended a hospital specialist at some stage. Most commonly prescribed drugs for this group were anti-spasmodics (38 %), and...
Results: In C-IBS, the MI and freq in response to a fat rich meal were significantly greater than to either protein (p=0.006, p=0.003) or carbohydrate (p=0.001 p=0.005) rich meals in the first hour but not in the second. In D-IBS, MI and freq were significantly higher for a fat rich meal compared to a protein rich meal (p=0.009 p=0.002) during the first hour and to a carbohydrate rich meal (p=0.027 p=0.048) in the second hour. In healthy controls, there was no significant difference in the MI and freq in the first hour between the three meals, however during the second hour, the MI and freq were significantly lower in response to a fat rich meal as compared to protein (p=0.003 p=0.001) and carbohydrate (p=0.003 p=0.001) rich meals.

Conclusion: This study shows that postprandial motor activity in IBS patients is different from healthy individuals. In keeping with the effect of a fat rich meal on gastric motility, healthy individuals respond to a fat rich meal with reduced MI and freq as compared to carbohydrat and protein rich meals. The IBS patients show an increased post-prandial MI and freq in response to a fat rich meal as compared to carbohydrate and protein rich meals. These opposing effects suggest that food handling by small bowel is abnormal in IBS patients.

306 POSTPRANDIAL SMALL BOWEL MOTILITY IN IRRITABLE BOWEL SYNDROME (IBS) PATIENTS AND HEALTHY CONTROLS IN RESPONSE TO ISOCALORIC MEALS

S. Zar, F.D. Castillo, A. Grundy, M.J. Benson, D. Kumar. St George’s Hospital Medical School, London, UK

Background: IBS patients frequently report postprandial worsening of symptoms suggesting that small bowel motility may be abnormal in this period. The aim of this study was to compare postprandial small bowel motor activity between IBS patients and healthy controls.

Method: Ambulatory small bowel manometry was performed in 19 IBS patients (2M/17F; 10 constipation predominant (C-IBS); 9 diarrhoea-predominant (D-IBS)) and 4 healthy controls (2M/2F). Each subject ingested 3 isocaloric test meals (fat, protein and carbohydrate rich) in a random order. Automated data analysis was performed using a validated software programme. Postprandial activity was analysed for Motility Index (MI), contractile frequency (freq) and median amplitude in one-hour epochs.

Results: D-IBS group had significantly higher MI (p<0.001), freq (p<0.001) and amplitude (p<0.001) compared to C-IBS group in the first hour. The difference in MI and amplitude were significant throughout the postprandial period, but freq difference was not significant after the first hour. C-IBS group had significantly lower MI (p<0.001) and amplitude (p<0.001) and freq (p=0.002) compared to controls. These differences were significant throughout the postprandial period except in the third hour where the difference in freq was not significant. D-IBS group had significantly lower MI (p=0.038) and freq (p=0.001) compared to controls. These differences were significant throughout the postprandial period and was significantly higher in the D-IBS group as compared to controls in the third (p=0.006) and fourth (p=0.008) hour but only reached borderline significance in the first (p=0.162) and second (p=0.082) hours.

Conclusion: In C-IBS patients, the MI, amplitude and freq were consistently lower in the postprandial period as compared to the healthy controls and D-IBS patients. This may result in the reduced bowel frequency observed in these patients. The D-IBS patients had reduced postprandial freq and MI but higher amplitude compared to healthy controls. This may help to explain the increased frequency and loose stools observed in these patients.

308 EFFECTS OF CALCIUM POLYCARBOPHIL ON COLONIC TRANSIT IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Background: Calcium polycarbophil is useful for improving abdominal symptoms in patients with irritable bowel syndrome (IBS). However, the effects of calcium polycarbophil on colonic transit have not been characterized.

Aim: To investigate colonic transit before and after administration of calcium polycarbophil in IBS patients.

Methods: A total of 22 IBS patients, 14 diarrhea type (9 women and 5 men) and 8 constipation type (8 women), were selected under the Rome II criteria: with a median age of 47 yr (range = 18–70 yr). Before administration of calcium polycarbophil, 3 sets of distinctive markers were ingested by IBS patients on 3 successive days. A single abdominal X-ray was taken on the 5th and 7th day. Mean colonic transits were calculated by the number of markers in the colon (Metalf AM, Phillips SF, 1987). Bowel movements and the Bristle scale score were also measured. After oral administration of 3,000 mg/day of calcium polycarbophil for 6 weeks, transit times of radiopaque markers were measured again.

Results: Diarrhea type: Mean colonic transits were 3.2 ± 2.9 hr (Mean ± SD) before administration of calcium polycarbophil, 10.4 ± 7.0 hr after administration (p<0.05). Bowel movements were 2.4 ± 0.9 times/day before, 0.7 ± 0.5 times/day after administration (p<0.05). The Bristle scale score was 6.2 ± 0.7 before, 4.8 ± 0.7 after administration (p<0.05). Constipation type: Mean colonic transits were 48.8 ± 32.1 hr (Mean ± SD) before administration of calcium polycarbophil, 23.4 ± 37.9 hr after administration. Bowel movements were 2.1 ± 0.4 times/week before, 0.0 ± 0.9 times/week after administration (p<0.05). The Bristle scale score was 1.9 ± 0.4 before, 3.0 ± 0.7 after administration (p<0.05).

Conclusion: Calcium polycarbophil is useful in improving colonic transit in diarrhea and trends to accelerate colonic transit in constipation. Bowel movements and stool type were improved in both conditions.

309 ALOE VERA LIQUID MAY IMPROVE SYMPTOMS IN IBS RESISTANT TO CONVENTIONAL TREATMENTS

K. Davis, D. Kumar, ‘M.A. Mendall. St George’s Hospital Medical School;’ Mayday University Hospital, UK

Background: There are anecdotal reports of the efficacy of Aloe Vera in IBS.

Aims: To assess the effectiveness of a liquid formulation IBSCOL.

Subjects and Methods: We performed a double-blind placebo controlled randomised trial. Subjects were aged 16–65 and met the Rome 2 criteria for IBS. All had failed conventional treatments with antisapomics or dietary manipulation. They were recruited from gastroenterology clinics at two hospitals. Treatment was with IBSCOL 50mls qds for 1 month. Subjects were interviewed at 0, 1 and 3 months. The IBS questionnaire of Whichor (APT 1997) was used to detect change in symptoms. The primary endpoint was a response to
population.

**Results:** 26 subjects were randomised into placebo and 32 into active treatment. 4 subjects in the placebo group and 2 in the active group failed to complete the study medication, the main reason being nausea reported by 3/26(12%) of the placebo group and 1/32(3%) of the active group respectively. 22/27(82%) and 27/32(84%) respectively of subjects were followed to 1 month and 6/8(76%) and 25/32(78%) for 3 months. 72% and 91% had diarrhoea predominant or mixed IBS. 10/22(45%) in the placebo and 18/27(67%) in the active group showed a response to treatment at 1 month (p=0.13). There was no difference by 3 months. There was significant improvement in pain score at 3 months (p=0.05). In the diarrhoea and mixed bowel habit subgroup, there was a trend towards an improvement in IBS score at 1 month, 44% v 67% improving (p=0.15), a significant improvement in the proportion of subjects with any pain in the past week p=0.046, a trend towards an improvement in the % of days without pain in the past week (p=0.06), and in satisfaction with bowel habit p=0.06. By 3 months these changes had disappeared.

**Conclusion:** In this study of resistant IBS, there was some evidence of efficacy for the IBSCol formulation of Aloe Vera that was well tolerated. These findings require replication in a larger, and older, group of patients.

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**Background:** IBS can develop after gastro-enteritis. Cognitive factors (such as illness representation) may be important influences on the development of post-infectious IBS but have not been extensively studied.

**Aims:** Do differences exist in illness perception in people with recent stool culture positive bacterial gastro-enteritis with and without a prior FGID and also in those who go onto develop a FGID compared with those who do not.

**Methods:** 217 people with recent bacterial gastro-enteritis completed a postal gastro-intestinal disease questionnaire (GIDQ) incorporating the Rome II modular questions relating to IBS, functional dyspepsia or functional diarrhoea asking about symptoms during the last year. The cases were divided into those with (n=82) and without a prior FGID (n=122). All cases then completed the Illness Perception Questionnaire (IPQ -Weinman et al.), which taps into 5 areas of illness perception: Causation, identity, timeline, consequences and control/metabolism. Those without a prior FGID were followed up and a similar GIDQ was completed at six months. 25 people subsequently developed a FGID and 82 did not.

**Results:** People with a prior FGID had significantly more symptoms (identity domain) and scored significantly higher on the timeline and consequence scores than those without. People who developed a FGID had higher consequence scores than those who did not and a non-significantly higher number of symptoms. Neither comparative group differed in the control/cure scores or causation scores.

**Conclusions:** People with recent bacterial gastro-enteritis and a prior FGID have more symptoms relating to their gastro-enteritis, think their illness will last longer and is more serious than those without a prior FGID. People who develop a post-infectious FGID tend to believe their gastro-enteritis is more serious than those who do not. We conclude therefore that having a FGID influences a person’s perception of bacterial gastro-enteritis. However, illness perception is not a strong predictor for the subsequent development of a FGID.

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**Gender Differences and Effects of Age on 5-Hydroxytryptamine (5-HT) Turnover: Implications for Irritable Bowel Syndrome (IBS)**

P. Whitaker, L.A. Houghton, W. Madira, J. Lune. - Dept of Chemical Pathology, University of Leicester; Dept of Medicine, University Hospital of South Manchester, Manchester, UK

Irritable bowel syndrome (IBS) is more common in women than men, suggesting that they may have a predisposition to the condition. As recent studies have suggested that 5-HT may play a role in the aetiology of IBS, we investigated whether fasting platelet depleted plasma 5-HT and its metabolite, 5-hydroxyindole acetic acid (5-HIAA), and platelet 5-HT concentrations are different between healthy males (n=22; aged 21–63 yrs) and females (n=22; aged 22–63 yrs). The effect of increasing age on fasting 5-HT and 5-HIAA concentrations was also assessed. 5-HT and 5-HIAA concentrations were measured by a reverse-phase high performance liquid chromatography (HPLC) with fluorometric detection.

**Results:** Healthy females had similar concentrations of both fasting platelet and plasma 5-HT (platelet: 603 ng/10

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**Modulation of the Human Swallowing Mechanism by Thermal and Chemical Stimulation in Health and After Brain Injury**

S. Hamdy, S. Jilani, V. Price, N. Hall, M. Power (introduced by D.G. Thompson). Department of GI Sciences, Hope Hospital, Eccles Old Road, Salford M6 8HD, UK

**Background/Aims:** Swallowing is a complex neuromuscular activity dependent on sensory feedback. Following stroke, dysphagia is commonly treated by sensory stimulation techniques including thermal and chemical stimulation. However, little data support the use of such methods to favourably swallow physiology. Our aims were to explore the effects of thermal (cold) and chemical (citrus) alterations on the performance of water swallowing in healthy and in stroke patients.

**Methods:** Healthy volunteers (n=65, mean age 45 yrs, 25 male, 40 female) and acute (72hrs) stroke patients (n=12, mean age 61.3yrs, 4 male, 8 female) admitted to a stroke rehabilitation unit were studied. A bedside timed 50 ml water-swallowing test was performed in a randomised manner at a) room temperature (RT), b) cold (4°C) (CD), c) 5% citrus (CT) and d) combined cold and citrus (CD+CT). The time taken to swallow (speed), and the number of swallows (capacity) per volume were measured with each condition on 3 occasions. Comparisons between each condition were made with ANOVA.

**Results:** In health, whilst both CD and CT alone showed a trend towards altering the swallow, compared to RT water, only combined CD+CT slowed the speed (10.3 vs. 11.3 ml/s, p<0.01) and the capacity (14.6 vs. 16.4 ml/swallow, p<0.01) of swallowing. A sub-analysis, based on age showed that this effect was present both in the young (<60yrs) and old (>60yrs) alike. When applied to stroke, compared to RT, CD+CT slowed both the speed (5.0 vs. 6.1 ml/s, p=0.06) and capacity (9.7 vs. 11.1 ml/swallow, p=0.05) of swallowing.

**Conclusions:** Combining thermal and chemical sensory modalities to water boluses can substantially alter the pattern of normal swallowing in health and after stroke. The ability to slow and reduce the amount of volume taken per swallow may be advantageous in patients with dysphagia where inappropriately judged bolus intake is a factor in the development of aspiration.
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313 DOES IMPLEMENTATION OF ANTIBIOTIC PROPHYLAXIS IN PEG INSERTION AFFECT INCIDENCE OF WOUND INFECTION?

V. Christopher, S.D. Hearing, J. Smithson, S. Hughes. Dept Gastroenterology, Southmead Hospital, Bristol, UK

Percutaneous gastrostomy (PEG) insertion is associated with a significant morbidity. Recent studies suggest that antibiotics given at the time of PEG insertion may reduce complications, in particular soft tissue infection. A previous audit of all PEGs from Feb 1998 to July 1999 performed in our unit revealed a high rate of PEG site infection, although most cases were not severe (14.2%). A policy of prophylactic antibiotics (Ampicillin 1g IV, Gentamicin 80mg IV) administered at the time of PEG insertion was instituted and complication rate was revised.

Methods: Retrospective case note review from Jan 2000 to April 2001.

Results: 79 PEGs performed, 51 (65%) notes were available for review. Mean age 70.8yrs (SD 13.3, range 36–98), M:F = 27:22. Indications for PEG: CVA/CNS disorders =27, pre-op ENT =6, malignancy =12, nutrition support =12. In both audits patient characteristics were similar and differed only in antibiotic use. Audit 1: 4/42 (9%) concurrent antibiotics, 38/42 (91%) none given. Audit 2: 37/51 (73%) antibiotics given, 14/51 (27%) none. See table.

Abstract 313

<table>
<thead>
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<th>Audit 1 n=42</th>
<th>Audit 2 n=51</th>
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Conclusions: On basis of this data, there was no statistically significant reduction wound sepsis, or mortality from the routine use of antibiotics at the time of PEG insertion. However, not all case notes were available and this reduced the number of subjects included in this audit. This reduction in numbers may mean that non-significance does not exclude a clinically important difference in PEG site, wound infection. Audit of complications following PEG insertion is continuing.

314 DO PATIENTS ON HOME GASTROSTOMY FEEDING NEED TO ATTEND ENDOSCOPY UNITS FOR MANAGEMENT OF MINOR COMPLICATIONS?

A. Hurst, A. Bassi, R. Nicholson, P. O’Toole. University Hospital Aintree (UHA), Liverpool, UK

Introduction: A growing number of patients are being discharged into the community with gastrostomy feeding tubes. Minor complications related to the tube are not uncommon in this group but availability of expert advice in the community is limited. As a result many patients contact the Endoscopy unit where the tube was inserted for help in managing minor complications.

Objectives: To identify the reasons that prompted review of patients with gastrostomy in the endoscopy unit. The advice given/action taken was also recorded to assess whether hospital attendance could be avoided if appropriate support care was available in the community.

Methods: Data was collected retrospectively over 2 years (01/99 -12/00) of patients attending the endoscopy unit at UHA with PEG tube related problems.

Results: Seventy patients attended our endoscopy unit with problems relating to their gastrostomy tube. The mean age of these patients was 64.5 years (range 32 – 85 years). The reasons for attendance were: red/inflamed and sore areas around the PEG stoma site (35%), broken/missing attachment (14%), blocked tubes (14%), leaking (12%), tube displacement (12%), hypergranulation (10%) and split tube (2%). The management of these problems included: trimming or attachment replacement (30%), cleaning and swabbing for infection around stoma sites (25%), advice regarding dressing (13%), change of PEG via endoscopy (15%) or without the aid of endoscopy (7%) and miscellaneous (10%). Eighty five percent of the presenting complaints could have been solved in the community by an appropriately trained staff.

Discussion: Our experience shows that more than three quarter of the problems could have been dealt in the home environment and would have required only one visit by the liaison nurse. This audit provides further evidence for the recommendation by the BAPEN that creating a suitable support system to continue treatment at home is desirable and would avoid unnecessary hospital attendance.

315 IMPROVED NUTRITIONAL RECOVERY ON AN ELEMENTAL DIET IN ZAMBIAN CHILDREN WITH PERSISTENT DIARRHOEA AND MALNUTRITION

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Introduction: The persistent diarrhoea-malnutrition syndrome (PDM) remains a leading cause of morbidity and mortality in many resource poor countries, but even in hospitals treatment is unsatisfactory. We report a randomised controlled trial of an elemental diet compared to standard nutritional rehabilitation for PDM in the University Teaching Hospital, Lusaka.

Study design: 200 children (106 HIV seropositive, 90 HIV seronegative) were randomised to an elemental diet with Neocate (ShS International) or to a skimmed milk-based followed by soy-based diet. Treatment was given for 4 weeks in hospital, and intestinal and systemic infection treated with routine therapies.

Results: 155 children completed 4 weeks of therapy, 39 died and 6 were lost. They were severely malnourished with median baseline weight-for-age z scores around –4.0; 9% were underweight, 23% had marasmus, 47% had kwashiorkor, and 21% marasmic-kwashiorkor. Weight gain was greater in the Neocate group (median gain in weight-for-age z score 1.23, interquartile range 0.89 – 1.57) compared to Control (0.87, 0.47 – 1.25; p=0.002), despite greater calorie intakes in the Control group. Increase in haemoglobin concentration was also greater in the Neocate group (0.8g/dl, 0 – 1.8) than the Control group (0.3, 0.6 – 1.6; p=0.04). Diarrhoea frequency and global recovery scores improved equally in both treatment groups. Mortality was higher in HIV seropositive children and those with cryptosporidiosis, but did not differ between treatment groups.

Conclusions: Exclusive use of an elemental diet for 4 weeks was associated with significantly improved nutritional recovery in children with severe PDM, irrespective of HIV infection.

316 PERCUTANEOUS ENDOSCOPIC GASTROSTOMY: PROSPECTIVE CLINICIAN REVIEW APPROPRIATELY DECREASES INSERTION

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Aims: Percutaneous endoscopic gastrostomies (PEG) are an increasingly frequent method for providing nutritional support. We set out to assess current practice surrounding referrals for PEG insertion in a district general hospital and their outcomes.

Methods: All patients who were referred for PEG insertion over a six-month period were assessed. Data were prospectively collected for each referral with regards to; duration between dates of admission, referral and insertion of PEG; indications; appropriateness of referral; prior clinical assessment by dietician or speech therapists and ability of patient to give informed consent for the procedure. Six-month follow up of all patients referred was then performed by case record examination.

Results: 50 patients were referred for consideration of PEG inser.

24% of patients were deemed inappropriate for PEG insertion. This was either because the patient was currently unfit/had a poor prognosis or was able to swallow or because it would be technically difficult. There was a 44% 30-day mortality rate in the PEG insertion group compared to a 50% 30-day mortality rate in the PEG not
inserted group (a 70% rate if patients who did not have a PEG inserted because they had an intact swallow are excluded from consideration). 60% of patients were unable to give informed consent for the procedure and these patients had a much higher 30-day mortality rate, 60% compared to 21% in those able to give informed consent. Mortality rates also varied appreciably according to the indication for PEG insertion. The overall six-month mortality rate for all patients referred was 70%.

Conclusions: The 30-day mortality rate following PEG insertion was higher than in published series, however this is offset by an even higher rate in patients in whom PEG insertion was declined. Clinician review appropriately reduced the number of PEG insertions, thereby reducing workload and preventing patients from undergoing an unnecessary procedure. Simple clinical predictors such as reviewing the indication for PEG insertion and the ability of patients to give informed consent may further reduce inappropriate PEG insertions. Special care needs to be taken when assessing patients unable to give informed consent as this vulnerable group has a much higher mortality rate.

POST-PYLORIC NASOJEJUNAL TUBE FEEDING IN CRITICALLY ILL PATIENTS
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Introduction: Enteral nutrition is regarded as superior to and is cheaper than parenteral nutrition in critically ill patients. Oral and nasogastric tube (NGT) feeding may not always be possible or successful in these patients due to vomiting or gastric stasis. Nasojejunal tube (NJT) feeding is an alternative method of providing enteral nutrition. The use of NJT feeding in 100 patients is presented.

Methods: Patients who had NJT feeding were identified from the dietetic records. Their records were reviewed and data on the indication for and outcome of NJT feeding was recorded.

Results: 102 separate instances of NJT feeding were attempted in 100 patients. 36 patients had failed NGT feeding and 23 patients had parenteral feeding prior to NJT feeding. The commonest indications for the use of NJT feeding were reduced oral intake during chemotherapy (24 patients), gastric oesophageal malignancy (14), prolonged or complicated post-operative recovery (14), acute pancreatitis (12), benign gastro-intestinal disease (10) and severe burns (10). 96 patients had an NJT successfully placed and in 88 nutritional requirements were successfully met. NJT feeding was continued for a median of 11 days (range 0–180 days). 65 patients were discharged home, 30 died as an in-patient and 7 were discharged to another hospital. 11 patients had NJ feeding continued at home. In 37 patients, medication was given by the NJT. There were one serious complication of a significant small bowel bleed possibly caused by NSAIDs given down the NJT. Minor complications included NJT displacement necessitating replacement (13), diarrhoea (6) and blocked NJT (4). 1 patient had small bowel obstruction that appeared to be related to their underlying malignancy.

Conclusions: NJT feeding can successfully and safely meet nutritional requirements of many critically ill patients. Patients with gastric stasis or vomiting, such as patients undergoing chemotherapy, with severe burns, prolonged or complicated post-operative recovery or with acute pancreatitis, can be successfully fed nasojejunally. There may be cost savings related to reducing the demand for parenteral nutrition.

FISH OIL REDUCES PGE2, SYNTHESIS BUT INCREASES IFN-γ AND IL-4 SYNTHESIS BY PBMC IN HEALTHY SUBJECTS
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Prostaglandin E2 (PGE2) is an eicosanoid synthesised by monocytes from the n-6 polyunsaturated fatty acid (PUFA) arachidonic acid (AA) with proposed effects on CD4+ T-helper cells (Th1 and Th2). Increased intake of the n-3 PUFA eicosapentaenoic acid (EPA) (in fish oil) may inhibit PGE2 production by substrate competition or enzyme inhibition. We investigated the effect of increasing dietary n-3 PUFA intake, with or without antioxidant co-supplementation, on plasma and erythrocyte phospholipid composition and ex vivo LPS stimulated monocyte PGE2, synthesis, and Con A stimulated T-cell proliferation (L prolif) and synthesis of interferon-γ (IFN-γ) (Th1) and interleukin-4 (IL-4) (Th2).

Sixteen healthy male subjects were randomised to 12 weeks of antioxidant co-supplementation (vitamins A, C and E and selenium (n8) or placebo (n8). All subjects simultaneously received identical regimens of fish oil equivalent to 4 weeks of 0.3 g/d, 1 g/d and 2 g/d n-3 PUFA consecutively. Venous blood was taken at baseline, 4, 8 and 12 weeks for phospholipid composition, cell isolation and culture. EPA incorporation increased incrementally in all phospholipid pools with increasing n-3 PUFA intake. Only T-cell proliferation was modulated by antioxidant co-supplementation (augmented response to n-3 PUFA), and therefore for cytokine/PGE2, production the two groups were pooled (n16). See table.

n-3 PUFA dietary supplementation is associated with inhibition of PGE2, synthesis by monocytes and parallel increases in Th1, and Th2, cytokine synthesis and T-cell proliferation, in a dose responsive manner. Therapeutic efficacy of n-3 PUFA may relate to the relative importance of monocyte or T-cell activation and PGE2, in the inflammatory response.

THE NASAL LOOP PROVIDES AN ALTERNATIVE TO PEG IN HIGH RISK DYSPHAGIC STROKE PATIENTS
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Background: The nasal loop (NL) is a novel method of securing nasogastric tubes (NGT) in dysphagic stroke patients that can be performed under light or no sedation. A loop of tape is passed round the nasal septum and this secures the NGT in place.

Aims: To demonstrate that NL in dysphagic stroke patients: (1) improves nutrition; (2) may offer an alternative to PEG in high risk patients; (3) may avoid premature PEG placement for NGT displacement.

Methods: A six month prospective audit of dysphagic stroke patients: referred for PEG. Patients referred to one gastroenterologist were offered NL. Others proceeded direct to PEG. NL patients had feed intake monitored prior to and post NL. Complications and outcome at 3 months were recorded for all patients.

Results: Group 1) 14 patients had NL for a median of 15 days (range 1 – 46). Median prescribed feed intake before NL was 0% (range 0 – 47%), after NL was 100% (range 67 – 100%). 4 patients recovered normal swallowing and 4 patients died. 6 proceeded to PEG of whom 4 died within 3 months, 1 recovered normal swallowing and 1 continued to be PEG fed.

Group 2) 7 patients proceeded direct to PEG, 1 died and 6 were alive and PEG fed at 3 months. There were 6 complications from PEG insertion (including 1 peritonitis, 2 aspiration pneumonias, 2 wound infections and 1 severe pain) and no patients recovered normal swallowing.

Mean (SD) values. *P<0.05 compared to baseline.
Conclusions: NL improves nutritional intake and allows some patients to recover swallow without PEG. NL may avoid PEG intervention in patients who have a poor prognosis. Mortality was higher in NL patients which may be due to referral bias.

[320] THE SHORT TERM EFFECTS OF TOTAL PARENTERAL NUTRITION (TPN) ON FATIGUE: A DOUBLE BLIND PLACEBO CONTROLLED STUDY
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Aim: We wanted to know if the feeling that some patients report of feeling better soon after starting TPN was real or due to placebo.

Methods: Design: Prospective, double blind, randomized study. Setting: Setting: University teaching Hospital. All patients who underwent liver biopsy between Nov 2000 and Aug 2001 had the proposed biopsy site localised by traditional ultrasound. The actual biopsy site was then determined using US by a single operator (trainee) in the same sitting. Percussion by a trainee or consultant. The actual biopsy site was then moved up by one space. The reasons for the change in site were, same space but more anterior or posterior placement in 9 patients, a change in biopsy site after US examination. The changes in the biopsy site were offered a choice between blind and US guided biopsy. 56 Liver biopsies were performed. Of these, 50% of patients. There is no difference in the blind localisation site by consultant and trainee (p=0.77) in (1) and a vessel (1) and the better depth of the biopsy needle (5).

Results: Between 2–6 hours the change in fatigue was significantly different between the two groups for RT (p<0.000) and GS (p=0.02). Over the period 2–24 hours there were significant differences between the two groups for RT (p=0.01) and GS (p<0.02). By 24 h the differences between the two groups had diminished. At 48h the results of the two groups were similar.

Conclusions: Within 6 hours of starting TPN, fatigue is improved. Water, Na, and K infusion, and placebo do not account for this effect.

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[321] ULTRASOUND ASSISTED PERCUTANEOUS LIVER BIOPSY
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Objective: To identify whether US makes a difference to the site of liver biopsy compared to the traditional blind method.

Methods: Design: Prospective study. Setting: University teaching Hospital. All patients who underwent liver biopsy between Nov 2000 and Aug 2001 had the proposed biopsy site localised by traditional percussion by a trainee or consultant. The actual biopsy site was then determined using US by a single operator (trainee) in the same sitting. Then the biopsy was performed using the most appropriate site, away from potential structures that can be encountered in the biopsy needle path.

Results: All patients preferred to have US guided biopsy when they were offered a choice between blind and US guided biopsy. 56 Liver biopsies were performed. Of these, 50% [28] of the patients needed a change in biopsy site after US examination. The changes in the biopsy site were, change in the angle of the needle in 4 patients, in the same space but more anterior or posterior placement in 9 patients, one or more spaces below in 8 patients and in 7 patients biopsy site moved up by one space. The reasons for the change in site were, proximity to gall bladder (12 patients), lung (6), bile duct (5), kidney (1) and a vessel (1) and the better depth of the biopsy needle (5). There was no difference between consultant and trainee (p=0.77) in the frequency with which the proposed biopsy site was changed after US examination.

Conclusions: US did make a difference in the liver biopsy site in 50% of patients. There is no difference in the blind localisation site by consultant and trainee. Adoption of US guided liver biopsy is preferable provided the resource is available.

[322] OBSERVER VARIATION IN STAGING RECTAL CANCERS BY ENDORECTAL ULTRASOUND
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Aim: To determine the accuracy of endorectal ultrasound and the intra and inter observer variation in the preoperative staging of rectal cancers between the specialties.

Methods: Rectal cancer patients undergoing primary surgery were included. Histopathology was used as the gold standard. The observers included two radiologists and two colorectal consultant surgeons.

Results: Endorectal ultrasound: Postoperatively looking at hard copies, surgeon 1 (S 1) ‘T’ staged 16 out of 31 cancers accurately. Kendall’s tau (K = 0.46) and surgeon 2 (S 2), ‘T’ staged 7 out of 31 accurately (K = 0.34). Radiologist 1 (R 1), ‘T’ staged 14 out of 31 cancers accurately (K = 0.242) and radiologist 2 (R 2), ‘T’ staged 15 out of 31 cancers (K = 0.302). (R 1) had an excellent intraobserver agreement in ‘T’ staging (K = 0.792) and (R 2) a perfect intraobserver agreement (K = 1) compared to their original preoperative staging. Between R1 and R2 interobserver agreement was good (K = 0.681). Between (S1) and (S2) interobserver agreement was moderate (K = 0.46) and between R1 and S1 agreement was good (K = 0.53). The intra and interobserver agreement for nodal ‘N’ staging were very similar to the T staging.

Conclusion: Endorectal ultrasound has been shown previously to be the most accurate method of staging to assess local invasion in rectal cancer. This study does not confirm that observation and it may be due to hard copies used rather than real time images and inflammation around the tumour leading to incorrect staging. However we found that the overall intra and inter observer agreement using hard copies is good.

[323] INITIAL EXPERIENCE WITH ENTERAL STENTS FOR PALLIATION OF NON-OESOPHAGEAL PRIMARY MALIGNANT OBSTRUCTION OF THE UPPER GASTROINTESTINAL TRACT
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Background: Expandable metal stents are increasingly used in the palliation of malignant obstruction in the gastrointestinal (GI) tract. It provides a non-surgical means of relieving obstruction in patients at high risk from surgical intervention.

Aims: To evaluate the technical success rate, complication rate and the effectiveness of enteral stents in providing symptomatic relief of upper GI obstruction during their initial use in our hospital.

Methods: The notes of all patients who had an enteral stent placed for malignant obstruction of a non-oesophageal primary site in the upper GI tract were reviewed.

Results: Enteral stent placement was attempted in 14 patients (11 male, 3 female, age 49–87, mean 70 years). 11/14 employed a combined endoscopic & radiological approach, 3 radiological alone, with 1 failure in each group. There were 5 cases of obstruction due to tumour recurrence following surgery, 5 cases of unresectable gastric carcinoma, 3 cases of unresectable pancreatic carcinoma and 1 ampullary carcinoma. Flamingo stents (Boston Scientific Int.) were used in 2 cases following Lewis oesophagogastronomy. Enteral Wall stents were used in the remainder of cases (Boston Scientific Int.). The technical success rate was 12/14 (86%). 1 patient required 2 stents and one 3 stents. 3 patients required metal biliary stents. There were no immediate complications. There were no cases of stent migration. 1 patient died unexpectedly within 24 hours of stent insertion. Symptom relief was obtained in the remaining 11 patients. 3 patients survived one week, all succumbing as inpatients to metastatic disease. 8 patients were discharged from hospital. 6 patients survived between 11 and 135 days (mean 35 days) and 2 are still alive at 2 and 4 months. The 2 patients who could not be stented survived 11 and 21 days.

Conclusions: This series demonstrates the effectiveness of enteral stenting in the palliation of malignant obstruction of the upper GI tract, enabling many patients to be supported out of hospital. Improved patient selection will optimise palliation. The preferred method of placement was a combined endoscopice radiological approach.

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THE CLINICAL USEFULNESS OF LIVER TRANSIT TIME WITH CONTRAST ENHANCED ULTRASONOGRAPHY IN THE DIAGNOSIS OF CIRRHOSIS

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Background: The transit time of an ultrasound contrast agent, Levovist (Schering AG, Berlin, Germany) between the antecubital and hepatic veins has been shown to be shorter in patients with cirrhosis compared to those without cirrhosis. (Albrecht T et al. Lancet 1999; 353: 1579–83)

Aim: To assess the clinical usefulness of this technique in distinguishing between hepatitis and cirrhosis.

Methods: We studied 8 subjects with biopsy proven cirrhosis (cirrhotic group), 8 with biopsy proven non-cirrhotic diffuse liver disease (hepatic group) and 7 healthy controls. A standard abdominal ultrasound study by a single radiologist (DC) was performed, looking at the hepatic echodensity, echotexture, spleen size, portal venous diameter and blood flow. A bolus injection of 2.5g Levovist at a concentration of 300mg/ml was given in an antecubital vein. The transit time was defined as the time interval between the start of the injection of Levovist and a 10% rise in the signal intensity from baseline in a pre-hepatic and hepatic vein. The peak and gradient of the upslope of the signal intensity curves were recorded.

Results: There was no difference in the echotexture and echodensity of the liver, the portal venous diameter and blood flow pattern between the 3 groups. 4/8 cirrhotic subjects had splenomegaly and none in the other 2 groups (p=0.011). The cirrhotic and hepatic groups had shorter transit time (mean=26.9 & 26.3 seconds, respectively) than controls (mean=36.7 seconds, p=0.012 & 0.006 respectively). There was no difference in transit time between the cirrhotic and hepatic groups. The cirrhotic group had a shorter peak time (mean=34.8 seconds) than control (mean= 52 seconds, p=0.004). However, there was overlap in these parameters between all 3 groups.

Conclusions: The transit time of Levovist was shorter in the cirrhotic and hepatic subjects than normal controls. The cirrhotic group had an earlier peak time than control and hepatic group. However, the presence of some overlap in these parameters between the 3 groups limited the clinical usefulness of this technique.

USE OF A NOVEL TECHNIQUE FOR AUTOMATED POLYP DETECTION IN CT COLONOGRAPHY


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Purpose: CT Colonography (CTC), also known as “Virtual Colonoscopy” is an emerging colon-imaging technique. Conventional analysis of the CTC datasets by radiologists is time-consuming and resource-intensive. We present initial results of a study using novel image analysis software to enhance current techniques and “flag” potential colorectal neoplasia.

Methods and Materials: CTC datasets were obtained by abdominal CT scanning according to established protocols. The raw datasets were downloaded to a standard PC workstation and analysed using our novel software. The first phase of the analysis process involved extraction, or segmentation of a model of the colon lumen from the raw datasets. The second phase of the analysis process involved flagging potential polypoid lesions, locating anomalies projecting from the colonic mucosa and flagging them as potential lesions based on their size and morphology. We present results obtained from the review of 5 patient datasets and calculation the centreline for this model. The centreline extraction, or segmentation of a model of the colon lumen from the raw datasets that is rapid, accessible, and comparably inexpensive. Validation of this software is currently taking place.

Conclusions: We have used 5 CT datasets to date for analysis. This technique takes a mean time of 57 seconds (range 48 – 72) to analyse the raw datasets, for review by an experienced radiologist and reduces review time by up to 50%. Although still in the early stages of development, the automated-flagging algorithm can detect polyps as small as 5mm and can cater for several different morphologies. The analysis results were viewed using several visualisation techniques, including 2D, standard 3D and “virtual reality” stereo.

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Conclusion: There has been a large increase in new cases of coeliac disease in South Glamorgan over the last quinquennia. This appears to be due to the large number of new adult patients including many aged over 70 at diagnosis. It is vital that all clinicians have increased vigilance for this condition to try to reduce possible associated morbidity.

INCIDENCE OF COELIAC DISEASE CONTINUES TO INCREASE IN SOUTH GLAMORGAN

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Introduction: The Coeliac Society is reporting increasing numbers of new members each year, a large proportion of whom are adults at diagnosis. It is unsure whether this is simply due to greater exposure of the ‘coeliac iceberg’ or reflects a genuine increase in disease.

Aim: We assessed all new cases of coeliac disease (CD) diagnosed in South Glamorgan between 1996 and 2000, identified their characteristics and presenting features and compared these to figures obtained between 1981 and 1995 in the same area.

Method: Data was obtained from clinical, pathology, dietetic and GP records in the area. Ethical approval was given Bro Tel BREC.

Results: In our population area of approximately 420 000, 125 new cases of coeliac disease were diagnosed between 1996 and 2000. Of these, 112 were adults (90%) and 13 were children at diagnosis. Whilst the number of children has remained stable there has been a significant increase in the number of adults compared to those in the previous 3 quinquennia [see table]. There was a male:female ratio of 1:2. The mean age at diagnosis in adults was 53yrs, with 68 (61%) of the adult patients aged over 50 and 20 (18%) aged over 70. 30 (24%) of all adult patients had a known affected first degree relative. The single most common presenting complaint was anaemia (50%) and 23 (20%) of the adults had osteoporosis at diagnosis. 14 (11%) had another autoimmune disorder.

INVESTIGATION OF UK PATIENTS WITHOUT THE COMMON DISEASE ASSOCIATED DQ2 GENOTYPE

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Coeliac disease is strongly associated with the HLA DQ2 (DQA1*0501 DQB1*0201) heterodimer encoded in cis on a DRB1*03 haplotype or in trans on DRB1*07 and DRB1*11 haplotypes. DQ2 negative coeliacs tend to have the disease associated DRB1*04 DQA1*0301 DQB1*0302 (DQ8) haplotype. DQB ancestral haplotypes differ at the DRB1*04 locus and in insulin dependent diabetes mellitus DRB1*04 subtypes have been shown to determine DQ8 associated risk in different populations. We aimed to address this issue in UK coeliacs, and also to describe HLA types of the rare DQ2 and DQ8 negative coeliacs.

Methods: 283 UK coeliacs were typed for the presence of the DQ2 heterodimer in cis or trans by PCR-SSP. All those found to be DQ2 negative were typed at a higher resolution for HLA class II alleles, with DRB1*04 subtyping of DQB haplotypes and HLA A, B, C typing of all DQ2 and DQ8 negative patients.

Results: 263/283 (93%) were DQ2 positive (252 in cis, 11 in trans), 20/283 (7%) were DQ2 negative. 15/20 of these were DRB1*04 DQ8 positive. 40% of DQ8 haplotypes in DQ2 negative coeliacs carried the DRB1*0404 allele, 30% the 0401 allele, 15% each 0402 and 0404 respectively. Of the 5 DQ2 and DRK4 DQ8 negative coeliacs, 4 carried one half of the DQA1*0501,
Background: It is recognised that coeliac disease and ulcerative colitis are associated with hyposplenism. Pneumococcal prophylaxis for hyposplenism in coeliac disease. Of these 25, the majority (17) use pneumovax. Five of these do not treat this hyposplenism. Patients presenting with symptoms suggestive of coeliac disease are associated with hyposplenism. Pneumococcal prophylaxis for hyposplenism in coeliac disease. The frequency of pneumovax and long-term penicillin [2]

Conclusion: Despite the suggestions of the Drugs and Therapeutics Bulletin and the British Haematology Guidelines, our findings suggest that current practice is not to assess or treat coeliac patients for hyposplenism in the UK. As severe pneumococcal disease has been encountered, we believe that gastroenterologists should reassess this practice and produce guidance for these patients.

Methods: To test for association of MH30 and CT60 with CD.

Aims: To compare the HLA haplotypes of Caucasian and South Asian CD patients.

Methods: Polymerase chain reaction using sequence specific primers capable of identifying the HLA class I and II alleles was used to compare the HLA haplotypes amongst Caucasians and South Asian coeliac patients with CD.

Results: Significantly more Caucasian patients were DQ2 positive compared to the South Asians (97.2% compared with 83.3%, P<0.0001). The haplotype counts (total number of positive chromosomes) for the HLA*A*01, A*03 and DQB1*02 alleles were significantly higher amongst the Caucasians, (P=0.015, 0.015, 0.002 respectively). By contrast, the HLA*A*26, A*32 and Cw*0702 alleles were more frequent amongst the South Asians, (P<0.0001, 0.002, <0.0001 respectively). The haplotype counts for the HLA*A*01, B*08, DRB1*03 and DQB1*02 haplotype combination was seen in 65.3% of Caucasian compared with 22.2% of South Asian coeliacs (P<0.001).

Conclusions: We have shown preliminary data of distinct HLA associations amongst Caucasian and South Asian patients with CD. This may explain the observed differential presentation in age and symptoms at diagnosis that we have previously reported. It suggests that non-HLA regions are likely to be strong determinants of CD susceptibility in South Asians compared to Caucasians.

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Introduction: Coeliac disease (CD) is a HLA associated disease that has become increasingly recognised among South Asians resident in the UK. No studies have compared the HLA haplotypes amongst Caucasian and South Asian patients with CD.

Aim: To evaluate the value of tTG antibodies for the diagnosis of coeliac disease since they have a sensitivity of 85–100% and specificity of 76–98% association compares favourably with the respective values for ETA (sensitivity 86–100%; specificity 94–100%).

Aim: To test for association of MH30 and CT60 with CD.

Methods: 149 family trios consisting of an affected individual plus unaffected spouses of individuals with CD were also genotyped as a control group. Absolute allele and genotype counts were compared with the 149 affected individuals using 2x2 and 2x3 contingency tables respectively.

Results: TDT compares allele transmissions from heterozygous parents to unaffected offspring: for MH30 G=70, C=65 [chi-squared=0.185, 1df, p=0.607], for CT60 G=77, A=67 [chi-squared=0.694, 1df, p=0.403]. Similar allele frequencies were also almost identical in both case and control groups.

Conclusion: Using both a TDT and a case-control design we demonstrated no evidence of association between CD and the MH30 or CT60 polymorphisms. Although CD, T1D and GD have all demonstrated association with 2q33, and the strongest association has also been demonstrated in other European populations, we found that DQ2 negative UK coeliacs mostly encode DQB in accordance with findings in other populations. Several different DQB ancestral haplotypes were associated with disease, suggesting a primary role for DQ8 itself. The frequency of DRB1*0404 carrying DQB haplotypes was marginally higher and DRB1*0401 marginally lower than the background population frequencies although this was not statistically significant. An interesting finding is that coeliacs without either DQ2 or DQ8 usually carry one part of the DQ2 heterodimer, suggesting that this may be enough to increase the affinity of a DQ heterodimer for binding and presenting gluten derived peptide fragments in someone genetically predisposed to develop coeliac disease.

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Methods: A questionnaire was posted to 292 UK gastroenterologists, three months later the results were collated and analysed.

Results: There was a 78% response rate (n=229).

Coeliac disease: Only 25 (11%) of respondents prescribe pneumococcal prophylaxis for hyposplenism in coeliac disease. Of these 25, the majority (17) use pneumovax. To select patients for treatment 22 respondents use haematological indices, two others use ultrasound for this purpose. Of the 229 who responded 9 (n=18) had encountered severe infections in coeliac patients and reported a total 36 severe infections. Severe pneumococcal septicaemia and coexisting immunocompromise were commented on as distinguishing features.

Ulcerative colitis: 6% (n=13) of respondents assess ulcerative colitis patients for hyposplenism. Five of these do not treat this hyposplenism. If treated these patients receive pneumovax alone (4) or a mixture of pneumovax and long-term penicillin [2]

Conclusion: Despite the suggestions of the Drugs and Therapeutics Bulletin and the British Haematology Guidelines, our findings suggest that current practice is not to assess or treat coeliac patients for hyposplenism in the UK. As severe pneumococcal disease has been encountered, we believe that gastroenterologists should reassess this practice and produce guidance for these patients.
TROPICAL ENTEROPATHY: A DYNAMIC RESPONSE TO EFFECTS OF GLUTEN FREE DIET ON COLONIC 

Background: Malabsorbed food residues in coeliac disease pass into the caecum and undergo bacterial fermentation. We aimed to assess the effects of a gluten-free diet on colonic fermentation in coeliac disease.

Methods: Five patients with newly-diagnosed coeliac disease underwent colonic fermentation studies after two weeks on a standardised 'normal western' diet provided from a metabolic kitchen. The studies were repeated after a further three months on a gluten free diet, the diet in the last two weeks being carefully matched for calorie, protein, fat and carbohydrate content, and for substrates of fermentation with the standard diet. A validated composite symptom score was completed daily. Colonic fermentation was assessed by continuous measurement of gaseous exchange in a 1.4m³ canopy for 24 hours, followed by end-expiratory breath hydrogen determination every 30 minutes for 3 hours after 20ml lactulose. Hydrogen was measured by electro-chemical cell (GM1, Renfrew, UK)

Results: See Table. There was a statistically significant reduction in total hydrogen production \( p=0.043 \), although this was not reflected in the breath hydrogen levels.

Table: Abstract 333

<table>
<thead>
<tr>
<th>Standard diet</th>
<th>Gluten free diet</th>
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<tbody>
<tr>
<td>Median symptom Score</td>
<td>(IQR 0.5-1.5) (IQR 71.3-140.)</td>
</tr>
<tr>
<td>Median hydrogen (total) (ml/24 hrs)</td>
<td>(IQR 28.5)</td>
</tr>
<tr>
<td>Median hydrogen (breath) (mls /12hrs)</td>
<td>(IQR 91.6)</td>
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</table>

Conclusion: Patterns of colonic fermentation improved in all five patients possibly because of reduced malabsorption on a gluten-free diet. Colonic fermentation may be an additional factor producing symptoms in coeliac disease.

ACTIVATION OF SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 1 IN CELIAC DISEASE

G. Manteleone, G. Mazzarella1, V.M. Salvati2, P. Lionetti3, R. Troncone1, T.T. MacDonald. Division of Infection, Inflammation and Repair, University of Southampton, School of Medicine, Southampton General Hospital, Southampton, U.K; 1Istituto di Scienze dell’Alimentazione, CNR, Avellino, Italy; 2Department of Pediatrics and European Laboratory for the Investigation of Food-Induced Diseases, University Federico II, Naples, Italy; 3Dipartimento di Pediatria, Universita’ di Firenze, Florence, Italy.

Background and Aim: Interferon (IFN)-γ is a key mediator of the immunopathology in celiac disease (CD). The aim of this study was to examine the involvement of STAT1, a transcription factor activated by IFN-γ and SOCS-1, a protein which negatively regulates the IFN-γ/STAT1 pathway, in CD.

Methods: Duodenal biopsies, taken from CD patients and normal controls, were analysed for STAT1 by Western blotting, EMSA, and immunohistochemistry, whereas SOCS-1 was analysed by Southern blotting. In cultured treated CD biopsies the effect of a JAK/STAT1 inhibitor on the gliadin-mediated induction of cytokinetic molecules was examined.

Results: High IFN-γ and a more pronounced phosphorylation and DNA-binding activity of STAT1 were seen in CD compared to controls. Despite CD samples contained high SOCS-1 RNA, SOCS-1 protein was undetectable. In cultured treated CD biopsies, gliadin induced activation of STAT1 but not SOCS-1. Furthermore, inhibition of STAT1 prevented the gliadin-mediated induction of ICAM-1 and B7-2.

Conclusions: Data suggest that exaggerated IFN-γ and defective SOCS-1 protein expression can result in a persistent STAT1 activation, thereby contributing to maintain and expand the local inflammatory response in CD.

EFFECTS OF GLUTEN FREE DIET ON COLONIC FERMENTATION IN COELIAC PATIENTS

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Background: Malabsorbed food residues in coeliac disease pass into the caecum and undergo bacterial fermentation. We aimed to assess the effects of a gluten-free diet on colonic fermentation in coeliac disease.

Methods: Five patients with newly-diagnosed coeliac disease underwent colonic fermentation studies after two weeks on a standardised ‘normal western’ diet provided from a metabolic kitchen. The studies were repeated after a further three months on a gluten free diet, the diet in the last two weeks being carefully matched for calorie, protein, fat and carbohydrate content, and for substrates of fermentation with the standard diet. A validated composite symptom score was completed daily. Colonic fermentation was assessed by continuous measurement of gaseous exchange in a 1.4m³ canopy for 24 hours, followed by end-expiratory breath hydrogen determination every 30 minutes for 3 hours after 20ml lactulose. Hydrogen was measured by electro-chemical cell (GM1, Renfrew, UK)

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Methods: Duodenal biopsies, taken from CD patients and normal controls, were analysed for STAT1 by Western blotting, EMSA, and immunohistochemistry, whereas SOCS-1 was analysed by Southern blotting. In cultured treated CD biopsies, gliadin induced activation of STAT1 but not SOCS-1. Furthermore, inhibition of STAT1 prevented the gliadin-mediated induction of cytokinetic molecules was examined.

Results: High IFN-γ and a more pronounced phosphorylation and DNA-binding activity of STAT1 were seen in CD compared to controls. Despite CD samples contained high SOCS-1 RNA, SOCS-1 protein was undetectable. In cultured treated CD biopsies, gliadin induced activation of STAT1 but not SOCS-1. Furthermore, inhibition of STAT1 prevented the gliadin-mediated induction of ICAM-1 and B7-2.

Conclusions: Data suggest that exaggerated IFN-γ and defective SOCS-1 protein expression can result in a persistent STAT1 activation, thereby contributing to maintain and expand the local inflammatory response in CD.

TROPICAL ENTEROPATHY IN FIRST AND SECOND GENERATION IMMIGRANTS TO LONDON

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Background: It has long been recognised that differences in small bowel morphometry are present in healthy immigrants from Africa and Asia compared to Caucasians. This may be due to increased inflammation in the small bowel mucosa.

Aims: To establish whether morphometric abnormalities persist in second generation immigrants and whether this is attributable to small intestinal (SI) inflammation.

Patients and Methods: 62 dyspeptic patients with no evidence of malabsorption had jumbo biopsies obtained from the distal duodenum. Demographic details were obtained by a questionnaire. Small bowel morphometry was carried out using an image analysis.
system and the intraepithelial lymphocytes counted. Further biopsies were snap frozen in liquid nitrogen and the levels of IFN gamma measured by RT-PCR.

Results: 28 native Caucasians, 27 first gen. immigrants from Africa, the Caribbean and Asia and 7 second gen. immigrants were studied. 3 of these had travelled to their parent’s country of origin in the last 2 years. There was a significant increase in crypt depth and decrease in villus height in both immigrant generations compared to Caucasians. There was a trend towards more marked changes in the first generation group (see table). In both immigrant groups there was a significant increase in intraepithelial lymphocytes and IFN gamma.

Discussion: Relative villus atrophy and crypt hyperplasia is present in first and second gen immigrants, which may be due to SII inflammation in response to an environmental antigen from their country of origin.

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A GENETIC ANALYSIS OF COELIAC DISEASE


Background and Aims: A genetic susceptibility to coeliac disease is well recognised. Although a strong association is seen between HLA-DQ2 and coeliac disease, this does not entirely account for the observed familial risk. In order to assess the contribution of HLA to coeliac disease and to identify non-HLA linked coeliac disease susceptibility genes, 3 complimentary strategies were adopted.

Methods: (1) Allele sharing across HLA was calculated by non-parametric linkage analysis. (2) A genome-wide linkage search for non-HLA linked susceptibility loci was performed on 24 multiplex families using ~240 microsatellite markers. (3) Analysis of candidate genes was undertaken by linkage, allelic association, and/or direct mutational analysis. Candidate loci tested were TGM2 (encoding tissue transglutaminase) and CTLA4-CD28 (on chromosome 2q33, implicated in a number of autoimmune diseases).

Results: (1) The HLA locus only accounts for ~40% of the familial risk of coeliac disease. (2) In addition to linkage to HLA, there was evidence of linkage to chromosomes 19p13.3 (p<0.02) and 4p14 (p=0.03). No significant linkage was observed at candidate regions previously reported in other reported linkage searches. (3) Mutational analysis of TGM2 did not show any disease-causing mutations. Analysis of the CTLA4-CD28 gene region showed evidence for linkage (p=0.0008) and association (p=0.0006). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these analyses with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0039).

Conclusions: Non-HLA gene(s) are likely to be a stronger determinant of disease susceptibility than HLA. Sequence variation in genes centromeric to CTLA4 confer an increased risk of coeliac disease, but are unlikely to account for all the non-HLA linked inherited susceptibility.

337 ROLE OF TRANSCRIPTION FACTOR NF-κB IN CYCLOXYGENASE-2 PROMOTER INDUCTION BY HELICOBACTER PYLORI IN ENDOTHelial CELLS

P.A. Corcoran, D.J. Fitzgerald, K.M. Sheehan, J.C. Atherton, F.E. Murray, M.F. Byrne. Dept of Gastroenterology and Clinical Pharmacology, Beaumont Hospital/Royal College of Surgeons in Ireland, Dublin, Ireland

Several studies have demonstrated that H. pylori induces COX-2 in gastric mucosa. We have described regulation of the COX-2 promoter by H. pylori in epithelial and endothelial cell models but the promoter elements involved remain unknown. H. pylori induces the transcription of NF-kB. NF-kB mediates the induction of COX-2 in response to cytokines and free radicals. The aim of this study was to determine the role of two NF-kB sites on the COX-2 promoter in H. pylori induction.

A parent 5’ flanking DNA fragment (-891/+9) and its NF-kB deletion mutants of the human COX-2 gene were constructed into a promoterless luciferase expression vector pcGL3. A proximal NF-kB site mutant (-222 to -213), a distal NF-kB site mutant (-447 to -438), and a double NF-kB mutant were used. Transfected cells BPAEC (vascular endothelial cells) were incubated for 24 hours with live H. pylori (strain 601904, tox++, cagA+). Firefly and renilla luciferase activities were measured.

Methylation of either or both of the NF-kB sites on the COX-2 promoter at -222 and -447 base pairs from the transcriptional start site reduced basal COX-2 promoter activity (normalised luciferase activity 0.26±0.03 x 0.19±0.02, parent v double mutant construct, p<0.05). H. pylori induced COX-2 promoter activity with all constructs (normalised luciferase activity 0.53±0.09 x 0.26±0.03, parent construct v H. pylori control medium, p<0.05) but this induction was unaffected by deletion of either of the NF-kB sites.

H. pylori induces COX-2 in vascular endothelial cells via gene induction. The resultant increased generation of endothelial cell prostanoylin may play a role in mediating mucosal blood flow, platelet function and inflammatory cell infiltration in response to H. pylori infection and may play a role in development of gastric cancers. However, this induction of COX-2 by H. pylori does not involve the NF-kB sites on the proximal portion of the promoter.

338 P53 MUTATIONS IN OEsoPHAGEAL ADEnocArcinomaR ARE COMMON AND ARE ASSOCIATED WITH DISEASE RESPONSE


Introduction: p53 is a key regulator of cellular response to radiation. Until recently, sequencing has been the gold standard for identifying inactivating mutations. However, sequencing can perform poorly when used to analyse material with a mixture of cell types such as tumour biopsies. The functional yeast assay (FYA) is a relatively new method of evaluating p53 mutations and outperforms sequencing when used on biopsy material. Duddy et al (J Mol Diagn 2000) found that sequencing p53 exons 5–8 identified only 54% of mutations detected by FYA. We sought to identify the frequency of mutations in adenocarcinoma of the oesophagus and to correlate mutational status with patient survival.

Methods: Tumour biopsies were obtained from 10 consenting patients with oesophageal adenocarcinoma who were to receive radiotherapy. The biopsies were assessed for p53 mutations using the FYA. Patient survival was compared with mutation data.

Results: 9 out of 10 tumours contained mutant p53. One patient has had a long post treatment survival (currently 23 months) the longest survivor of the remaining 9 patients was 17 months, median 9 months. The surviving patient was found to have no evidence of disease at endoscopy 22 months after treatment. Mutational analysis showed a His273 p53 mutation in this patients tumour.

Discussion: Although small, this cohort has a higher p53 mutation frequency than previously reported. The one long term survivor has a mutation which has been extensively studied in vitro. Restoration of functional activity of this mutant is possible through a variety of mechanisms including interaction with small peptides and antibodies. It is likely that similar mechanisms occur in vivo. Given that the presence of a mutation is very common, this factor alone is unlikely to predict response, indeed the precise nature of the mutation is likely to be more important. We have demonstrated this in our small cohort.

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339 DOWNREGULATION OF αβ, INTEGRIN PRECEDES THE INDUCTION OF APOPTOSIS BY BUTYRATE IN COLORECTAL CANCER CELL LINES

A. Buda, M.A. Jepson1, D. Martinez1, M. Pignatelli (introduced by M. Pignatelli). Department of Pathology and Microbiology, Department of Biochemistry, University of Bristol, Bristol, UK; 2Department of Surgical and Gastroenterological Sciences, University of Padua, Italy

Background: Integrins mediate cell-matrix adhesion and regulate growth and cell survival. In colonic epithelial cells αβ, integrin controls glandular differentiation and proliferation. Butyrate stimulates differentiation and induces apoptosis in vitro.

Aim: We investigate whether butyrate induction of apoptosis was associated with perturbation of integrin-mediated cell matrix adhesion.

Methods: Four colon cancer cell lines (SW 1222, HT29, SW620, LS174T) were studied. Adhesion to extracellular matrix proteins was investigated by a cell-matrix adhesion assay. Expression and cellular localization of αβ, integrin were studied in adherent cells after treatment with 4 mM/L butyrate by FACS analysis and confocal microscopy. Apoptosis was assessed by Annexin V binding. A selective COX-2 inhibitor (NS-398) was also used as a control.

Results: Butyrate decreased the attachment to type I collagen in HT-29 (p=0.004) and SW620 (p=0.003) cells and type I (p=0.01) and IV (p=0.03) collagen in LS174T cells. The decreased cell attachment was associated with downregulation of αβ, and increase in apoptosis in adherent cells (SW620 9.6±0.5 vs. 3.5±0.2, p=0.000; HT29 6.1±0.4 vs. 2.3±0.1, p=0.01; LS174T 9.3±0.6 vs. 4.3±0.3, p=0.003). No changes in αβ, expression and matrix adhesion were seen in SW620 cells, which were found less sensitive to the butyrate-induction of apoptosis (2.4±0.2 vs. 3.3±0.4 p=0.123). Treatment with NS-398 increased apoptosis (5.9±0.08 vs. 2.06±0.14, p=0.000) without affecting integrin expression and cellular localization. Downregulation of αβ, integrin occurred in viable cells and preceded the detection of apoptosis.

Conclusion: Cell detachment and apoptosis induced by butyrate are associated with downregulation of expression and functional activity of αβ, integrin. Perturbation of cell matrix adhesion may be a novel mechanism by which butyrate induces apoptosis in colorectal cancer cells.

340 HIGH LEVELS OF MICROSATellite INSTABILITY (MSI-H) IN HYPERPLASTIC POLYPSYSIS (HPP) ASSOCIATED COLORECTAL CANCER (CRC) PROVIDES EVIDENCE FOR THE SERRATED CRC PATHWAY

M. Lockett, W. Smale, J. Lloyd, K. Pack, S. Burke, I. Talbot, I. Tomlinson, W. Akin. ICRF CRC Unit, St. Mark’s Hospital, Harrow, Middlesex, UK

Background: MSI-H occurs in 10–15% sporadic CRC. The precursor is unknown but may be the hyperplastic polyps (HPP) (serrated CRC pathway). In HPP there are multiple, large HPs and an increased CRC risk. If CRC in HPP showed MSI and the MSI-H phenotype (proximal, multiple, CRCs in females with mucinous, undifferentiated histology and a prominent lymphocyte infiltrate), this would support the serrated CRC pathway.

Aim: To describe the phenotype and microsatellite (MS) status of CRC in HPP to provide evidence for the serrated CRC pathway.

Methods: HPP patients were identified after a national call for cases and using the UK flexible sigmoidoscopy screening trial database. Clinical and histological features were described. Paraffin-embedded tissue samples were microdissected and DNA was extracted. MSI analysis was performed by PCR at Bat25, Bat 26, D15S221 and D17S250 and compared to extracted. MSI analysis was performed by PCR at Bat25, Bat 26, D15S221 and D17S250 and compared to extracted.

Results: 42 HPP patients were identified. 32 CRCs occurred in 18 patients (multiple CRCs in 6). 72% of the 18 CRC patients were male (median age 63 years male, 52 years female). None had a family history of CRC. 69% of CRCs were proximal to the splenic flexure, differentiation was poor in 31%, moderate in 47% and well in 9%. 22% showed mucinous or signet ring cell histology. 19% had a Crohn’s like or conspicuous lymphocyte infiltrate. 6/22 (27%) CRCs were MSI-H and were proximal and showed HM1 loss. 5 (23%) were MSI-L and 50% MSS.

Conclusions: Both MSI and chromosomal instability pathways are important in HPP carcinogenesis. There is an increased prevalence of MSI CRC in HPP. This suggests that the HP is the precursor of MSI CRC in HPP. This supports the theory that the HP may also be the precursor of sporadic MSI-H CRC.

341 PROGAstrin Stimulates Murine Colonic Epithelial Mitosis After DNA DAMAGE

P.D. Ottewell1, A.J.M. Watson1, T.C. Wang2, G.J. Dockray3, D.M. Pritchard1. Departments of Medicine and Physiology, University of Liverpool, UK; University of Massachusetts Medical Center, Worcester, MA, USA

Background and Aims: The non-omitted precursors of gastrin stimulate proliferation of colonic epithelial cells. Transgenic mice which overexpress human progastrin (hGAS) are more susceptible to the induction of colonic adenomatous crypt foci and adenomas by the chemical carcinogen azaemethane than wild type mice (FVB) and mice which overexpress amidated gastrin (INS-GAS). We have investigated in murine intestinal epithelium in vivo whether alterations in the regulation of apoptosis or mitosis following DNA damage contribute to the procarcinogenic effects of progastrin.

Methods: Apoptosis and mitosis were assessed on a cell positional basis by light microscopic assessment of small intestinal and colonic crypts from 10–12 week mice, following 1 or 8 Gy γ-irradiation. Mice were progastrin overexpressing (hGAS), gastrin overexpressing (INS-GAS) and gonadectomised INS-GAS (GASKO) alone or with their wild-type counterparts (FVB and C57BL/6). p21VAF expression was analysed by immunohistochemistry and Western blotting using a rabbit polyclonal primary antibody.

Results: 4.5h following 1Gy and 8Gy γ-irradiation, apoptosis was increased to similar levels in the small intestinal and colonic crypts of all mice. Colonic mitosis was inhibited to almost undetectable levels by 8Gy γ-irradiation in wild type, GAS-KO and INS-GAS mice. However, significant mitotic inhibition persisted in hGAS mice 4.5h following 8Gy γ-irradiation. GAS-KO also showed increased length of colonic crypts compared to FVB and INS-GAS. γ-irradiation caused induction of p21VAF expression to similar levels in hGAS and FVB colonic epithelium.

Conclusions: (1) 4.5h after DNA damage by 8Gy γ-irradiation, mice with elevated progastrin exhibit significantly higher levels of colonic mitosis than wild-type or gastrin overexpressing mice. (2) Progastrin induced stimulation of mitosis following DNA damage may account for its procarcinogenic properties.

342 NSAIDS INHIBIT β-Oxidation of Palmitate and Arachidonate in HCT-116 CELLS

M.J. Garle1, B. Middleton1, C.J. Hawkey1. 1School of Biomedical Sciences, 2Division of Gastroenterology, University Hospital Nottingham, UK

Introduction: Non-steroidal anti-inflammatory drugs (salicylic deriva- tives in particular) are useful for prevention of colon cancer. Earlier reports describe inhibition of palmitate β-oxidation by NSAIDS and demonstrate that elevated cellular arachidonate levels cause apoptosis.

Methods: We hypothesised that inhibition of β-oxidation of arachidonate would lead to arachidonate accumulation and possibly cell death. So we determined effects of NSAIDS on palmitate and arachidonate β-oxidation and cell viability. HCT-116 cells were grown to confluence on 24-well cluster plates and were incubated over 2 hours in DBPS with 1H-palmitate or 1H-arachidonate (100µM, at 42 and 48 dpm/pmoles respectively) in the presence of defatted BSA (1.2mg/ml). β-Oxidation rates were measured by 1H-water production. NSAIDS including indomethacin, sulindac sulphoxide, sulindac sulphide and ibuprofen (0–1000µM) and a palmitoyl carnitine transferase-1 inhibitor (etomoxir 10µM) were incubated in DBPS containing defatted albumin for 45 min prior to 2hr incubation of chemicals with 1H-palmitate or 1H-arachidonate. Effects of NSAIDS on cell death was determined over 48 hr in serum free DMEM, using resazurin reduction as a viability marker. Rates of 1H-palmitate or 1H-arachidonate β-oxidation were 152 ± 5.0 and 21 ± 2.0 pmoles/min/mg protein respectively. Both activities were reduced by etomoxir (10µM) to less than 10% of control values.

Results and Conclusions: Effects of NSAIDS on β-oxidation and cell viability are shown in the table below. Ibuprofen caused an unexpected 2-fold stimulation of 1H-arachidonate β-oxidation at concentra- tions up to 500µM. Results represent mean +/- sem of 150 (µM), (n=4). See table.


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**Viability**

<table>
<thead>
<tr>
<th>Compound</th>
<th>1% palmitate</th>
<th>1% arachidonate</th>
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<tr>
<td>Sulindac sulphide</td>
<td>120±7.4</td>
<td>85±3.4</td>
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<tr>
<td>Indomethacin</td>
<td>251±15</td>
<td>140±15</td>
</tr>
<tr>
<td>Sulindac sulphoxide</td>
<td>775±16</td>
<td>561±32</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Naproxen</td>
<td>&gt;1000</td>
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A ROLE FOR VON WILLEBRAND FACTOR IN HELICOBACTER PYLORI-INDUCED PLATELET AGGREGATION

P.A. Corcoran, S. Kerrigan, D. Cox, J.C. Atherton, D.J. Fitzgerald, F.E. Murray, M.F. Byrne. Dept of Clinical Pharmacology/Gastroenterology, Beaumont Hospital/RCSI, Dublin, Ireland

Human and animal data have demonstrated platelet aggregates in gastric vascularisation in association with H. pylori infection. We have previously shown that certain strains of H. pylori induce platelet aggregation via the platelet glycoprotein GPIb. The GPIb receptor mediates adhesion to von Willebrand factor under high shear. We sought to further characterise this interaction and investigate the role of plasma factors such as von Willebrand factor.

An aggregating and non-aggregating strain of H. pylori (60190 and J104) were grown under standard conditions. 50μl of bacterial suspension [4x10⁶ CFU/ml] were added to 50μl of polyclonal anti-WF antibody or a monoclonal anti-WF antibody and incubated for 30 minutes. The bacteria were then centrifuged and the pellet re-suspended in PBS and FITC-labelled anti-mouse secondary antibodies for 30 minutes at 37°C. Stained bacteria were analysed on a FACScan flow cytometer. H. pylori strain 60190 bound anti-WF antibody [mean fluorescent intensity: polyclonal anti-WF 324±75 and 112±4 for control; monoclonal anti-WF 52±4 and 10±1 for control]. However, the non-aggregating strain J104 showed reduced binding of the polyclonal anti-WF antibody [strain J104: Geometric mean 223±23, p<0.005, n=3, Test]. In addition, H. pylori 60190 failed to induce aggregation of washed platelets (5.5±3.9% aggregation, n=3). However, H. pylori pre-incubated in platelet poor plasma induced platelet aggregation (28±6.4% aggregation, n=3). The polyclonal anti-WF antibody inhibited this platelet aggregation (95±2% inhibition, n=3). Plasma immunoglobulin plays a role in this interaction.

H. pylori induces platelet aggregation in a strain specific manner and plasma factors, notably von Willebrand factor, are involved in the interaction with platelet GPIb. Induction of platelet aggregation by H. pylori may be a critical early event in the inflammatory cascade in gastrointestinal pathogenesis and may also explain the putative link with cardiovascular events.

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343 A ROLE FOR VON WILLEBRAND FACTOR IN HELICOBACTER PYLORI-INDUCED PLATELET AGGREGATION

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Objectives: the primary culture of intestinal enterocytes has been an elusive goal for many years. The reasons that enterocytes fail to growth in culture are multiple, but the single most important factor is that cells die from detachment-induced cell death (DICD) when stripped from the underlying lamina propria. Understanding the mechanisms that result in this form of apoptosis may provide insights into the long-term primary culture of human enterocytes.

Methods: Human duodenal biopsies were isolated from consenting patients presenting with irritable bowel syndrome and iron deficient anemia. All biopsies showed normal histology. Whole biopsies were incubated for 4 hours at 4°C in cell dissociation fluid (Harris sparse), after which time they were shaken vigorously to free the enterocytes from the lamina propria. Both the enterocyte fraction and the lamina propria were washed and assessed for purity using Western blotting. Fractions were incubated at 37°C in serum free media for various times. Apoptosis was assessed by assessing surface expression of phosphatidylserine (PS) using flow cytometry and by DNA ladder- ing. Activation of the apoptotic proteins poly(ADP-ribose) polymerase (PARP), BAX interacting domain death agonist (BID), caspase 3, caspase 8 and caspase 9 were assessed by Western blotting.

Results: Matrisperse treatment of human duodenal biopsies produces a pure, non-apoptotic population of enterocytes. Isolated enterocytes undergo rapid DICD as assessed by surface expression of PS and DNA ladderin. DICD is independent of de-novo protein synthesis, is evident within 30 mins of detachment and is accompanied by the activation of caspase 3, caspase 8 and caspase 9. In support of these observations cleavage products of the genomic surveillance protein PARP and the caspase 8 substrate BID were detected. DICD can be delayed but not halted by the addition of the broad spectrum caspase inhibitor (Boc-D-FMK) and the selective caspase 8 inhibitor (Z-IETD-FMK).

344 A ROLE FOR VON WILLEBRAND FACTOR IN HELICOBACTER PYLORI-INDUCED PLATELET AGGREGATION

P. McPherson, P.W. Dettmar, P.E. Ross. Gastroenterology Research Laboratory, Ninewells Hospital and Medical School, Dunfermline, DD1 9SY; 2Reckitt Benckiser Healthcare (UK) Ltd, Donsam Lane, Hull, UK

Background: There has been a dramatic rise in oesophageal disease over the past thirty years. Gastroesophageal reflux disease (GORD) is a debilitating condition that may lead to Barrett’s Oesophagus, a pre-cancerous condition to oesophageal adenocarcinoma. Acid suppression therapy has been the preferred method of treatment in the shape of H2 antagonists and proton pump inhibitors (PPI).

There is evidence to suggest that epidermal growth factor (EGF), and its receptor (EGFR), play an important role in tissue repair, cell proliferation and migration. Alginateglycosides are widely used in the treatment of gastroesophageal reflux disease (GORD) and impart cytoprotective biological effects. In this study we have investigated the impact on fluid phase endocytosis (FPE) of alginates and EGF.

Results: We have used human oesophageal cell lines, squamous cell carcinomas and 2 adenocarcinomas. Cells were incubated with fluorescent microspheres or EGF or alginate or combinations. Incubation time was one hour. Analyses was carried out by flow cytometry and confocal microscopy.

Conclusions: All alginate upregulate FPE significantly. EGF upregulates FPE. EGF and alginate added together upregulate FPE. Alginate a coding change. The different allitic forms were relatively common and were all expressed in duodenum. No relationship was found between these haplotypes and the level of RNA expression.

345 APOTOTIC PATHWAYS OF DETACHMENT INDUCED CELL DEATH IN ISOLATED HUMAN ENTEROCYTES

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Objective: the primary culture of intestinal enterocytes has been an elusive goal for many years. The reasons that enterocytes fail to growth in culture are multiple, but the single most important factor is that cells die from detachment-induced cell death (DICD) when stripped from the underlying lamina propria. Understanding the mechanisms that result in this form of apoptosis may provide insights into the long-term primary culture of human enterocytes.

Methods: Human duodenal biopsies were isolated from consenting patients presenting with irritable bowel syndrome and iron deficient anemia. All biopsies showed normal histology. Whole biopsies were incubated for 4 hours at 4°C in cell dissociation fluid (Harris sparse), after which time they were shaken vigorously to free the enterocytes from the lamina propria. Both the enterocyte fraction and the lamina propria were washed and assessed for purity using Western blotting. Fractions were incubated at 37°C in serum free media for various times. Apoptosis was assessed by assessing surface expression of phosphatidylserine (PS) using flow cytometry and by DNA ladder- ing. Activation of the apoptotic proteins poly(ADP-ribose) polymerase (PARP), BAX interacting domain death agonist (BID), caspase 3, caspase 8 and caspase 9 were assessed by Western blotting.

Results: Matrisperse treatment of human duodenal biopsies produces a pure, non-apoptotic population of enterocytes. Isolated enterocytes undergo rapid DICD as assessed by surface expression of PS and DNA ladderin. DICD is independent of de-novo protein synthesis, is evident within 30 mins of detachment and is accompanied by the activation of caspase 3, caspase 8 and caspase 9. In support of these observations cleavage products of the genomic surveillance protein PARP and the caspase 8 substrate BID were detected. DICD can be delayed but not halted by the addition of the broad spectrum caspase inhibitor (Boc-D-FMK) and the selective caspase 8 inhibitor (Z-IETD-FMK).

346 THE IMPACT OF ALGINATE BIOPOLYMERS AND EPIDERMAL GROWTH FACTOR ON FLUID PHASE ENDOCYTOSIS

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Background and Aims: Over expression of various matrix metalloproteinases (MMPs) has previously been speculated to correlate with tumour progression in a variety of cancers. The aim of this study was to investigate whether GlyG17, a hormone known to be significantly expressed in colorectal cancers, has any effect on the expression of MMP-2 and -9 in a mouse fibroblast cell line transfected with one of the CCK-2 receptors.

Methods: Gelatinzymography and real-time PCR were used to investigate the protein and gene expression of MMP-2 and -9 in four cell lines with or without the stimulation of GlyG17 (10 µM) and or the addition of 3 different CCK-2 receptor antagonists (YM022, JB95008 and JMV1155). The cell lines investigated were: HT1080 fibrosarcoma HT1080 transfected with MT1-MMP, and the mouse fibroblast NIH 3T3 transfected with classical CCK-2 or truncated CCK-2 receptors. Matrigel invasion chambers were used to assess the invasiveness of the cells with GlyG17 stimulation.

Conclusion: The stimulations of cells by GlyG17 has been shown to be cell line specific but not receptor specific. GlyG17 has the ability to increase protein levels of pro and active MMP-2 and proMMP-9. GlyG17 increased the invasiveness of cells that already express active MMP-2 but has no effect on cells that express only the pro form. The blocking of the CCK-2 receptor reduces GlyG17 stimulation of MMP-2 expression.

Introduction: Endocytosis is a process whereby mammalian cells take up extracellular material by a variety of different mechanisms. In this investigation we look specifically at receptor mediated endocytosis (RME). Gangliosides are necessary for the efficient functioning of this process. We look at the relationship between EGFR and gangliosides Gpl and G92 in four oesophageal cell lines, and the impact of gangliosides on RME.

Background: EGF is a 6 kDa polypeptide that has a role in tissue repair, cell proliferation, ulcer healing and cell migration. Many gangliosides have been identified on the basis of their carbohydrate structure that is mainly expressed on the outer surface of the plasma membrane. Gangliosides act like receptors for some viruses, bacteria and bacterial toxins allowing passage into the cell.

Methods: Four oesophageal cell lines were used in this study, two squamous cell carcinomas and two adenocarcinomas cell lines. Cells were transfected with fluorescent proteins for human EGFR and GT1-2 and harvested for confocal microscopy. Immunogold electron microscopy images indicate colocalisation of EGFR and ganglioside. Increased levels of EGFR are present in squamous cell carcinoma cell line than that of adenocarcinomas. Gpl inhibits the mode of action of EGF in squamous cell carcinoma cell lines but not in adenocarcinoma cell lines.

Conclusion: These results provide us with information on the location of EGFR and gangliosides on the cell membrane. Their location suggests that a co-operative relationship exist between them. This evidence indicates that gangliosides are directly involved in the signalling mechanism that is induced when EGF binds to EGFR, and that Gpl acts as a monitor for the binding of EGF to EGFR.

Introduction: The human oesophageal squamous epithelium is exposed to environmental extremes of heat and low extracellular pH. These stressors are thought to be predisposing factors for metaplastic change to Barrett’s epithelium, a precursor of oesophageal adenocarcinoma. Many human and animal epithelial cells such stressors activate classical heat shock protein responses. This laboratory has previously demonstrated, in human oesophageal squamous epithelium epi-xy, that HSF70 is down-regulated and that SEPT7 is up-regulated in response to thermal, ethanol, lar pH and glucocortic stress. Further study of this novel observation will help to elucidate the involvement of molecular chaperones in the control of mechanisms such as p53 pathways and their role in the oesophageal metaplasia-dysplasia-adenocarcinoma sequence. The present study investigates expression of SEPT7 and HSF70 in paired normal and Barrett’s tissue.

Methods: Pinch biopsies of normal squamous and Barrett’s metaplastic epithelium were obtained from patients undergoing upper GI endoscopy for investigation of reflux symptoms. Western blot analysis, using mouse monoclonal antibodies to HSF70 and SEPT7, was performed on tissue lysates prepared using urea or detergent lysis buffers.

Results: Identification of tissue as squamous cells or Barrett’s was confirmed by detection of Barrett’s specific hAG-2 protein. HS70 was present in squamous epithelium. It was, however, variably expressed in Barrett’s samples. SEPT7 was expressed in normal squamous epithelium but in Barrett’s tissue urea lysates demonstrated a laddering of SEPT7 immunoreactivity to different molecular weights.

Conclusion: The laddering of SEPT7 immunoreactivity may be due to detection of sub-cyttoplasmic pools. This could reflect selective targeting for ubiquitinisation as part of the control of heat shock protein responses in this tissue. Alternatively, it may be due to a generalised dysregulation of proteosomal degradation pathways in Barrett’s metaplasia. Further study of this phenomenon will clarify the dynamics of the novel heat shock protein response in this tissue.

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Results: Incubation of Caco-2 cells with butyrate resulted in decreased secretion and mRNA expression of IGFBP-3. To examine if the inhibitory effect of butyrate on IGFBP-3 was dependent on de novo protein synthesis, Caco-2 cells were stimulated with butyrate in the presence and absence of cycloheximide (CHX). At doses of up to 10μM, CHX did not affect the butyrate-induced down-regulation of IGFBP-3. Butyrate caused an up-regulation of IGFBP-2 mRNA and this effect was again not altered by the protein synthesis-blocking effects of CHX. We verified that 10μM CHX inhibited protein synthesis by interrupting IGFBP-2 expression.

Conclusion: Our data indicate that the modulatory effects of butyrate on IGFBP-2 and -3 are independent of de novo protein synthesis. Therefore, butyrate’s effects are not through the synthesis of a repressor of IGFBP-3. This suggests that butyrate has direct inhibitory effects which may involve the modification of the acetylation status of proteins in the nucleus.

351 ALGINATES ENHANCE THE EARLY RESPONSES OF MUCOSAL REPAIR BY STIMULATING MIGRATION IN VITRO

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Background: Alginates are a group of naturally occurring polysaccharides found in seaweed. Alginates are composed of blocks of two uronic acids, β-mannuronic acid (M) and 1-4 linked α-L guluronic acid (G). The proportion and distribution of which determines the molecule’s chemical and physical properties. Previous in vivo experiments have shown that one M-rich alginate H120L protects the stomach of rats against ulceration while a G-rich alginate, LFR5/60 does not. It is thought that the trend in G- and M-make up of the alginates may be important in influencing this protective activity.

Methods: Three alginates, H120L (low fraction G-residues), LFR5/60 (high fraction G-residues) and Poly M (95% M-residues) were tested for their ability to stimulate migration of two human oesophageal and gastric cell lines. Previous experiments have shown that one M-rich alginate H120L protects the stomach of rats against ulceration while a G-rich alginate, LFR5/60 does not. It is thought that the trend in G- and M-make up of the alginates may be important in influencing this protective activity.

Results: All cell lines migrated in response to H120L and EGFI. Poly M stimulated a weaker migratory response than H120L, no migration occurred in response to LFR5/60.

Conclusion: H120L caused stronger migration in all cell lines compared to LFR5/60 suggesting that M monomers are important in inducing migration in gastrointestinal cell lines. G blocks may also play a role as Poly M (only M blocks) causes migration but to a much lesser degree than H120L. Thus the composition of alginates may influence the migratory response and aid in the restitution process.

ENDOSCOPY POSTERS

352 AUDIT: TO DETERMINE THE QUALITY OF INFORMED CONSENT IN PATIENTS ATTENDING FOR OGD, COLONOSCOPY AND FLEXIBLE SIGMOIDOSCOPY

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An audit carried out last year examining the degree of informed consent in competent adults found that although the majority of patients understood what the procedure involved and had been interviewed by a health care professional, 34% had poor understanding of the benefits of the test and 75% had little or no idea of any associated risks. This audit determines whether modifications made to information to include risk sent to patients in the light of these findings led to an improvement in the level of understanding.

118 patients were interviewed. As last year, 97% were aware which investigation was to be performed and the region to be examined. 69%(63% last year) had received information prior to the procedure, with 80% acknowledging receipt of printed information. 99% of patients had spoken to a health care professional, a proportion similar to last year. Only 60% (88% last year) were deemed to have a good understanding of what was to occur during the test and 66% (90% last year) were aware of what was to happen after the procedure. 70% (34% last year) had poor understanding of the benefits of the test. 48%(25% last year) were aware of the risks.

Conclusion: Changing the literature produced an improvement in understanding of associated risks, however, only 30% of patients were aware of the benefits of the test, and less than half were clear on what would happen during and after the investigation. This may reflect inter-observer variation, although the question does arise whether a certain proportion of patients have the cognitive ability to grasp the information presented to them—it may be pertinent to explore this issue further. Asking patients to complete a checklist is one way of ensuring that they have read material sent to them and been given the opportunity to ask questions.


353 PROSPECTIVE AUDIT OF 12 MONTH REFERRALS FOR GASTROSCOPY UNDER THE “THREE DAY RULE”: AN INITIATIVE TO REDUCE WAITING TIME FOR SUSPECTED MALIGNANCY

F. Parente, S. Bargigia, G. Bianchi Porro. Department of Gastroenterology, L.Sacco University Hospital, Milan, Italy

Background: A regional initiative, called the “Three Day Rule” (TDR), has been recently introduced in our country in order to facilitate the earlier diagnosis of malignancy. It requires patients with suspected severe diseases to have a diagnostic procedure done within three working days of referral by General Practitioners (GPs).

Aim: To assess prospectively the effectiveness and compliance with TDR for upper digestive malignancies.

Methods: We studied prospectively patients referred for gastroscopy under the TDR initiative with contemporaneous open access referrals over a 12 month period at a single large teaching hospital of Western Milan. We compared prevalence of malignancies and other serious non-neoplastic diseases as well as the waiting times in the two groups. The appropriateness of the indications for each referral was also reviewed by a gastroenterologist blinded to the outcome of the test.

Results: 142 patients referred for gastroscopy under the TDR scheme and 767 routine referrals were studied. Significantly more oesophageal/gastric cancers (6% vs 1%) and serious benign GI lesions (grade II–III oesophagitis or peptic ulcer) were diagnosed in TDR patients in comparison with routine referrals (p<0.05, table). The rate of inappropriate referral was significantly lower in the TDR than in the open access group (39% vs 22%) (p<0.01). The estimated cost of the TDR scheme (in extra list examinations alone) was 10 780 Euros, which rate about 11 980 Euros per diagnosis of cancer but only 229.5 Euros per “useful” diagnosis (including PUD and oesophagitis).

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Referred by TDR</th>
<th>Open access referral</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic oesophagitis</td>
<td>14%</td>
<td>10%</td>
<td>0.2</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>12%</td>
<td>7%</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastric/duod. erosions</td>
<td>6%</td>
<td>8%</td>
<td>0.3</td>
</tr>
<tr>
<td>Oes/gastric cancer</td>
<td>6%</td>
<td>1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
<td>10%</td>
<td>0.3</td>
</tr>
<tr>
<td>Normal findings</td>
<td>51%</td>
<td>64%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusions: Significantly more upper GI cancers and serious benign diseases can be found within a short period to comply with the TDR scheme. However, some GPs appear to over read alarm symptoms, and this may lead to some inappropriate referrals. Better awareness of appropriate urgent referral criteria is needed in order to ensure that the best possible use is made of the resources available for this initiative.

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THE DEVELOPMENT OF A PSYCHOMETRIC SCALE TO \( \chi^2 \) THE INFLUENCE OF MEDICAL AND NON-MEDICAL FACTORS UPON GENERAL PRACTITIONERS' DECISIONS TO REFER PATIENTS WITH GASTROINTESTINAL (GI) SYMPTOMS

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Background: Factors that influence GPs' referral decisions for GI complaints have received little attention in the literature. A greater understanding of this process is essential for developing guidelines and improving services, yet retaining aspects of the valuable primary care screening function. This has become ever more important since the implementation of "Two week rule" referrals and the Government's Direct Booking Project Initiative.

Aims & Objectives: To design a scale to measure and rank order the influence of medical and non-medical factors upon GP referral decisions for patients presenting with common upper and lower GI symptoms.

Methods: 21 GPs in a single health district were given an 80 item questionnaire separated into potentially potent medical (signs, symptoms, and clinical history) and non-medical factors (patient and fear of malpractice. Contrary to expectations, patient age, patient anxiety, weight loss, and GPs' experience of GI symptoms had a negligible perceived impact upon referral decisions. The strongest referral inhibitors (in rank order) were: intermittent symptoms, symptoms inconsistent with GI referral guidelines, and the presence of a plausible explanation for presenting symptoms.

Conclusions: The scale was well received as a simple and quick method for assessing the relative importance GPs assign to factors involved in referral decisions. This tool is helping us to work with primary care colleagues to develop our direct access booking system.

VARIFICATION OF REPORTING OF GASTROSCOPIES BY DIFFERENT ENDOSCOPISTS AT A SINGLE CENTRE

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Introduction: Gastroscopy is a fundamental investigation for the gastrointestinal endoscopist. At present, approximately 1% of the UK population undergoes this procedure each year. The BSG and JAG have been involved in drawing up training guidelines to ensure technical and diagnostic competence. Historically however, the ethos has been "see one, do one, teach one". Consistent reporting of endoscopic findings is essential to patient care and consequently the nation's health costs. Much more emphasis must be placed during training and on the correct interpretation of gastrosopies.

Abstract 355

<table>
<thead>
<tr>
<th>Endoscopic diagnosis</th>
<th>Total</th>
<th>Range (%)</th>
<th>( \chi^2 )</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>880</td>
<td>18–60</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>323</td>
<td>4–65</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Duodenitis</td>
<td>263</td>
<td>2–33</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>310</td>
<td>2–22</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Haustus Herina</td>
<td>440</td>
<td>8–36</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>450</td>
<td>18–35</td>
<td>&lt; 0.0004</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: There are major discrepancies in the reporting of endoscopic examinations. We may be failing to accurately and consistently report our findings. This has major implications for the patients' perception of their illness, the GPs' on-going management and consequently the nation's health costs.

ULCER HAEMOSTASIS BY THE HEATER PROBE: BIGGER MAY NOT BE BETTER

1Western General Hospital, Edinburgh, UK; 2Aberdeen Royal Infirmary, Aberdeen, UK; 3Ninewells Hospital, Dundee, UK; 4Gartnavel General Hospital, Glasgow, UK; 5Scottish National Blood Transfusion Service, UK; 6University of Edinburgh Medical School, Edinburgh, UK; 7Royal Infirmary, Edinburgh, UK.

Introduction: The heater probe is a widely used thermal modality, which is used in many centres to effect ulcer haemostasis. It has been stated that the large (3.2 mm) probe is more effective than the small (2.4 mm) probe, but this statement is not evidence based.

Method: As part of a large clinical trial, 247 patients with major peptic ulcer bleeding were treated with a heater probe in combination with endoscopic injection. Choice of heater probe was influenced by the availability of a large probe and also by the availability of an endoscope with a 3.7 mm working channel. In 216 patients the small probe was used (group A); in 31 patients (group B) the large probe was applied.

Results: The amount of energy used in both groups was similar (120–160 W) respectively. Injection volume was 3.5 ml in both groups. The groups were well matched for age, shock, comorbidity, and endoscopic stigmata.

Failure of permanent haemostasis followed treatment in 17% of group A and 23% of group B patients; urgent surgery was necessary in 11% of group A and 19% of group B. Mortality at 30 days (9% and 7%) was similar in both groups. Adverse events occurred in 5% of group A and 7% of group B patients.

Conclusion: The efficacy and safety of both heater probes, used in association with endoscopic injection is similar.

COLONOSCOPY SKILL: THE LEARNING CURVE REVISITED

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Although there has been substantial progress in the ability to teach gastrointestinal endoscopy there are still few valid and reliable tools for assessment of these skills. In part this reflects the lack of agreed standards for comparison. There is now agreement that training should result in colonoscopists being able to reach the curium in 90% of patients but demonstrating this degree of competence presents problems.

Assessment should, in addition to showing compliance with a standard, provide feedback to stimulate improvement and help to evaluate training programs. Cumulative sum (Cusum) analysis is an established method of quality control in laboratories and has recently proved useful both in anaesthetics and cardiac surgery. Its use in assessment of colonoscopy has been previously described but it has never been widely adopted.

We have re-examined the value of this technique for assessing completeness of colonoscopy and describe a simple practical method for making it available to both trainees and experienced colonoscopists.

The basis of the analysis is the assignment, to pass/fail events, of appropriately different scores that are summed and charted to show when there is sustained achievement of the required standard. In the case of 90% success for complete colonoscopy being required, each success is assigned a score of minus 0.1 and each failure a score of plus 0.9. With sequential outcomes the graph of this function will rise for as long as the success rate is below 90%, flatten out when the standard is attained and fall if the standard is consistently exceeded.

We present such a curve for one trainee's first 140 cases. After 20 incomplete examinations intensive structured training was given. This was followed by increasing success until, by about 70 cases, the standard was being achieved consistently.

We have applied the equation to an Excel program into which the colonoscopist enters each examination coded for "pass" or "fail" and is then able to produce a graph after suitable numbers of examinations.
A NEW METHOD FOR RAPIDLY MEASURING THE FLEXURAL RIGIDITY OF ENDOSCOPES
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2Mechanical, Materials and Manufacturing Engineering, Newcastle University, UK;
3Medical Sciences Faculty, Sunderland University, UK; 4Department of Electrical and Electronic Engineering, Newcastle University, UK

Introduction: There is increasing interest in the use of both variable stiffness colonoscopes and thinner "flippable" flexible sigmoidoscopes. We have previously argued that a simple beam displacement methodology to determine flexural rigidity (EI) has the advantage of being relatively easy, reproducible, and inexpensive to perform. The disadvantage is that in our experience it takes between one and two hours to accurately determine EI every 10 cm along the shaft of a typical colonoscope. The aim of this study was to develop a method of rapidly and accurately measuring EI.

Methods: A unique, computer-based system has been developed that enables EI to be continuously measured along the entire shaft of an endoscope in <60 seconds. The user (1) places the shaft between three low-friction rollers/pulleys (2) applies a known load using a standard weight and (3) pulls or pushes the endoscope through the rollers. The system's software records data from optical encoders mounted on two pulleys, one of which measures the position of the load on the shaft relative to the instruments distal end, and the other the load deflection itself.

Results and Discussion: The new system accurately logged EI data in a fraction of the time (<60 seconds) that it had previously taken using our manual system. It recorded data at 1 mm (compared to 100 mm) intervals and had the additional advantage over the manual system that the EI data could be saved to computer in raw and processed forms. These could then be displayed in either numeric or graphical format using standard Windows applications such as Microsoft Excel. A systematic comparison of the EI of a number of commercially available endoscopes is now in progress.

A CASE CONTROL STUDY OF NITROUS OXIDE/OXYGEN (N2O/O2) AND BENZODIAZEPINE/OPIATE IN LOWER GI ENDOSCOPY
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Intravenous benzodiazepine/opiate (IV) is normally used for sedation and analgesia in lower GI endoscopy. Disadvantages of this approach include significant cardiorespiratory complications and prolonged recovery time. The aim was to compare N2O/O2 (Gas) with IV in patients undergoing flexible sigmoidoscopy (FS), or colonoscopy (CO). Consecutive patients (42 FS, 72 CO) were offered sedation with gas or IV. The endoscopist determined the amount of sedation to be given, and recorded the procedure duration and completeness. Patients recorded degree of discomfort and dissatisfaction using a standardised scoring system. An endoscopy nurse recorded recovery time. FS-gas was compared with FS-IV, likewise for CO. Data were analysed on an intention to treat basis. Median values (range), 95% confidence interval for difference of the means (CI) and p values are shown.

One patient refused gas for CO. Three patients undergoing CO required IV as well as gas. Duration, in minutes, of FS (CI 1.2 (0.5–2.9)) and CO (CI 2.9 (0.5–5.6)) and completion rate (100% FS both groups, and 92% and 88% CO for gas and IV, respectively) was not significantly different between the groups. Patient discomfort using gas is mild for FS and CO, but not as good as when using IV. For both FS and CO, recovery time is significantly shorter using gas. N2O/O2 is effective sedation and analgesia in lower GI endoscopy in the majority of patients.

MAGNETIC ENDOSCOPE IMAGING: A NEW TECHNIQUE FOR LOCALISATION OF COLONIC LESIONS
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Background: It has already been shown that nurses are effective in providing safe and accurate gastroscopy and flexible sigmoidoscopy. In this unit the nurse endoscopist has performed over 3000 diagnostic and therapeutic flexible sigmoidoscopies and assisted in 50 colonoscopies. A nurse endoscopy training programme, based on JAG 2001 guidelines, has been developed to assess whether nurse endoscopists can provide a safe and effective colonoscopy service. This is the first 160 procedures performed by the nurse endoscopist.

Aims: To review the first 160 colonoscopies performed by the nurse endoscopist.

Methods: A nurse endoscopy training programme was developed. The first 100 cases were performed under the direct supervision of an expert (BPS/SGS). An assessment of nurse endoscopist performance was evaluated after the first 100 procedures (BPS). The following 60 cases were performed without supervision. Routine polypectomy was performed by the nurse endoscopist on polyps <10 mm. Details of referrals, examinations, and complications were recorded.

Results: 160 cases were performed (67 male, 93 female) in which the mean age was 56 years (16–94). Indications included intracolonic bleeding (30%), assessment of IBD (15%), altered bowel habit (15%), pain (11%), diarrhoea (9%), anaemia (8%), cancer follow up (5%), polyph loop follow up (4%), FH cancer (2%) other (1%). The overall caecal intubation rate was 94% (146/160) (assistance given in 8% of cases due to looping/fixed sigmoid). Video documentation of the caecum and procedure extubation were recorded in 100% of cases. Median sedation administered was pethidine 25 mg, midazolam 1.25 mg, and buscopan 20 mg. Overall findings were normal 70 (48%), IBD 25 (17%), adenomas 18 (12%), diverticular disease 13 (9%), cancer 9 (6%), metastatic polyps 7 (5%), and others 4 (3%). Polypectomy was performed by the nurse endoscopist in 21 (14) cases with no complications.

Conclusion: A nurse endoscopist with an experienced background in flexible sigmoidoscopy can, with specialised training, safely progress to perform colonoscopy for diagnostic referrals.
Results: Twenty-nine consecutive patients were enrolled. The overall accuracy of MEI when compared to the air-contrast “enema” was 90% (26 of 29 cases). There were three slight errors of localisation (clips localised to proximal rather than mid-descending colon [1], or to either side of the mid-transverse [1] and hepatic flexure [1]) but which were not considered to be of surgical or clinical importance.

Conclusions: MEI is a reliable and accurate method for determining the anatomical position of the endoscopist tip during colonoscopy. When commercially available, we believe the use of MEI will avoid the need for unnecessary barium enema for preoperative localisation of lesions, prior to definitive surgery.

362 RELIEF OF MALIGNANT DYSPHAGIA WITH PLACEMENT OF OESOPHAGEAL METAL STENTS: DO THE BENEFITS OUTWEIGHT THE RISKS?

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Background: Malignant dysphagia due to oesophageal cancer results in much patient morbidity. This is in addition to the late diagnosis of this cancer and the poor overall prognosis. This study is a review of our experience of metal oesophageal stent insertion for oesophageal cancer to identify factors associated with poor outcome.

Patients and Methods: observational study of the protocol led management of 100 consecutive patients undergoing stent insertion for oesophageal cancer from 1 May 1996 to 31 December 2000.

Results: Patients can expect a mean improvement of 4.2 (SD 2.6) points in their dysphagia score, a median hospital stay of five days (IQR 2–10), and a median life expectancy post stent insertion of 86.5 days (IQR 30–168). There is an increased complication rate in older patients. Improved survival in dysphagia score appeared to be worse in those who experienced complications (p=0.09). Overall five day mortality in this series was 3% and perforation rate was 1%.

Conclusion: Palliation of malignant oesophageal strictures with expandable metal stents in the majority of cases provides significant improvement in dysphagia with a short hospital stay and is associated with a low incidence of serious complications. Complications are largely confined to elderly patients with comorbid conditions. Optimisation of patients prior to stent insertion is vital if complications are to be minimised.

363 PUSH-ME-PULL-YOU FLEXIBLE PLASTIC STENTS

A. Fritscher-Ravens, D. Mukerjee, S. Masse, P. Swain. Address required

Background: Plastic stents are commonly used to provide drainage of obstructed biliary and pancreatic ducts for benign and malignant disease. They are simple flexible tubular structures, pre-shaped by heat to fit the obstructed duct, with flaps or pig tail curves to prevent displacement. They are delivered over guide wire, guide catheter, or both. A pushing catheter is used to push the stent into position. The pushing catheter can push but cannot pull the stent backwards towards the endoscope. One difficulty with stent insertion is that if the stent is inadvertently pushed too far through the ampulla it can be difficult or impossible to retrieve it so many endoscopists deploy longer stents than necessary to prevent inadvertent loss through the ampulla. But longer stents block more quickly and can erode into the duodenal wall.

Aim: To design, develop, and test a stent which can be pushed and pull backwards over a guidewire or catheter.

Methods and results: An S-shaped curve was formed in the tip of a variety of plastic stents and a perfectly fitting s shape was also cut into the tip of the pushing catheter so that the stent and pushing catheter were locked together when placed over a guide wire or catheter but which would separate as soon as the wire or catheter was withdrawn. A variety of stents of 5, 7, 10, and 12 French size were created and various locking shapes were tested including dovetails and interdigitating bars. These stents were formed from nylon, polytetrafluoroethylene, included flaps and were either straight or heat formed into curves. Some locking mechanisms were formed with a metal tip to the stent and pusher, some were made with plastic. A friction fit lock was also tested. This mechanism was also used to deliver experimental anastomotic stents, which required the means to pull back the stent once in place to exert tension against another structure to form an anastomosis. They were first tested using duodenoscopes in models of the bile duct and pancreatic duct. Subsequently they were tested in post mortem dissections with the duodenoscope held in a jig. Finally these stents were delivered to the pancreatic and bile duct in survival studies in pigs. This type of stent could be delivered significantly more quickly and with fewer misplacements than comparable stents without the lock. The locks always released instantly.

Conclusion: A simple releasable lock on the tip of a plastic stent allowed better control of stent delivery. The stent can be pulled back into an optimum position.

364 COMPARISON OF THE DIGITAL ACQUISITION SYSTEM AND SCREEN FILM SYSTEM DURING ERCP

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ERCPs are employed in the diagnosis and treatment of biliary and pancreatic disorders. Modern fluoroscopy systems usually allow acquisition of images for hard copy using a digital acquisition system (DAS) instead of a screen film system (SFS). It is thought that the DAS is associated with a lower radiation dose.

The aim of the study was to prospectively compare the radiation doses to patients from digital imaging and the screen-film system. DAP reading [Gy-cm²] which is a convenient measure of radiation exposure, screening time, and number of films were recorded.

Data was recorded on 33 patients (10 diagnostic) using the digital imaging and 20 (8 diagnostic) using the screen-film system. Average DAP for the DAS was 16.8 Gy-cm² for diagnostic, and 63 Gy-cm² for therapeutic ERCP. Average DAP for the SFS was 13.5 Gy-cm² for diagnostic, and 66.8 Gy-cm² for therapeutic ERCP. Average screening time for the DAS was 2.7 mins for diagnostic and 7.4 mins for therapeutic ERCPs. Average screening time for the SFS was 2.3 mins for diagnostic and 10.5 mins for therapeutic ERCPs. The average number of films taken using the SFS was 2.8 for diagnostic and 3.7 for therapeutic ERCPs.

In conclusion, there was no significant difference between the radiation dose in the two systems of image acquisition. The number of images taken with the DAS was however higher, a possible explanation of which is the ease with which images can be taken since films do not need loaded each time.

365 HOW DOES THE RECEIVING CLINICIAN’S ASSESSMENT OF URGENCY OF ENDOSCOPY AFFECT WAITING TIMES AND ENDOSCOPIC FINDINGS?

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Introduction: open access endoscopy and the two week cancerinitiative have increased pressures on endoscopy units. In our unit all requests for GI endoscopy are prioritised by consultants and allocated a routine, soon, or urgent slot. The purpose of this study was to analyse the relationship between the urgency of the endoscopy, as designated by the gastroenterologist, and the waiting time. We also wanted to know whether this assessment of urgency influenced the findings.

Methods: retrospective analysis of prospectively collected data. Twenty-nine consecutive patients were enrolled. The over-riding indication was to assess the influence of which is the ease with which images can be taken since films do not need loaded each time.

Conclusion: There was no significant difference between the radiation dose in the two systems of image acquisition. The number of images taken with the DAS was however higher, a possible explanation of which is the ease with which images can be taken since films do not need loaded each time.

Results: For upper GI endoscopy 28% were routine, 51% soon, and 22% urgent, the average waiting times were 154 days, 39 days, and 19 days respectively. The proportions of cases in each category were not significantly different for flexible sigmoidoscopy. Significant upper GI pathology was found in 33% of routine cases (6 cancers), 39% of soon cases (30 cancers), and 57% of urgent cases (35 cancers). Carcinoma of the stomach or duodenum was found in 18% of urgent cases, as many urgent cases as in routine cases (p=0.01). In flexible sigmoidoscopy, significant pathology was found in 24% of routine cases (1 cancer), 44% of soon cases (10 cancers), and 54% of urgent cases (8 cancers). Nine times as many carcinomas were found in urgent cases as in routine cases (p=0.01). This study confirms that alarm symptoms are more predictive of the finding of serious pathology in patients with lower bowel symptoms and although alarm symptoms often reliably predict serious upper GI disease in over half of patients considered urgent, a significant proportion of patients with upper GI cancer will have no alarm symptoms.
366 ACHIEVING THE “TWO WEEK STANDARD” FOR SUSPECTED UPPER GI CANCERS: CONTINUING PAIN WITH MINIMAL GAIN: A RETROSPECTIVE AUDIT


Introduction: Gastrointestinal endoscopy units UK wide continue to strive to meet the two week standard for diagnosis of suspected upper GI cancers. In many cases this has put additional strain on already overstretched departments with negligible improvement in outcome and potential counterproductivity.

Methods: We performed a retrospective audit of patients referred for urgent open access gastroscopy over a six month period. Referrals were made on a standard proforma or letter marked “urgent” and mentioning the word “cancer”. These were coordinated via our Cancer Office with fax and online facilities. We collected clinical and demographic data and analysed both the decision to refer to actual referral time (ideally 24 hours) and the receipt of referral to appointment time.

Results: Data were collected on 79 patients (46 female and 33 male), mean age 69 yrs, from April-September 2001. All but three were faxed proforma referrals. One patient DNA’d, 33% had a normal endoscopy. Only three cancers were detected (4%), all within 14 days of referral. These were all unresectable OG junctional adenocarcinomas.

Conclusion: Whilst the majority of patients were gastroscoped within two weeks of referral, a significant number fell short of the standard. This was due to in part to a delay in GP referral time. Despite this, it remains to be seen whether overall achievement of the two week standard translates into reduced mortality from upper GI cancer.

Abstract 366

<table>
<thead>
<tr>
<th>GP referral time</th>
<th>Within 24 hrs</th>
<th>24–48hrs</th>
<th>&gt; 48hrs</th>
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<tr>
<td>Referral scope time</td>
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<td>51/79 (65%)</td>
<td>12/79 (15%)</td>
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<td>Within 2 weeks</td>
<td>2–3 weeks</td>
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<td>95/79 (75%)</td>
<td>14/79 (17%)</td>
<td>5/79 (8%)</td>
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367 PATIENT CHARACTERISTICS AND GENERAL PRACTITIONERS’ REFERRAL DECISIONS FOR GASTROENTEROLOGY

A. Douglass¹, D. Flynn¹, P. van Schaik², A. van Wersch³, P. Cann¹
¹Endoscopy Centre, James Cook University Hospital, Middlesbrough, UK; ²University of Teesside (Social Sciences), Middlesbrough, UK.

Introduction: A previous retrospective pilot study identified key factors that influenced gastrointestinal (GI) referral decisions in two local practices.

Aim & Objectives: (1): to further assess the weighting of drivers and inhibitors, identified from the pilot, for GP’s referral decisions with patients presenting with common GI complaints; dyspepsia (D), upper GI (i.e. dyspepsia, GORD, or upper abdominal pain), and inhibitors, identified from the pilot, for GPs’ referral decisions with patients presenting with common GI complaints; dyspepsia (D), upper GI (i.e. dyspepsia, GORD, or upper abdominal pain), and lower GI (i.e. isolated rectal bleeding (RB), change in bowel habit +/- rectal bleeding (Ch.BH +/- RB)).

Results: Expressed as total number for main classes per sub-service and (% over 45 years of age). 1303 referrals were received in the two months, further examples, there were 12 patients with unexplained iron deficiency anaemia without any GI symptoms. 111 referrals were labelled urgent and 26 as “Two week rule” referrals.

Discussion: This and the more detailed analysis of our total GI referral load from primary care, is allowing us to engineer a restructuring of the number of “slots” we must make available on the “pooled effort direct booking system” for each clinical sub-group category. It also informs our designation of “appropriateness” of these slots for relevant clinician, nature of first contact, and speed of first contact.

Abstract 367

<table>
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<td>Total 50</td>
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<td>212</td>
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368 VOLUME AND DISTRIBUTION OF GP REFERRALS TO A GASTROENTEROLOGY (GI) UNIT: PLANNING FOR A POOLED, WEB-BASED, DIRECT BOOKING SERVICE

A. Douglass, P.A. Cann. Endoscopy Centre, James Cook University Hospital, Middlesbrough, UK

Introduction: A pooled Medical/Surgical approach to GI services would enable referrals to be distributed according to Consultant specialist interest, allow an even spread of workload, avoid problems arising from leave, give direction to clinic, or procedure as first contact and facilitate efficient prioritisation. Do we know how much we all get of what?

Aims & Objectives: To examine the volume, distribution, and sub group clusters of GI referrals from GPs to a busy GI unit. To explore options for redistribution/prioritisation of these referrals.

Methods: The unit serves a 300 000 population and provides open access (OA) gastroscopy and colonoscopy services. It employs three GI physicians, three colorectal surgeons, and one upper GI surgeon. All GI (Medical, Surgical, and Open Access) referrals from GPs to our unit for a two month period were reviewed and analysed. General Surgical (non GI) referrals excluded. Main classes: dysphagia, upper GI (i.e. dyspepsia, GORD, or upper abdominal pain), and lower GI (i.e. isolated rectal bleeding (RB), change in bowel habit +/- rectal bleeding (Ch.BH +/- RB)).

Results: Expresses as total number for main classes per sub-service and (% over 45 years of age). 1303 referrals were received in the two months, further examples, there were 12 patients with unexplained iron deficiency anaemia without any GI symptoms. 111 referrals were labelled urgent and 26 as “Two week rule” referrals.

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369 SEVERITY AND FOLLOW UP OF COELIAC DISEASE AS ASSESSED BY THE OLYMPUS “ZOOM” ENDOSCOPE


Introduction: A previous retrospective pilot study identified key factors that influenced gastrointestinal (GI) referral decisions in two local practices.

Aim & Objectives: (1): to further assess the weighting of drivers and inhibitors, identified from the pilot, for GP’s referral decisions with patients presenting with common GI complaints; dyspepsia (D), upper GI (i.e. dyspepsia, GORD, or upper abdominal pain), and lower GI (i.e. isolated rectal bleeding (RB), change in bowel habit +/- rectal bleeding (Ch.BH +/- RB)).

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www.gutjn1.com
endoscopic findings. Cases were classified as: Group A = minimal villous changes but expanded lamina propria (Marsh 1 and 2). Group B = mild to moderate villous atrophy (Marsh 3a). Group C = marked villous atrophy (Marsh 3b/c).

Results: There were six patients in group A, three characterised endoscopically as Z1, and three as Z2 (mean Z score 1.5). Four cases in group B, three were Z2, and one Z3 (mean 2.3). Seven cases were in group C, two were Z3 and five Z4 (mean 3.7). The sensitivity of “Zoom” endoscopy in identifying villous atrophy is 100%.

Conclusions: Although this is a small preliminary study, results suggest that the Zoom endoscope may well be effective at identifying villous atrophy and assessing its severity. We found that patients responded positively to seeing visual evidence of villous recovery.

370 PERCUTANEOUS ENDOSCOPIC JEJUNOSTOMY (PEJ): INDICATIONS, SUCCESS, AND OUTCOME
K. Matthewson, S. White, M. Atkins, S. Clark, A. Torrance, P. Bottrell, R. Farrell. Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK

PEJ insertion was attempted in 17 patients (10M, 7F, median 74 years) with an indication for enteral feeding. Four were unable to tolerate standard percutaneous endoscopic gastrostomy (PEG) feeding due to intractable vomiting or feed regurgitation and 13 were not suitable for standard PEG insertion. Of these, three had abnormal gastric anatomy preventing PEG insertion, four had previous gastric surgery, three had diabetic gastrectomy, one had oesophago-gastric cancer, one had intractable vomiting with naso-gastric feeding, and one had meconium ileus equivalent due to cystic fibrosis requiring N-acetyl cysteine perfusion.

Patients were sedated with midazolam (mean 4.9mg) with the addition of pethidine (mean 50mg) in six patients and hyoscine (mean 28mg) in five patients. Prolipharycoc co-mixivacud was used in eight patients and other combinations of antibiotics in eight. A videocapsule was used in 11 and videogastroscopy in six patients. The scope was advanced and withdrawn until good transillumination with single finger indentation of the jejunum was achieved, followed by intubation of the jejunal loop. The trochar was then connected and pulled through the abdominal wall into position. If transillumination was not achieved within 30 minutes the procedure was abandoned.

The procedure was successful in 13 of the 17 patients (76%). The four failures were due to inability to transilluminate. Two of these had a surgical jejunostomy. One patient with advanced oesophagogastric cancer died three days post procedure from aspiration pneumonia. One patients developed refeeding syndrome from which they recovered. Seven patients died from their underlying disease a median of two months post procedure and five were alive a median of one year post procedure. One patient with successful PEJ insertion tolerated bolus feeding whilst the remainder had continuous infusions using a feeding pump. When conventional PEG feeding is not possible or poorly tolerated, PEJ insertion is a feasible option.

371 AN AUDIT OF COLONOSCOPY PRACTICE AND LONG TERM FOLLOW UP IN 505 CONSECUTIVE PATIENTS
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Background: Colonoscopy is the gold standard procedure for examining the colon. The procedure has been under great scrutiny in recent months.

Aims: To prospectively audit all aspects of colonoscopy performed at this unit including long term follow up.

Methods: Details of referral, examination, endoscopist, complications, and follow up were recorded prospectively. Patients completed 100 point visual analogue scales for pain and satisfaction following their procedure. 300 patients (246 male) underwent colonoscopy (by 27 different endoscopists), median age 57 years (13–92), 468 (93%) were outpatients. 64% patients were symptomatic and 36% patients were having surveillance or follow up colonoscopy. 19% of cases were stated as being “very urgent” or “urgent”. Median waiting times were four weeks (0–13) in urgent cases and one week (0–66) for routine cases. The overall caecal intubation rate was 93% (72–100%), with surgeons, physicians, and experienced trainees performing similarly well (89%, 92%, 94%) and experts 98%.

Photodocumentation of the caecum was performed in 85% of cases and verified by two experienced endoscopists in 88%. In only one case was an inexperienced trainee (<100 procedures) left unsupervised. Pain scores estimated by the endoscopist were well managed with those given by the patient 29 (0–100) and 26 (0–100). Median satisfaction score was 96 (0–100). Pain perception was less if CO2 insufflation was used median score 24.5 compared to 27.5 for air. Immediate complications were recorded in 16 (0.03%), five sedation, six vasovagal, three polyphlebitis haemorrhages, two mucosal injuries (neither requiring treatment), 69 patients returned their six month follow up questionnaire. They reported a median of one day off work or of being unwell at home. 32 patients (0.01%) reported minor bleeding, none requiring treatment. Three patients died within six months of follow up but none were related to their colonoscopy.

Conclusions: Completion rates were adequate for all endoscopists studied and a good level of supervision is available for trainees. There was a high level of satisfaction with the procedure and very few immediate or long term complications.

372 THE IN VITRO ASSESSMENT OF A NOVEL “CONTINENT” AND DISPOSABLE CORRUGATED SIGMOID VENTILATION FISTULA FOR COLONOSCOPY
G.D. Bell, J. Butler, S. Dogramadzi, J. Hancock, D. Nylander, J. Painter, K. Burn, R. Bicker. 1Medical Sciences Faculty, Sunderland University, UK; 2Advanced Surgical Concepts, Bray, Eire; 3Department of Electrical and Electronic Engineering, Newcastle University, Newcastle, UK; 4Department of Medicine, Sunderland Royal Hospital, UK; 5School of Computing, Engineering and Technology, University of Sunderland, UK; 6Department of Mechanical, Materials and Manufacturing Engineering, Newcastle University, UK

Introduction: Our group have extensive experience in the use of different stiffening sigmoid overtubes in combination with both adult and paediatric colonoscopes (Gut 1998,42(suppl I):A18 and Gut 2000,46(suppl II):A33). All the overtubes were relatively expensive and had the additional disadvantage of not having an air-tight seal to prevent leakage of inflated air and fluid faecal material.

Aims and Methods: To assess in vitro a recently patented inexpensive disposable corrugated overture developed by Advanced Surgical Concepts Ltd, Bray, Eire (ASCOT). We used the combination of a colonoscopy simulator and an Olympus variable flexion colonoscope (CF-240AL) set on its floppiest mode. Magnetic endoscope imaging was used to assess whether the ASCOT adequately splined the left side of the colon.

Results and Discussion: The ASCOT satisfactorily splinted the left side of the colon when repeated simulated colonoscopies were performed by three experienced endoscopists. The valve at its tip remained airtight despite numerous passages of the endoscope along the colon simulator. The ASCOT was less stiff (<0.001) than the Williams split overture and its corrugated surface reduced friction between the colonoscope and its inner surface. The results are sufficiently encouraging to consider formal clinical assessment in lightly sedated patients undergoing colonoscopy with either adult or paediatric colonoscopes.

373 ST.THOMAS’S HOSPITAL BARRETT’S OESOPHAGUS AUDIT
P.G. Thatcher, R.P.H. Thompson. St Thomas’s Hospital, Lambeth Road, London, UK

Introduction: Barrett’s oesophagus was first described in 1950 and is said to have an increased cancer risk of between 20 and 125 fold. This has led to endoscopic surveillance programmes.

Aims: To assess the number of patients with Barrett’s oesophagus found on endoscopy between November 1999 and December 2000, histological characteristics and whether follow up had found any carcinomas during that period.

Methodology: Data were collected from the endoscopy reporting system using the terms “Barrett’s” and “oesophagus”. Histology was found via the RRS computer reporting system and analysed in relation to the OGD reports.

Results: 280 patients were found (181 female, 99 male) to have an endoscopic diagnosis of Barrett’s out of a total of approximately 2800 patients.
7000 procedures. Histological confirmation was made in 75% of cases. 172 had no dysplasia, 29 mild dysplasia, one moderate, and two severe dysplasia. Eight had carcinomas, none were found as part of any surveillance programme. The three moderate/severe dysplasias had endoscopies every three months, but none progressed to carcinoma in the one-year period.

Discussion: The discrepancy in endoscopic and histological diagnosis was probably due to the number of biopsies taken which varied between two and eight (not in keeping with the world congress of Gastroenterology recommendations). However, this audit did highlight that no carcinomas were found as part of any surveillance program and that the dysplastic patients didn’t progress to carcinoma in this period. This further supports recent papers, which have challenged the effectiveness of endoscopic surveillance.

374 UTILITY OF TERMINAL ILEAL (TI) BIOPSIES AT ROUTINE COLONOSCOPY

D.G. Power, A.N. Keeling, M.F. Byrne, E.W. Kay, F.E. Murray. Departments of Gastroenterology, Pathology and Clinical Pharmacology, Beaumont Hospital and RCSI, Dublin, 9, Ireland

Aim: The aim of this study is to compare TI biopsies (BXs) taken by endoscopists with the histology of these BXs. Thus we can see if TI views at colonoscopy and subsequent BXs taken, actually are proven TI.

Methods: We analysed all the colonoscopy reports in one centre which reported taking TI BXs. Only colonoscopies performed by Consultant Gastroenterologists and Specialist Gastroenterology Registrars were used. The Entoscopy programme, set up in the endoscopy suite of our 630 bed Dublin teaching hospital, was the means by which we accessed the reports. We then cross-referenced each individual TI BX taken at colonoscopy with its histopathology report.

Results: Our study period was 2 Oct 2000 – 2 Oct 2001. A total of 111 TI BXs were sent for histology, with 106 being actual TI histologically and thus five proved to be colonic mucosa. These results showed a mismatch rate of 4.5% between endoscopic TI and histological TI. We also examined the indications for procedure, these included: altered bowel habit, unexplained abdominal pain, weight loss, blood per rectum, anaemia (iron and B12), poly/ carcinoma surveillance, radiological abnormalities, inflammatory bowel disease, previous ileal TB, pseudomembranous colitis, suspicion of MALTomas. We concluded that the most frequent indication for colonoscopy was investigation of altered bowel habit: a total of 49% of all procedures performed. The actual TI histological findings were varied and included: normal villous architecture (88%), apthous ulceration (6%), and others (6%). When TI BXs did not correlate with appropriate TI histology, we found normal colonic mucosa +/- mild architectural atypia.

Conclusion: Our gastroenterology service performed a total of 111 TI BXs at colonoscopy over the study period. 106 of these were actually TI. The remaining five were colonic mucosa, giving a 4.5% mismatch. This small retrospective study was interesting in that it highlighted the fact that an endoscopists view of TI does not always correlate with actual TI histologically. No reason was reported for the five erroneous BXs. It appears that experienced endoscopists have a lower endoscopic to histological mismatch.

375 A COMPARISON OF NURSE AND DOCTOR PERFORMED COLONOSCOPY

S. Pathmakanthan, K. Smith, G. Thompson, H.G. Amer, M.T. Donnelly, S.A. Riley. Department of Gastroenterology, Northern General Hospital, Sheffield, UK

Background: Colonoscopy is the investigation of choice for examining the colon but as the demand for colonoscopy increases and JAG begin to specify quality targets, there have been shortfalls in practise confirmed by a recent national audit. We have developed the role of nurse colonoscopist and now present a prospective comparison of doctor and nurse performed colonoscopy.

Methods: Patients attending for routine diagnostic colonoscopy were invited to participate taking TI BXs. Endoscopists were performing using standard videoeendoscopies and were video recorded for independent review. Endoscopists were instructed to use midazolam, pethidine, and buscopan according to their usual practice. Endoscopists and nurse assistants graded the patients’ pain and tolerance on visual analogue scales (VAS) and a validated questionnaire and VAS were given to the patient following the procedure.

Results: 84 patients (38 female, aged 29 to 83 years) were examined by the doctor and 83 (48 female, aged 23 to 87 years) by the nurse. Intention to treat caecal/ileal intubation rates were 98/83% and 94/72% respectively. Failure to reach the caecum was due to obstructing cancer (1) and diverticular disease (1) in the doctor group, and patient discomfort (3), poor preparation (1), and obstructing Crohn’s stricture in the nurse group. Pain and tolerance scores were similar but the nurse used more midazolam and pethidine. The pathological spectrum was also similar but with more diverticular disease in the doctor examined group. No significant complications occurred.

Conclusions: Appropriately trained nurses perform safe and effective colonoscopy examinations with caecal and ileal intubation rates exceeding JAG recommendations. Expansion of the nurse colonoscopist role may help to meet the increasing demand for diagnostic colonoscopy.

376 IN INCOMPLETE BOWEL OBSTRUCTION, SELF EXPLANTING METAL STENTS FOR PALLIATION OF BOWEL CANCER CAN BE DEPLOYED WITHOUT FLUOROSCOPIC IMAGING

A.A. Saeed1, M.T. Hendrickse2, P. Isaacs3, C.J. Sharrock4. Queen Elizabeth Hospital, Gateshead, UK; 1Blackpool Victoria Hospital, Blackpool, UK

Background: Self expanding metal stents offer an attractive treatment modality for palliation in patients with large bowel obstruction due to cancer. We present our experience with endoscopically inserted stents, with and without the use of fluoroscopy.

Methods: 21 metal stents were placed in 18 patients, to relieve symptoms of obstruction due to malignancy. All patients had clinical or x-ray evidence of obstruction or obstructive symptoms, such as distension and pain. None of the patients had complete obstruction. In 10 procedures, fluoroscopic imaging was not used and the stents were deployed under endoscopic control.

Results: Metal stents were successfully placed in 21 out of 22 procedures. Relief of symptoms was achieved in 14 out of 18 patients (78%). Of these three patients were alive after a median follow up of 4.3 months, 11 of them died after a median FU of 2.1 months. One patient died due to perforation. (Procedure related mortality 6%). The only other complications were incontinence and stent migration (33%). There was no difference in the success rate of the procedures done with or without fluoroscopic guidance.

Conclusions: When it is possible to traverse the malignant stricture endoscopically, palliative colonic stenting can be safely performed without fluoroscopic imaging.

377 ENTERAL STENT PLACEMENT FOR MALIGNANT GASTRIC OUTFLOW OBSTRUCTION: SUCCESSES AND FAILURES

S.G. Nugent, A.F. Stone, M.J. Benson. Department of Gastroenterology, St. Helier Hospital, Carshalton, Surrey, UK

Background: Gastric outflow obstruction due to locally advanced malignant disease causes distressing symptoms. Historically, patients have been treated with surgical bypass, with a substantial morbidity. Self expanding metal enteral stents are now available enabling endoscopic palliation. We describe our experience with this technique over a 23 month period from December 1999 to October 2001 in a district general hospital setting.

Methods: All patients presenting with symptoms of mechanical gastric outflow obstruction due to inoperable malignant disease, were included. At endoscopy, a guide wire was manipulated across the stricture, under fluoroscopic control. Placement of Wallstent enteral stent [Boston Scientific] was achieved using wire guided, “through the scope” technique and a large channel (4.2mm) operating gastro-scope (Olympus GIF 2T240). Pre-dilatation of the stricture was not performed routinely.

Results: 15 patients, median age 78 years, (range 60–92 years) had a total of 15 enteral stents. Outflow obstruction was due to carcinoma of antrum (n=3), pyloric canal (n=3), duodenum (n=1), bile duct (n=3), and pancreas (n=5). One patient had three stents placed in series to “bridge”a long stricture involving the gastric antrum and duodenal cap. One patient required a second stent four days later, due to proximal stent migration. One patient with a pyloric canal tumour was found to have a second distal duodenal stricture after...
Abstract 378 The surface roughness of 4 biliary stents. Ra value is the average of 3 measurements from 10µm² AFM images; standard deviation of the data is shown in the brackets.

<table>
<thead>
<tr>
<th>Material</th>
<th>Manufacturer</th>
<th>Design</th>
<th>Roughness Ra (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teflon</td>
<td>Wilson Cook</td>
<td>Soehendra</td>
<td>30.43 (6.76)</td>
</tr>
<tr>
<td>Teflon</td>
<td>Olympus</td>
<td>Tannenbaum-type</td>
<td>13.26 (2.09)</td>
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<tr>
<td>Polyethylene</td>
<td>Wilson-Cook</td>
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<td>30.00 (5.04)</td>
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<tr>
<td>Polyethylene</td>
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<td>Rapid Exchange</td>
<td>248.75 (24.5)</td>
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</table>

Conclusion: AFM images the native stent surface within air or liquid with a higher resolution and allows quantification of surface roughness. AFM is a useful tool for the study of stent materials and proposed surface chemistry modifications prior to clinical trials.

Abstract 379 RAPID ACCESS UPPER GI CANCER SERVICE (RAUGICS) VERSUS OPEN ACCESS ENDOSCOPY (OAE): IMPACT OF THE “TWO WEEK RULE”

A. Bassi, R. Sturgess, K. Bogder. University Hospital Aintree, Liverpool, UK

Background: To improve access to investigation for patients with suspected cancer, the NHS Executive has introduced a two week out patient waiting time standard. Despite provision of an OAE service at our hospital (>2000 procedures/year; target population 330,000; waiting time <6 weeks), achieving this benchmark for patients with suspected UGI cancer (UGIC) demanded a new initiative. The RAUGICS was set up in parallel to OAE to allow GPs to request “fast track” direct access endoscopy (and subsequent clinic review) for “high risk” subjects.

Aims: (a) to evaluate the impact of introducing a RAUGICS on the total number of direct referrals (DRs) for endoscopy; (b) to compare the profile of endoscopic diagnoses for RAUGICS with that of OAE before (OAE) and after (OAE) introducing the new service; (c) to assess the resource implications of RAUGICS in terms of direct costs (endoscopy plus clinic) per cancer diagnosed.

Methods: Information was obtained from “Endorscribe” for OAE and prospectively for RAUGICS. Two six month periods were compared (OAE: 01.01.00 to 30.06.00; OAE & RAUGICS: 01.01.01 to 30.06.01). Major diagnoses and disease stage of cancers were verified by case record review.

Results: After launch of RAUGICS: (a) total DRs increased by 33% (953 to 1264) with 51% of DRs (645/1264) designated as requiring the “fast track” service (rapid endoscopy, then clinic review); (b) the prevalence of UGI cancer amongst DRs overall was unchanged (1.57% vs 1.6%), but most cancers (20/21) were diagnosed in the RAUGICS group (3.1% yield); (c) Cost-per-cancer diagnosed within the new service was £7740; (d) Stage of cancers diagnosed by direct access endoscopy was unchanged (OAE versus RAUGICS).

Conclusions: Referral criteria were effective in channelling patients with UGI cancer into the RAUGICS arm of the direct access service, but demand for “rapid access” was high (half of all DRs). The low cancer rate [3.1%] suggests either poor specificity of referral criteria or a high level of “inappropriate” referrals.

<table>
<thead>
<tr>
<th>No. of referrals</th>
<th>OAEB</th>
<th>RAUGICS</th>
<th>OAEB</th>
<th>RAUGICS + OAEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>55 (15.7)</td>
<td>60 (15.6)</td>
<td>51 (16.2)</td>
<td>56 (16.5)</td>
</tr>
<tr>
<td>UGI cancers, UGC [%]</td>
<td>15 (1.57)</td>
<td>20 (3.1%)</td>
<td>1 (0.16%)</td>
<td>21 (1.6%)</td>
</tr>
<tr>
<td>Nil or Minor findings [%]</td>
<td>836 (88%)</td>
<td>553 (86%)</td>
<td>523 (85%)</td>
<td>1078 (83%)</td>
</tr>
<tr>
<td>Peptic ulcer (GU or DU)</td>
<td>41</td>
<td>26</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>Benign Oes. Stricture</td>
<td>7</td>
<td>13</td>
<td>1</td>
<td>14</td>
</tr>
</tbody>
</table>

* RAUGICS v OAEB p=0.06; v OAEB p=0.001; ** RAUGICS v OAEB p=0.044; v OAEB p=0.002
## 380 ASSESSMENT OF AN OPEN ACCESS IN-PATIENT GASTROSCOPY SERVICE

E. Quinton, W.P. Goddard, R.G. Long, K. Teahan. Department of Gastroenterology, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1FB, UK

**Introduction:** There is a significant body of literature assessing open access outpatient gastroscopy (OGD). Little is written about the use of organisation of the service OGD for inpatients except in the situation of gastrointestinal bleeding. In late 1998 we switched our inpatient gastroscopy service from a “Consultation first” service to an “Electronic Open Access Service”. This study evaluates the impact of these changes in inpatient service organisation.

**Methods:** (1) The number of and reason for requests for OGD since 1998 was retrieved from the electronic database. (2) “Reason for request” categories were selected randomly for review to allow review of 25% of the records. (3) On review of the records the demographic details, reason for admission, reason for referral for and outcome of OGD, eventual diagnosis, and routine laboratory parameters were recorded. (4) The pre OGD admission record of each patient was summarised and reviewed anonymously and independently by three consultant gastroenterologists to determine appropriateness of the request for OGD.

**Results:** During the period from 1998 there was a 19% increase in emergency medical and surgical admissions and a 27% increase in OGD requests but this varied from a 13% increase in referrals for melaena to a 56% and 80% increase in referrals for nausea/vomiting and abdominal pain respectively. When the appropriateness of referrals was assessed 67% of all requests were considered appropriate but the value varied (abdominal pain 41%, haematemesis 74%, melaena 83%, anaemia 84%, and nausea/vomiting 57%). The eventual diagnosis was achieved at OGD in all patients in 52% (abdominal pain 29%, haematemesis 79%, melaena 65%, anaemia 38%, nausea/vomiting 38%).

**Conclusion:** An electronic open access service is appropriate for inpatients with GI bleeding and anaemia although more selective referral questions may improve the appropriateness of referrals. Pre-procedure consultation is more appropriate for most other categories of inpatient referrals.

## 381 GENERAL PRACTITIONERS’ PERCEIVED UTILITY OF A PROPOSED COMPUTERISED DECISION SUPPORT SYSTEM FOR WEB BASED REFERRAL OF PATIENTS WITH GASTROINTESTINAL (GI) DISORDERS

D. Flynn1, P. van Schaik2, A. van Wersch1, A. Douglass1.1 Endoscopy Centre, James Cook University Hospital, Middlesbrough, UK; 2University of Teesside (Social Sciences), Middlesbrough, UK.

**Introduction:** A web based, direct booking system for GP referrals to a GI clinic or procedure is under development for our unit. Guidelines for referral of clinical sub groups will be incorporated as algorithms within the software. The computerised decision support booking system. This will enable the most appropriate slot for the patient to be identified and booked directly in real time. “ Appropriateness” will relate to relevant clinician, nature (clinic or procedure,) and speed of first contact and provide patients with some choice of appointments.

**Aims & Objectives:** To assess GPs’ attitudes to the principles, design, and their eventual usage of such a system.

**Methods:** 21 GPs were given a description of the proposed system and asked to rate each of eight potential benefits on a 0-5 scale. GPs were also given the opportunity to discuss the potential impact of the system on their clinical practice and patients.

**Results:** The five most highly scored potential benefits were [i] faster and more reliable communication between primary and secondary care (mean 5.22), [ii] appropriateness of the first assessment received by patients (mean 5.19), [iii] facilitating adherence to local clinical guidelines (mean 5.43), [iv] facilitating the explanation of referral decisions, tests and procedures to patients (mean 4.42), and [v] provision of information on evidence-based reports for GIs (mean 4.37). 52% of GPs indicated that they would use the system in real time only if it generated no more than two additional minutes on consultation times. 21% of GPs were concerned that the system could increase administrative workload, and create unrealistic expectations of open access services for patients.

**Conclusions:** The majority of GPs recognised potential benefits of the proposed system, but the impact on consultation times is a core design issue that will determine acceptance and usage of such a system. Other members of the primary care team may help to minimise the need for the GP to spend “real time” online.

## 382 GASTRIC BIOPSY: WHERE FROM AND HOW MANY USING THE UPDATED SYDNEY SYSTEM TO EVALUATE GASTRITIS, ATROPHY, AND INTESTINAL METAPLASIA?

M.M. Walker, R.P. Negus, A. Rice, V. Loh, J. Teare, M.R. Thurz. Faculty of Medicine, Imperial College of Science, Technology and Medicine, St Mary’s Campus, London W2 1PG, UK

The topography of gastritis predicts a likely outcome in Helicobacter pylori infection. Histological markers of cancer risk include severe atrophy and intestinal metaplasia. The updated Sydney system for reporting gastritis report five biopsy sites, which is time consuming. This study aims to establish if all five gastric sites are necessary for an accurate appraisal of gastric pathology in routine practice.

**Patients and Methods:** 100 patients, 45 men, median age 57, range 21–88 years, attending for upper gastrointestinal endoscopy had five gastric sites routinely biopsied according to the updated Sydney protocol. Biopsies were placed in order on a cellulose acetate strip, processed, and reported by two pathologists according to the Sydney System. Results were analysed to assess concordance of diagnosis by site and to determine which of the five sites were optimal to assess gastric pathology.

**Results:** The majority of presenting symptoms for endoscopy were dyspepsia or abdominal pain (47 patients). At biopsy for gastritis, including grade of gastritis, there was excellent concordance between body sites (100%), and good concordance between antral sites (94%). No further information was gained from separate analysis of the biopsy of the incisura. Intestinal metaplasia (IM) was found with greatest prevalence in A2 (inferior antrum)-17% all biopsies and B2 (greater curve, body) - 5%. In contrast, atrophy was found with greatest prevalence (21%) at A1 (superior antrum) but also as in IM, 10% of B2 biopsies showed atrophy. The overall prevalence of IM in this study was 19% and atrophy, 21% from analysis of biopsies of all sites.

**Discussion:** This study shows that when histological assessment of gastritis is required, in the absence of a visible lesion, two biopsies, one from the antrum and one from the body are adequate for a clinical diagnosis of grade and type of gastritis. However if only two sites are biopsied, IM (a histological marker of cancer risk) will be missed in 7% of cases relative to the full Sydney protocol.

## 383 THE APPROPRIATENESS OF A 24 HOUR BLEEDING SERVICE: PROSPECTIVE AUDIT OF GUIDELINES FOR THE MANAGEMENT OF GASTROINTESTINAL HAEMORRHAGE

M.C. Gallagher, F.R. Vicary, V.S. Wong. Department of Gastroenterology the Whittington Hospital London N1, UK

**Background:** Acute upper gastrointestinal haemorrhage (UGIH) constitutes a medical emergency with an incidence of 100 per 100 000 and mortality rate of 14%. The Whittington Hospital departmental guidelines state that patients should undergo endoscopy the day after admission unless there are criteria for “emergency endoscopy” (out of the hours 9 am–5 pm): suspected varices, large bleed/continued bleeding, or history of aortic graft. Two consultant physicians, (and their SPRs) and two consultant surgeons provide 24 hour endoscopy cover.

**Aims:** To perform a six month prospective audit of the management of unselected cases of acute UGIH at the Whittington Hospital.

**Methods:** All suspected cases of acute UGIH were included. Data were collected on a standard proforma and case notes reviewed after discharge. Outcome measures included the timing of endoscopy, use of “out of hours” endoscopy services, endoscopic diagnosis, and mortality rates. Rockall scores were calculated for all patients who required endoscopy.

**Results:** 95 cases of suspected UGIH were identified. 76 patients (80%) presented via A&E and 19 (20%) were existing inpatients. 90 patients underwent endoscopy. In 92% of cases, endoscopy was performed within 24 hours of admission/inpatient bleeding episode. Of these, 20 patients achieved criteria for emergency endoscopy. 17 were endoscoped out of hours and three patients presented within hours. The average Rockall score for patients endoscoped within hours was 3.5 (range 1–10) and out of hours, 6.5 (range 1–10).

Endoscopic diagnoses were as follows: peptic ulcer 37%, varices
1.5%, normal 12%, erosions 9%, oesophagitis 9%, Mallory-Weiss tear 2%, other 16%. Endoscopic therapy was required in 29 cases (30%). The overall Mortality Rate was 10.5%.

Conclusion: The proportion of patients in this series endoscoped within 24 hours (92%) compares favourably with published data (50 and 56% in the BSG National Audits) within 24 hours (92%) compares favourably with published data (50 and 56% in the BSG National Audits). Recent research by et al. BMJ 1995;311:222–6 2. Rockall et al: Gut 1997;41:606–11

**384** SELF ADMINISTERED PHOSPHATE ENEMA IN BOWEL PREPARATION FOR FLEXIBLE SIGMOIDOSCOPY: AN AUDIT OF EFFICACY AND PATIENT SATISFACTION

T.A. Raven, J. Whelan, I. Fretwell, M. Aston, P. Whitney. Endoscopy Department, Chesterfield Royal Hospital, Derbyshire, UK

Background: Patients attending endoscopy for a flexible sigmoidoscopy (FS) examination were being prepared using picolax except one doctor who used phosphate enemas on arrival. Recent research by W. Atkin (2000)1 has shown that an phosphate enema administered on the day of the examination is as effective as picolax. To see if this could be successful in our endoscopy unit an audit was conducted.

Aims: To improve the way in which patients are prepared for (FS) without compromising the quality of bowel preparation.

Methods: 53 Patients were selected using two (FS) lists and had the option of taking the enema at home instead of picolax for bowel preparation. A questionnaire was prepared for patients to complete while they were waiting for the (FS). A note was made of patients unable/unwilling to administer the enema. Nursing and medical information was collected to assess the acceptability and quality of bowel preparation.

Results: 98% of patients administered the enema successfully at home. 74% of the (FS) tests were completed to 60cm. 100% of patients using the enema would use it again, 12% telephoned the department for advice, 38% experienced mild side effects, and 27% needed help from someone at home. The bowel preparation was excellent to good in 75% of cases.

Conclusion: Patients found the enema easy to use and acceptable as a method of bowel preparation. Although only a small number of cases were audited the results are very similar to those reported in the BMJ. 1. Akin et al: BMJ 2000;320:1504–9

**385** USE OF A PAIR OF PRESSURE SENSITIVE GLOVES TO DETERMINE MECHANICAL WORK DONE DURING EITHER OGD OR COLONOSCOPY: A PILOT STUDY IN 10 PATIENTS

J. Hancock1, S. Dogramadzi2, G.D. Bell1, C. Allen1, K. Burn1, I. Fletcher1, R. Bicker2. 1Medical Sciences Faculty, Sunderland University, UK; 2Department of Electrical and Electronic Engineering, Newcastle University, UK; 3School of Computing, Engineering and Technology, University of Sunderland, UK; 4Department of Mechanical, Materials and Manufacturing Engineering, Newcastle University, UK

Introduction and aims: Torque steering is now the preferred method of teaching intubation of the tortuous sigmoid colon. One of the criticisms of many teaching simulators is that the “feedback” forces are not needed/unwanted to administer the enema. The overall Mortality Rate was 10.5%.

Conclusion: The proportion of patients in this series endoscoped within 24 hours (92%) compares favourably with published data (50 and 56% in the BSG National Audits). Recent research by W. Atkin (2000)1 has shown that an phosphate enema administered on the day of the examination is as effective as picolax. To see if this could be successful in our endoscopy unit an audit was conducted.

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**386** HAEMORRHAGIC RADIATION PROCTITIS: AN ENDOSCOPIC SCORE MAY GUIDE THERAPY

R. Zinica1, M.D. Rutter1, G. Falasco1, V. Cennamo2, S. Contini2, B.P. Saunders1 1Wolfson Unit for Endoscopy, St. Mark’s Hospital, UK, 2Endoscopia Digestiva, Ospedale Bellaria, Bologna, Italy

Background: Management of haemorrhagic radiation proctitis (HRP) remains controversial. Recently both endoscopically delivered argon plasma coagulation (APC) & local rectal application of 4% formalin (LRAF) have been reported as effective treatments. However the exact role of these therapies is not clearly defined. We evaluated the efficacy of APC, and developed a new endoscopic score to guide therapy.

Methods: 12 patients with significant rectal bleeding due to HRP were retrospectively reviewed. Patients were classified using a new endoscopic grading of HRP from endoscopic videoprints, assessing conflunce and distribution of telangietasias, percentage of surface area involved, and presence of fresh blood. All patients were treated with APC initially.

Results: Using the new endoscopic grading, five patients were categorised as grade I (mild) HRP, four patients grade II (moderate) HRP, three patients grade III (severe) HRP. In 10 patients (83.3%), bleeding improved significantly following APC therapy. All patients with grade I & II were treated successfully by APC (median two sessions, range one to four). In two grade III patients APC failed, but subsequent formalin application was successful.

Conclusions: Our endoscopic score may help guide appropriate treatment for HRP. APC appears safe, efficacious, and should usually be considered first line therapy, particularly in grade I & II HRP. However with extensive (grade III) HRP, topical formalin application may be more effective.

**387** ARE MULTIPLE BIOPSIES NECESSARY IF A COLONOSCOPY IS NORMAL?

M.C. Follows, B.J. Rembacken, D.M. Chalmers, A.T.R. Axon. Centre for Digestive Diseases, the General Infirmary at Leeds, Great George St, Leeds, LS1 3EX, UK

Aims: To correlate the histological and clinical findings in patients with a macroscopically normal, total colonoscopy.

Method: A search was made of all colonoscopy reports performed during 2000. Reports from patients with a macroscopically normal, total colonoscopy in which a set of serial biopsies (caecum, ascending, transverse, descending, and sigmoid colon and rectum) had been taken were identified. The histology result for each patient was found and the indication for the examination noted in each case. Cases were excluded if any endoscopic abnormality was noted or if a full set of biopsies had not been taken.

Results: See table

Conclusions: Five cases of IBD (inflammatory bowel disease/ microscopical colitis) were identified in 282 patients. In all diarrhoea was a presenting symptom (i.e. 4% of patients with diarrhoea had IBD). If diarrhoea was not an indication no patients were found to have IBD on serial biopsies. We recommend serial biopsies should be taken in patients with a normal colonoscopy but only if the predominant symptom is diarrhoea.
AN AUDIT OF ROUTINE ILEOSCOPY: PROCEDURE TIME AND DIAGNOSTIC YIELD
S. Cherian, A. Cherukuri, P. Singh. Staffordshire General Hospital, Stafford ST16 3SA, UK.

Introduction: Ileoscopy is not routinely attempted because of its perceived technical difficulty. We believe routine ileoscopy is useful in quality assurance and provides additional diagnostic yield.

Methods: We examined colonoscopy data from September 1995 to October 2001 of a single gastroenterological firm. For documentation of completeness of examination, visualization of ileocaecal valve or ileal intubation were the only criteria used. A registrar endoscopist performed 80 colonoscopies independently. For analysis of intubation rates, these 80 and a further 56 procedures in patients with prior colonic resection were excluded. During the last year of the audit, data were prospectively collected on procedure times (PT).

Results: There were 1602 colonoscopies. The median age was 60 years (range 8–95). The male to female ratio was 4.5:5.5. The diagnostic yield from 73 ileoscopies and 67 sets of biopsies in 66 patients with colonic IBD was: 63 normal; seven Crohn’s ileitis; and three non-specific inflammation in ileum and colon in three. In addition to the above 21, nine additional positive histologies were as follows: five non-specific ileitis, three villous atrophy (two also had duodenal villous atrophy), and one amyloidosis. The main indications for obtaining histology in the absence of an endoscopically visible lesion were diarrhoea and/or anaemia. Overall ileoscopy rate (IR) was 1.25 ± 1.9 months. Five patients are still alive, the longest being seven months. Twelve patients (67%) died during the follow-up period from causes unrelated to the stent. Both were successfully treated, by inserting further co-axial stents to bridge the stenoses. There were no short term complications. Two patients (11%), who were successfully stented, complained of abdominal pain post insertion. Two patients were readmitted with vomiting at six and nine months respectively. The first was due to tumour overgrowth and the second to distension caused by the stent. Both were successfully treated, by inserting further co-axial stents to bridge the stenoses. Twelve patients (67%) died during the follow-up period from causes unrelated to the stent insertion, with a median survival time of three months. Five patients are still alive, the longest being seven months. One patient was lost to follow-up.

Conclusions: Stent implantation was technically successful in eighteen (85%) patients. On two occasions a wire could not be passed and in a third, a previously placed plastic stent could not be changed preventing enteral stent deployment. Nausea, vomiting, and dysphagia improved in all cases that had a stent successfully placed. There were no short term complications. Two patients (11%), who were successfully stented, complained of abdominal pain post insertion. Two patients were readmitted with vomiting at six and nine months respectively. The first was due to tumour overgrowth and the second to distension caused by the stent. Both were successfully treated, by inserting further co-axial stents to bridge the stenoses. Twelve patients (67%) died during the follow-up period from causes unrelated to the stent insertion, with a median survival time of three months. Five patients are still alive, the longest being seven months. One patient was lost to follow-up.

Conclusion: In our experience, the endoscopically placed enteral stent is a safe and efficacious procedure that provides an effective means of palliation to patients with an inoperable malignant upper GI obstruction.

A SEVEN YEAR OUTCOME OF ENDOSCOPIC LASER THERAPY FOR PALLIATIVE UPPER AND LOWER GASTROINTESTINAL MALIGNANCY IN A DISTRICT GENERAL HOSPITAL
R.P. Arasaradnam, P. Hancock, T. Woodward, G. James. Department of Gastroenterology, Doncaster Royal Infirmary, Doncaster, UK.

Background: Laser therapy is useful not only in extensive oesophageal tumour and stent overgrowth but also for inoperable recto-sigmoid tumours in reducing the risk of obstruction or bleeding.

Aim: To determine retrospectively outcome and complication rate of procedures carried out over a seven year period.

Subjects & Method: A total of 95 patients received laser therapy from 1994 until 2001, 31 of whom had lower, while 64 had upper gastrointestinal laser therapy.

Results: Out of the 31 lower gastrointestinal procedures 15 (50%) were for rectal carcinoma, six (19%) recto-sigmoid carcinoma, five (16%) sigmoid carcinoma, three (9%) tubulovillous adenoma, one (3%) sigmoid adenoma and one (3%) colonic angiodysplasia. 19 (61%) were male; mean age of 78 (range 74–97). 13 (42%) had cardiovascular co-morbidities, three (9%) cerebrovascular accidents (CVA), 5 (16%) chronic obstructive airway disease (COAD), and three (9%) and other. Median number of procedures was 4 ± 1.2 over a duration of 4 ± 1.9 months. Nine (29%) remained alive (one colonic angiodysplasia, three tubulovillous adenoma, two rectal carcinoma (later had surgery), one sigmoid adenoma and one recto-sigmoid carcinoma). Complication rate was 0%.

For the 64 upper gastrointestinal laser procedures, 39 (61%) had oesophageal carcinoma, 15 (23%) gastric carcinoma, six (8%) stent overgrowth, one (2%) oesophago-gastric carcinoma, one (2%) gastric arteriovenous ectasia (GAVE), one (2%) Hereditary haemorrhagic telangiectasia (HHT), and one (2%) gastric angiodysplasia. 35 (55%) were male; mean age of 75 (range 61–97). 27 (42%) had cardiovascular co-morbidities, eight (13%) CVA, 14 (22%) COAD, and five (8%) had other primary malignancies. Median number of procedures was 1.25 ± 0.9 over a 2.5 ± 0.5 month period. 12 (18%) remained alive (three gastric carcinoma, one gastric angiodysplasia, one HHT, one GAVE: eventually required Argon plasma coagulation and six oesophageal carcinoma: one eventually requiring a stent). Complication rate was 0.05% (two with aspiration pneumonia within two weeks of the procedure and one bled after 12 hours of treatment).

Conclusions: Laser therapy is safe and an effective method of palliation for inoperable malignancy when performed in a District General Hospital setting by an experienced endoscopist.
Method: A prospective study of 212 patients undergoing laparoscopic cholecystectomy was performed. A detailed postal symptom questionnaire was designed and piloted. Patients completed these preoperatively and at three and 12 months postoperatively.

Results: 169 patients were female. The median age of patients was 57 years (range 21–81). Complete data was available on 68% (143 patients). 34 patients (23%) continued to be symptomatic. Only one patient (0.06%) reported their abdominal pain/discomfort had become worse. Of the symptomatic patients with continuing abdominal pain, 15 (44%) claimed their pain was identical to that pre-operatively. 55% (26) of the symptomatic patients consulted their GPs during the one year follow up period.

Conclusion: A significant number of patients are dissatisfied one year after laparoscopic cholecystectomy. All patients should be pre-operatively counselled about the risk of persistence of some pain symptoms after laparoscopic cholecystectomy. The tolerability should be a high index of suspicion for upper GI conditions and more patients should undergo diagnostic endoscopy before subjecting them to surgery.

NEOPLASIA POSTERS 392–409

392 CURRENT MANAGEMENT OF IRON DEFICIENCY ANAEMIA BY GENERAL PHYSICIANS DOES NOT COMPLY WITH BRITISH SOCIETY OF GASTROENTEROLOGY GUIDELINES

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Introduction: Iron deficiency anaemia is a common problem encountered in all medical specialties. In men and post menopausal women common causes are gastrointestinal blood loss or malabsorption. The British Society of Gastroenterology (BSG) recently produced guidelines on the management of this condition.

Aim: To establish current practice in the investigation of iron deficiency anaemia.

Methods: The laboratory identified all patients with a haemoglobin and mean cell volume below the normal range, for the six month period between January and July 2001. The charts of those patients under the care of consultant physicians were reviewed. Data collected included details of history taking, examination, investigations performed, treatment and follow up.

Results: 74 patients were identified with both a low haemoglobin and mean cell volume (age range 15–90 years), 70% were female. A rectal examination was performed in 16%. 13 patients (18%) had antedisciplinary antibodies tested. 27 patients (36%) had colonoscopy or barium enema performed, planned or were unsuitable for investigation. 25 (34%) had an OGD or barium meal performed, planned or were unsuitable. One patient had duodenal biopsy. A reason for anaemia was found in 24 patients (32%). In this group five had colonic or gastric carcinoma, and no diagnosis of coeliac disease was made. 38 patients (52%) were placed on iron supplements. Excluding four patients who were unsuitable for follow up, 49 (70%) had a hospital review arranged.

Conclusion: A low proportion of patients underwent follow up and lower GI tract investigation although five patients were diagnosed with carcinoma. No cases of coeliac disease were detected, but only 18% had antedisciplinary antibodies tested, and one duodenal biopsy was performed. We have produced a summary of the BSG guidelines to improve management of these patients and encourage early referral for endoscopy.

393 SPEED OF DIAGNOSIS OF UPPER GASTROINTESTINAL CANCER: DOES THE METHOD OF REFERRAL MATTER?

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All cases of upper gastrointestinal (GI) cancer diagnosed at two district general hospitals in south Wales between 1/7/93 and 30/6/99 have been reviewed. Cases were identified from pathology, endoscopy and clinical information systems and data extracted from hospital and primary care records, using a structured proforma. Case finding was cross checked with the local cancer registry and data held in central returns. The data extracted were validated on a randomly identified 10% sample. Four hundred and thirty-nine cases were identified and data obtained on 418. Median age was 73, range 36–96 years, male:female 258:160, cancer site oesophagus (150), stomach (265), duodenum (2), lung primary (1).

Over the six years of the study, during which open access services (OAG) and a “one stop” Rapid Opinion Clinic (ROC) were introduced, there was an overall decrease in the median interval from first presentation to the General Practitioner to diagnosis by histology (from 68 to 17 days, p<0.001, when first and last six months compared). This overall NHS delay was significantly longer for those patients referred through outpatients (173 cases; mean interval 111.3; median 70; range 5–956 days) compared with admission (144 cases; mean 34.6; median 13, range 0–546 days), OAG (89 cases; mean 56; median 27; range 3–335 days), and the ROC (12 cases; mean 43.2; median 13; range 4–185 days; p<0.05 for all comparisons compared with outpatients). The main reason for this delay was the time taken to reach the diagnosis after the initial contact in hospital (mean 61.3 days for outpatients versus 26.7, 12.8, and 22.8 for admission, OAG, and ROC respectively; p<0.05 for all methods compared with outpatients). Most patients presented with a combination of symptoms which included loss of appetite or weight, but isolated dysphagia occurred in 14 patients (youngest 52 years) and isolated abdominal pain or dyspepsia was noted in eight (youngest 63 years).

We conclude that if upper GI cancer is suspected patients should be referred for “one-stop” assessment, or admission, rather than outpatients. Cancer may present as isolated abdominal pain or dyspepsia.

394 THE ROLE OF FDG-PET IN THE EARLY DETECTION OF RESPONSE OF COLORECTAL LIVER METASTASES TO CHEMOTHERAPY

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Aim: To determine if 2-[18F]-Fluoro-2-deoxy-D-glucose (FDG)-Positron Emission Tomography (PET) could detect early response to combination chemotherapy in patients with liver metastases from colorectal primary cancers.

Methods: Seventeen patients were imaged immediately prior to the first cycle of 5-Fluorouracil (5FU)/ Leucovorin using FDG-PET. Thirteen patients had follow up scans at 14 days. Tumour / Liver Ratios (TLRs) were used to quantify the PET images. Computed Tomography (CT), serum Carcinoembryonic Antigen (CEA) levels and survival figures were used as comparative evidence of response.

Results: Areas of enhanced FDG uptake in comparison to adjacent normal liver tissue were seen in all patients on pre chemotherapy scans. Thirty-four liver metastases were assessed for evidence of response in the thirteen patients completing both scans. A change in tumour/liver ratio of less than 20% was seen in 25 of 34 lesions. Non-uniform changes in activity were seen in five patients. Two patients with uniform reductions in FDG uptake greater than 20% had prolonged survival.

Discussion: FDG PET is reliable in the detection of metastatic colorectal cancer including those patients with low CEA levels. The changes seen in tumour FDG uptake at two weeks were small and often not uniform within patients. Sizable uniform reductions in activity, suggestive of response, were seen in only two of 13 patients both of who had longer than median survival. It is possible that these two patients were the only genuine early responders and that PET has the ability to identify this small group of patients.

395 P53 MUTATION DOES NOT INFLUENCE COX-2 IMMUNOREACTIVITY IN GASTRIC ADENOCARCINOMA

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Both COX 2 over-expression and p53 mutation are common findings in gastric adenocarcinoma, being seen in 60% and 40% of cancers respectively. Recently, it has been suggested that wild type p53 expression suppresses COX-2 mRNA transcription by competing for the COX-2 promoter site. If this is the case, COX-2 expression should be markedly increased in tumours with mutated p53 compared with those with wild type p53.
Abstract 395

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<th>p53 positive</th>
<th>p53 negative</th>
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<tr>
<td>COX2 positive</td>
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<td>COX2 negative</td>
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Method: Paraffin embedded tissue sections from gastric adenocarcinomas (n=45) were sectioned and immunohistochemistry carried out utilizing a polyclonal antibody raised against human COX-2 (Cayman) or the DO-7 clone of mutated p53 (DAKO). An avidin-biotin detection system and a DAB chromogen (Vector laboratories) were used. Positive controls slide derived from an oesophageal adenocarcinoma (DAKO) and negative controls comprising serum from the host animal were utilized. COX-2 antibody specificity was determined by western blotting and negative controls comprising serum from the host animal were utilized. COX-2 and p53 positivity was determined as expression by at least 50% of malignant cells in the section. Results were analyzed using a 2x2 table and Chi testing.

Results: COX-2 and p53 positivity was 71% and 44% respectively. The results are shown in the table above. Chi analysis demonstrated that the frequency of COX-2 positivity was unchanged between p53 positive and negative tumours (Chi value = 0.88).

Conclusion: The rate of COX-2 dysregulation is not altered by p53 gene mutation in gastric carcinoma.

396 A SYSTEMATIC EVALUATION OF THE SIGNIFICANCE OF IMMUNOHISTOCHEMICALLY DETECTED LYMPH NODE MICROMETASTASIS IN LOCALISED COLORECTAL CANCER

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Background: Regional lymph node metastasis in colorectal resections is routinely detected by examination of H&E stained tissue sections. There is no consensus regarding the clinical significance of lymph node micrometastasis detected solely by immunohistochemistry.

Design: Formalin fixed, paraffin embedded tissue sections of all pericolic lymph nodes dissected from 155 patients with Duke’s A/B colorectal cancer who had undergone a curative resection were immunostained using cytokeratin antibodies (Pan cytokeratin and AE1/AE3). Pre-operative and follow up information was sought by review of case notes and death registration where appropriate. Study end points (adverse outcome) were tumour recurrence and cancer related death. Five patients who died in the immediate post-operative period and 41 patients who received pre-/post-operative radio/chemotherapy were excluded from adverse outcome analysis.

Results: Eight hundred and ninety eight lymph nodes (range 1–20, median 5) were identified in the 155 resection specimens. Immunohistochemically detected micrometastasis, generally as single cells in the subcapsular sinus, was present in 155 (17.3%) lymph nodes (range 1 to 10, median 2) from 67 (43.2%) of patients (7/24 Duke’s A, 58/115 Duke’s B, 2/16 Duke’s A/B with history of pre-operative radiotherapy).

Adverse outcome was recorded in eight (15%) of 52 patients with micrometastasis detected by immunohistochemistry in comparison with twelve (20%) of 60 patients without immunohistochemically detected micrometastasis. No significant association could be found between immunohistochemically detected lymph node micrometastasis and adverse outcome in both univariate (p=0.316) and multivariate (p=0.414) Cox regression analysis.

Conclusion: Immunohistochemically detected micrometastasis in morphologically benign lymph nodes from resections for colorectal cancer is a common phenomenon but appears to be of no clinical significance.

397 EXPRESSION OF HEPARIN BINDING EPIDERMAL GROWTH FACTOR (HBEGF) IN TUMOUR AND EMBRYONIC CELL LINES

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Background: HBEGF binds to the epidermal growth factor receptor (EGFR) with high affinity and has increased mitogenic potential compared to other EGF ligands. Many solid tumours overexpress the EGF receptor. Co-expression of HBEGF by tumour cells would thus provide a powerful autocrine mechanism for tumour cell growth.

Aim: To assess expression of HBEGF in tumour and embryonic cell lines.

Methods: Using an anti-HBEGF antibody (Santa Cruz, USA), with immunoblotting, we examined lysates from 6 tumour and embryonic cell lines for expression of HBEGF: HepG2 (human hepatocyte carcinoma), WRL68 (human liver embryonic), C170HM2 (liver metastasizing human colon carcinoma), PLC/PRF/5 (human liver hepatoma) and MCA RH7777 (rat hepatoma).

Results: We found immunodetectable HBEGF in WRL68, C170HM2, PLC/PRF/5 cells but not in HTC, HepG2, or MCA RH 7777 cells. The three positive cell lines there was a band of ~30 kD which was not present when anti-HBEGF antibody preabsorbed with the immunizing peptide was used. In the C170HM2 cells only there was also a specific band present at ~51 kD.

Conclusion: These results suggest that HBEGF is present in human cell tumour and embryonic cell lines and may be important as an autocrine growth factor.

398 THE IMPACT AND CLINICAL APPROPRIATENESS OF THE TWO WEEK WAIT SCHEME FOR SUSPECTED CANCER

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Introduction: The two week wait scheme for patients with suspected cancer was introduced in April 2000. Guidelines as to which patients are suitable for this scheme have been produced. The evidence base that the scheme will produce clinical benefit is limited.

Methods: all patients referred to the two week cancer wait scheme in its first year with suspected gastro-oesophageal cancer (GOC) or colorectal cancer (CRC) were audited. After taking the history and examining the patient, the consulting doctor was asked to assess the indication for and appropriateness of the referral. The eventual diagnosis was recorded and correlated to the indication for referral. The out-patient (OP) waiting times for non-urgent cases during the year were documented.

Results: 394 patients were referred with suspected CRC and 280 with suspected GOC. The table shows the commonest referral indications, defined by the guidelines, and the pick up rate for cancer. 27 cases of GOC and 46 cases of CRC were detected in patients referred via the scheme. During the same period 49 cases of GOC and 77 cases of CRC were detected in patients referred out with the scheme. The OP waiting times for non-urgent cases increased from 9 to 16 weeks during the year.

Discussion: The guidelines are inadequate for detecting patients with cancer and are not adhered to for many referrals. The majority of cancers do not present through the scheme. It is likely that the scheme is having an adverse effect on non-urgent waiting times.
**A SEVEN YEAR EXPERIENCE OF MANAGEMENT OF OESOPHAGEAL CANCER**

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We conducted a retrospective review of all patients seen with oesophageal cancer at our institution over the last seven years. 225 patients were seen (mean age 49.6y, range 18-85y; 121 males).

**Tumour site:** 72 starting in upper 1/3 (69 squamous cell carcinoma [SCCA]), three adenocarcinoma [ACA]), 67 mid 1/3 (64 SCCA, 2 ACA, one collision tumour), 86 lower 1/3 or G.O. junction (45 ACA, 34 SCCA, one lymphoma, six simultaneous).

**Results:** 52 received no treatment (36 of these were lost to follow up during work up). 67 received purely palliative treatment, such as PEG/surgical gastrostomy, APC or other ablative techniques, radiation [DXT] or DXT/chemotherapy. Average age 51.8yrs. 22 ACA, 43 SCCA, 2 others. 15 upper 1/3, 20 mid-1/3, 32 lower 1/3. 50 had surgery with curative intent, either alone or in combination with DXT/chemotherapy in adjuvant or neo-adjuvant setting. Average age 48yrs. 43 SCCA, 13 ACA, two others. Four upper 1/3, 18 mid-1/3, 28 lower 1/3. 56 had treatment with either DXT or DXT/chemotherapy. Average age 46.4yrs. 52 SCCA, 4 ACA. 37 upper 1/3, 12 mid-1/3, seven lower 1/3.

**Outcome:** 61 patients were lost to follow up during investigation. 14 patients died (10 had surgery, three treated with palliative intent, one with primary DXT). Median survival 20 months. 34 definitely dead (3 had surgery, 13 treated with palliative intent, 10 DXT/chemotherapy, 8 had no treatment). Median survival 5.5 months. 116 patients lost to follow-up after median follow up of eight months.

**Conclusions:** (1) The average age of patients seen with oesophageal cancer is lower in our series than reported in the literature. (2) 25% of patients seen were younger than 40 yrs old and may represent a subgroup for further study as to the aetiology of this cancer. (3) In our country, it is difficult to follow up patients, particularly those from rural areas and with limited means of communication, as evidenced by the large number of patients lost to follow up.

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**MATRIX METALLOPROTEINASE-2 CONCENTRATION CORRELATED POSITIVELY WITH PATHOLOGICAL TUMOUR STAGE IN PATIENTS WITH ADENOCARCINOMA OF THE OESOPHAGUS OR GASTRIC CARCINIA**

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**Introduction:** Matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9) facilitate tumour invasion and metastatic spread by degrading type IV collagen, the main structural component of the basement membrane. The aim of this study was to determine if these endopeptidases are markers of disease progression in adenocarcinoma of the oesophagus or gastric cancer.

**Methods:** Approval for this study was obtained from the local ethics committee. All patients presenting with adenocarcinoma of the oesophagus or gastric cancer, obtained at the time of surgery, were homogenised, centrifuged and the supernatants analysed for expression of MMP-2 and -9 using matrix metalloproteinase activity assay systems (Biotrak ECL). There was no correlation between MMP-2 and MMP-9. The latter enzyme had significantly more activity in human pathological gastric cancer as compared to the pathological stage of tumour invasion, vascular involvement, or lymph node metastasis. MMP-9 was confirmed in a group of patients with advanced pathological stage gastric cancer but not in early stage gastric cancer.

**Conclusions:** The expression of MMP-2 and MMP-9 may offer new therapeutic potential in combating the high morbidity and mortality associated with cancer patients with weight loss (2.2 ±0.47 arbitrary units) compared both with controls (0.39 ±0.20) and with cancer patients who had not lost weight (0.47±0.23; p=0.02). MMP-2 mRNA levels did not differ significantly between groups, suggesting that MMP-2 is regulated by a different mechanism in human muscle and may have a different physiological role in this context. Elevation in muscle MMP-2 activity may enhance energy expenditure and contribute to the tissue catabolism seen in cancer associated cachexia. Manipulation of UCP expression may offer new therapeutic potential in combating the high morbidity and mortality associated with muscle wasting both in malignancy and other wasting conditions such as HIV.

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**MIP–1 IN METASTATIC CARCINOID TUMOURS REMOVED AT LIVER TRANSPLANTATION: RELEVANCE TO PROGNOSIS**

A.H.G. Davies, A.D. Amarapurkar, A.J. Stangou, D.G.D. Wright, B.C. Portmann, J.K. Ramage. Institute of Liver Studies (Carcinoid Clinic), Kings College Hospital, London, UK; Department of Histopathology, Addenbrooke's Hospital, Cambridge, UK

**Introduction:** Metastatic carcinoid tumours are difficult to manage. Histopathology generally fails to provide prognostic information. In spite of multidisciplinary approach, including orthotopic liver transplantation (OLT), the recurrence rate is high with a poor prognosis.

**Aim:** To assess MIP–1 as a prognostic marker of early recurrence and death in a group of patients undergoing Orthotopic Liver Transplantation for Carcinoid/neuroendocrine tumours of the liver.

**Results:** 14 cases were studied with an average age of 47 years. The patients were divided into two groups, those having MIP–1 index of ><2% and another group with MIP–1 <2%. There was a trend for patients with MIP–1 index of ><2% to exhibit a late recurrence (>24 months) as compared to those with MIP–1 index >2%. There was a trend for recurrence to be found in 85.7% and specificity 17.1%. Those having MIP–1 <<2% showed a longer survival than with MIP–1 ><2% with a sensitivity of 83.3% and specificity of 62.5%.

**Conclusion:** MIP–1 antibody staining was found to be a useful method of predicting the prognosis of metastatic carcinoid/neuroendocrine tumours. This method can provide an additional parameter for a rational approach to therapy. However this study is very small and a larger number of patients studied prospectively will be needed to confirm our findings.

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**METABOLIC THERAPY INHIBITS GENOTOXIC DAMAGE IN REGENERATING INTESTINAL EPITHELIUM**

K. Atherton, A.K. Daly, D.H. Phillips, F.C. Campbell. Dept of Surgery and Pharmacological Sciences, Newcastle,UK; Institute of Cancer Research, Surrey, UK; Dept of Surgery, Queen's University of Belfast, Northern Ireland, UK

**Adverse effects of many dietary carcinogens are increased in conditions of tissue regeneration. This study tests the hypothesis that metabolic therapy may inhibit DNA damage from dietary carcinogens in regenerating human intestinal epithelium.**

**Methods:** Metabolic therapy aimed at (i) inhibition of carcinogen bioactivating enzymes (CYPA11/1A2) using ellipticine or furafylline and/or (ii) promotion of Glutathione –S transferase (GST) enzymes responsible for carcinogen detoxification, by ethoxyquin or oltipraz.
FEW GASTRO-oesophageal Malignancies Are Identified Through Two Week Rule

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Aim: To identify the proportion of patients diagnosed to have a gastro-oesophageal malignancy through Two Week Rule (TWR) referral.

Methods: All TWR referrals for a suspected gastro-oesophageal malignancy (GOM) were identified from the cancer audit office over a 14 month period (July 2000–August 2001). The number of patients eventually diagnosed to have a tumour through this referral mode was noted. During the same period, the total number of GOMs identified were recorded using a combination of coding and histopathology records. Time from referral to assessment in clinic and time to diagnosis and treatment were recorded for patients referred through TWR and conventional routes.

Results: 199 patients were referred through TWR during the study period. Only 11 patients were subsequently diagnosed to have a malignancy (5.5% of TWR referrals, 29% of total malignancies diagnosed). 27 patients were diagnosed to have a tumour through other modes of referral (emergency admission: 14 (37%), outpatient clinic: 6 (16%), direct access endoscopy: 7 (18%).

Conclusions: Only a minority of patients (5.5%) referred through TWR had a malignancy; the majority (94.5%) had alternative diagnoses. Possible reasons for this includes: (i) referral criteria used in TWR forms may be poor discriminators for GOM (ii) over interpretation of alarm symptoms may lead to inappropriate referrals. There is no evidence that the TWR system has resulted in reduction in time to diagnosis and treatment of GOM. However, larger series are required to confirm these findings.

Abstract 404

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<th>TWR</th>
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<td>Median age</td>
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<td>Median time to appointment</td>
<td>5 days (1-32)</td>
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<tr>
<td>Median time to diagnosis</td>
<td>13 days (7-65)</td>
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<tr>
<td>Median time to treatment</td>
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Figures in brackets represent range

GASTRO-oesophageal Cancer in Scotland

K.G.M. Park for the Scottish Audit of Gastric and Oesophageal Cancer, UK

The prospective population based Scottish Audit of Gastro-oesophageal Cancer identified 3293 consecutive patients between 1997 and 1999 with oesophageal or gastric cancer. Patient characteristics and details of presentation within Scotland, as a whole, and within different geographical regions were identified. The hospitals were divided into 4 bands according to the number of patients with gastro-oesophageal cancer seen each year: Band 1: <75 cases, band 2: 34–74 cases, band 3: 11–34 cases, and band 4: <10 cases.

In common with other western series oesophageal adenocarcinomas predominate over squamous cell carcinomas. All tumour types were most common in the 65–74 age group and were associated with significant co-morbid disease (40% ASA grades 3–5). The 3293 patients presented to a total of 53 different hospitals, only 1/3 of the patients initially presented to hospital seeing in excess of 75 cases per year. There were differences between regions in terms of the time between referral of cases and final diagnosis. A greater than four week delay occurred in between 13.7% of patients in the region with the shortest waiting times and 31.6% of patients in the longest. Delays were less in patients initially presenting to band four hospitals—13% of patients waiting greater than four weeks compared with 22% in band one units. There were no differences between the size of the hospital of presentation and the time taken between diagnosis and commencement of treatment. Overall survival at one year was 29%, 32.7% and 34.5% for oesophageal, gastric and gastro-oesophageal junctional, and gastric tumours and at two years: 13.8%, 16.6%, and 20.4% respectively. There was no difference between the size of the hospital of presentation and survival.

Any reorganisation of services must take cognisance of the fact that the majority of patients currently do not present to specialised centres. Patients are not disadvantaged by this and services in smaller units should be supported to ensure continued equity of access.

GASTRO-oesophageal Cancer in Scotland

K.G.M. Park for the Scottish Audit of Gastric and Oesophageal Cancer, UK

The prospective population based Scottish Audit of Gastro-oesophageal Cancer identified 3293 consecutive patients between 1997 and 1999 with oesophageal or gastric cancer. Patient characteristics and details of presentation within Scotland, as a whole, and within different geographical regions were identified. The hospitals were divided into 4 bands according to the number of patients with gastro-oesophageal cancer seen each year: Band 1: <75 cases, band 2: 34–74 cases, band 3: 11–34 cases, and band 4: <10 cases.
Results: The mean recovery (%±SD) for each analyte in aqueous solutions at pH 1.5, 2.5, and 7 for probes not assembled in NG tube (NA) and probes assembled in NG tube (A) are shown in the table. The recoveries were independent of sample concentration. NO2 recovery was pH-dependent with lowest recovery at pH 1.5 (%78%) and highest at pH 7 (%91%). The results were similar in gastric juice. The intra-probe coefficient of variation for recovery of NO2, SCN, AA and TVC respectively were ± 6, 5, 18, and 17% for unassembled probes the respective recoveries were ± 9, 8, 16, and 18%. The probes also proved to be reliable under dynamic conditions simulating the interaction between NO2 in swallowed saliva and AA secreted in GJ under the condition of NO2 > AA and AA> NO2.

Conclusion: Multiple MD probes mounted on NG tube allows simultaneous measurement of nitrosation chemicals within different localised regions of the upper GI tract.

Liver posters 410–441

410 URINARY TAURINE AND HIPPURATE ARE USEFUL MARKERS OF ALCOHOLIC CIRRHOSIS
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Both taurine and hippurate are mainly produced by the liver and their excretion rate in the urine could provide us with markers in liver dysfunction. We aimed to evaluate the usefulness of urinary taurine and hippurate levels as markers of cirrhosis.

Materials and Methods: Urine was collected from 40 patients with alcoholic cirrhosis (18 males and 12 females) aged 37-74 (mean age: 59.6) and 20 controls (25 males and 15 females) aged 21-68 years old (mean age: 49.9) with normal liver function. All patients had moderate to severe liver disease (mean Child’s Pugh score 9.3) due to ethanol abuse. We used 1H NMR spectroscopy to quantitatively measure levels of taurine and hippurate in the patients urine. Both taurine and hippurate were expressed as excretion indexes relative to the amount of creatinine in each sample. ANOVA was applied to compare values between the groups.

Results: Taurine excretion index was significantly higher in cirrhotics than controls (0.27 ± 0.04 vs 0.046 ± 0.005; p=0.009). Hippurate excretion index was significantly lower in patients with cirrhosis than controls (0.097 ± 0.016 vs 0.25 ± 0.06; p<0.014). If the two values were combined then the results were again highly statistically significant (p<0.00126).

Conclusions: A combination of low hippurate and high taurine excretion is highly significant as a marker of alcoholic cirrhosis and can be a cheap non invasive marker of the disease.
questionnaire. 281 patients answered the questionnaire and 46 patients (16.4%) had an AUDIT score >9 (specificity for hazardous or harmful drinking=0.98). 40/46 had an alcohol history taken on admission; 27 of these reported excessive drinking (>21 U/Wk (M) or 14 U/wk (F)). Despite this, in only 15 of the 46 patients (32.6%), did subsequent review of the continuity notes pertaining to the admission, reveal an awareness of hazardous drinking. Only 12 of the 46 (26%) had action taken about the drinking problem. 30 of the 46 had laboratory evidence of alcohol excess (raised MCV, γGT or AST/ALT ratio, reduced platelets); of these, only 13 (50%) were identified and in 12 (40%) was action taken. b) In 68 of 71 patients with first presentation of decompensated ALD and who had had previous admissions to local hospitals (237 episodes), notes were reviewed. In 156 admission episodes (60.3%), laboratory data or symptoms suggested excess drinking. Admission alcohol history had been recorded > once in 63 patients (92.5%) during 161 previous admissions (67.9%). 41 of these 63 patients (65%), during 74/161 admissions, reported drinking >60U/wk (M) or >40U/wk (F). Of these, awareness of excessive drinking was evident from the continuity notes in 36/41 (87.8%) patients (54/74 admissions; 73%); action had been taken in 26/41 (63.4%) patients (37/74 admissions; 50%).

Conclusion: hazardous drinking remains common, under-diagnosed and under-managed in hospital inpatients.

**412 FUNCTIONAL POLYMORPHISMS IN THE RENIN-ANGIOTENSIN SYSTEM (RAS) ARE NOT RELATED TO FIBROSIS IN CHRONIC HEPATITIS C (HCV) INFECTION**

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Background: Angiotensin II (AngII), the main effector molecule of the RAS, may influence hepatic fibrosis. Functional polymorphisms in components of the RAS (angiotensinogen (Ang), angiotensin converting enzyme (ACE), AngII receptor (AT1R)) which alter gene expression and RAS phenotype are recognised. We aimed to assess the role of functional RAS polymorphisms in the progression of liver fibrosis in Scottish patients with chronic HCV.

Methods: 195 patients with HCV (RT PCR positive) and chronic hepatitis on biopsy were grouped by stage of liver fibrosis. Rates of RAS polymorphism were recorded in each fibrosis group.

Results: Patients homozygous for 2 or 3 high expression RAS mutations had similar stages of fibrosis compared with those homozygous for one or none (p = 0.93). Rates (%) of RAS polymorphism in each fibrosis group are shown in the table. On multiple linear regression advanced fibrosis was associated with a history of excess alcohol consumption (p<0.01). Previous studies have shown that mutations affect B- or T-cell epitopes during the course of acute HBV infection. It has been speculated that the vigorous and broadly reactive nature of the CTL response during acute infection prevents the emergence of CTL escape mutants. We investigated six patients with acute resolving hepatitis and four patients who progressed to chronic infection for the emergence of CD8+ cells. Our methodology included PCR, cloning, denaturing gradient gel electrophoresis and DNA sequence analyses. All non-synonymous mutations detected in the core region occurred in regions previously mapped as B, CD4+ or CD8+ epitopes. Four patients who were HLA A*0201. Tetramers containing the A*0201 restricted core epitope 18–27 showed that three patients with acute resolving hepatitis developed CD8+ T-cells directed at this epitope regions previously mapped as B, CD4+ or CD8+ epitopes. Four patients who were HLA A*0201. Tetramers containing the A*0201 restricted core epitope 18–27 showed that three patients with acute resolving hepatitis developed CD8+ T-cells directed at this epitope whereas the patient who developed chronic infection did not. All three patients with detectable CD8+ CTL response developed mutations encompassing the core 18–27 epitope while the remaining seven patients showed genetic stability within the same core region (p=0.01). Previous studies have shown that mutation within the core 18–27 epitope is less efficiently recognised by the prototypic anti-core 18–27 CD8+ CTL response than the wild type sequence, confirming that these variants represent CD8+ CTL escape mutants. However, our study demonstrated that patients with acute HBV infection and CD8+ CTL escape mutants ultimately cleared HBV from serum indicating that the broadly reactive nature of the immune response was capable of clearing such evolving mutants and preventing viral persistence.

**413 THYROID HORMONE (T3) INCREASES THE FUNCTIONAL CAPACITY OF THE INTACT LIVER**

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Background: We characterised the time course and magnitude of effect of tri-iodothyronine (T3) as a primary mitogen for the liver in rats. A single [4mg/kg] s.c dose of T3 induces a proliferative response within the liver, which peaks at 24h (7% cell proliferation index) followed by a gradual decline. This increase in cell proliferation results in an increase in liver mass that peaks at 10 days. The 15% increase in liver mass at 10 days (compared to controls) is associated with corresponding increases in total DNA and liver protein levels confirming an increased cell number.

Aim: To assess if T3 induced increases in liver mass confer a useful increase in hepatic function, using galactose elimination capacity (GEC).

Method: Two groups of rats (n=5) were assigned to either T3 or control (vehicle only) ten days prior to assessing the galactose elimination capacity by: (1) Administering 0.5 ml of 50% galactose via the internal jugular vein approach. (2) A 0.5ml venesection performed every ten minutes between 20 and 50 minutes. (3) A bladder puncture performed at the end to collect urine. Galactose elimination capacity was calculated as the ratio of the injected amount of galactose (with correction for urinary excretion) and the extrapolated time to zero concentration. All animals were approximately 250g to eliminate variations in GEC due to bodyweight. Results are given as the mean ± standard deviation of the sample. Statistical differences were determined using the two tailed t-test and reported if p<0.05.

Results: In rats receiving T3, the GEC was 9.3 ± 0.8 umol/min as compared to control rats in which the figure was 7.9 ± 0.4 umol/min (p<0.01).

Conclusion: Single injection of thyroid hormone results in an increase in liver mass that peaks at 10 days. This increase in liver mass enhances the metabolic capacity (as assessed by GEC) of the intact rat liver by 20%. The ability to increase functional hepatic mass could be therapeutically valuable if applicable to man.

**414 TRANSIENT GENERATION OF CORE CD8+ CYTOTOXIC T-CELL ESCAPE MUTANTS DURING PRIMARY HBV INFECTION**

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Previous studies have found little evidence that mutations affect B- or T-cell epitopes during the course of acute HBV infection. It has been speculated that the vigorous and broadly reactive nature of the CTL response during acute infection prevents the emergence of CTL escape mutants. We investigated six patients with acute resolving hepatitis and four patients who progressed to chronic infection for the emergence of CD8+ cells. Our methodology included PCR, cloning, denaturing gradient gel electrophoresis and DNA sequence analyses. All non-synonymous mutations detected in the core region occurred in regions previously mapped as B, CD4+ or CD8+ epitopes. Four patients who were HLA A*0201. Tetramers containing the A*0201 restricted core epitope 18–27 showed that three patients with acute resolving hepatitis developed CD8+ T-cells directed at this epitope whereas the patient who developed chronic infection did not. All three patients with detectable CD8+ CTL response developed mutations encompassing the core 18–27 epitope while the remaining seven patients showed genetic stability within the same core region (p=0.01). Previous studies have shown that mutation within the core 18–27 epitope is less efficiently recognised by the prototypic anti-core 18–27 CD8+ CTL response than the wild type sequence, confirming that these variants represent CD8+ CTL escape mutants. However, our study demonstrated that patients with acute HBV infection and CD8+ CTL escape mutants ultimately cleared HBV from serum indicating that the broadly reactive nature of the immune response was capable of clearing such evolving mutants and preventing viral persistence.

### Abstract 412

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INCREASED INTESTINAL PERMEABILITY IS ASSOCIATED WITH ALTERATIONS IN LIVER FUNCTION TESTS (LFTS) IN HEALTHY SUBJECTS BUT EFFECT IS NOT MEDIATED THROUGH SYSTEMIC ENDOTOXEMIA

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Non-alcoholic steatohepatitis (NASH) is associated with increased small bowel permeability. Nothing is known about the interaction of intestinal permeability, systemic endotoxaemia, and LFTs in healthy subjects. Faecal calprotectin is a surrogate marker of intestinal permeability and correlates well with urinary excretion of enterically administered 14C-EDTA.

Aims: To assess the interaction between faecal calprotectin, systemic endotoxaemia and LFTs in healthy middle aged subjects.

Methods: 230 subjects (155 male, 75 female) aged between 50 and 70 were recruited at random from GP lists in South London. Patients with known liver disease were excluded. A previously validated lifestyle questionnaire was completed. LFTs were measured by auto-analysers. Endotoxin was analysed using the Limulus amoebocyte lysate (LAL) assay. A stool sample was analysed for calprotectin by ELISA.

Results: Using Spearman’s Rank test there was a positive association between calprotectin tertiles and alkaline phosphatase (p=0.004), aspartate transaminase (p=0.02) and γ GT (p=0.007). There was no correlation with bilirubin or alanine transaminase. There was no association between systemic endotoxin and LFTs.

The finding that a surrogate marker of intestinal permeability is associated with alterations in LFTs confirms that this may be of pathophysiological importance in NASH. Systemic endotoxin does not affect LFTs in healthy middle aged subjects. Bacterial translocation across a ‘leaky intestine’ into the portal circulation may be the mechanism by which intestinal permeability affects LFTs.

1% OF ADULTS HOMOZYGOUS FOR THE C282Y MUTATION OF THE HFE GENE HAVE BEEN CLINICALLY DIAGNOSED WITH IRON OVERLOAD: EVIDENCE FROM THE SOUTH WALES HAEMOCHROMATOSIS STUDY

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Background: The clinical significance of HFE mutations remains uncertain with a large discrepancy between the frequency of the predisposing genotype and clinical disease. To our knowledge this is the first study to examine in detail the hospital burden of disease in the UK within a defined population area.

Aim: To establish accurately the number of patients treated for hereditary haemochromatosis [HH] in Bro Taf and Gwent Health Authorities within a 2-year period [Jan 1998-Dec 1999] and to compare this with the number of subjects homozygous for C282Y calculated from the genotype frequencies of 10,556 healthy blood donors from S Wales. In addition to determine the proportion with moderate to severe iron overload (≥4g iron).

Methods: Hospital patients were identified from: information obtained from PEDW/APC data using ICD10 codes; laboratory data and correspondence with all gastroenterology and haematology consultants.

Results: 81 patients were considered to have HH with varying iron phenotypes. 59 were confirmed C282Y homozygotes (see table). 34 (42%) had moderate to severe iron overload. In S Wales 1 in 147 blood donors are C282Y homozygous. We have calculated that only 1.1% of adult homozygotes have been diagnosed and treated for iron overload.

Conclusions: Genetic screening would detect many thousands of healthy subjects in S Wales. Of the 1% likely to be diagnosed with HH 45% will have moderate to severe iron overload based on established criteria.

THE PREVALENCE OF PORTAL HYPERTENSION (PHT) IN PRIMARY BILIARY CIRRHOSIS (PBC)

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Data from our patient cohort suggest that the development of PHT in PBC may be associated with a more adverse outcome than has previously been thought to be the case. Estimation of the overall extent of the morbidity associated with PHT in PBC has been hampered by a paucity of accurate data relating to its prevalence in the patient population. Previous studies (which have shown prevalences ranging from 23-75%) have been limited to case series subject to patient inclusion bias. In order to further quantify the scale of the problem posed by PHT in PBC we studied the prevalence of PHT in a comprehensive cohort of patients defined by geographical residence rather than specific clinical attendance.

A comprehensive and exhaustive case finding exercise was performed to identify all prevalent cases of PBC within the study area. At the census point 166 PBC patients were prevalent within the study area. The point prevalences of portal hypertension, endoscopic varices and histological varices or haemorrhage were 25% (42/166), 8% (13/166) and 1% (2/166) respectively. 58/166 (35%) of the prevalent patients had histologically confirmed advanced disease [Scheuer stage III/IV] at the study point. The point prevalence of PHT in this diagnosed advanced disease subgroup was 52% (19/38).

In addition to the prevalent cases a further 146 deceased PBC patients were identified whose last residence was within the study area. The total number of patient years at risk was calculated for the whole patient cohort from the point of diagnosis until the development of the relevant complication (PHT, oesophageal varices or variceal haemorrhage), death, liver transplantation or the study end-point. The total number of at risk years for PHT, oesophageal varices and variceal haemorrhage development were 1710, 2106 and 2266 respectively. The incidence rates for PHT (129/312), oesophageal varices (69/312) and variceal haemorrhage (36/312) development were therefore 75/1000, 33/1000 and 16/1000 patient years at risk respectively.

Conclusions: PHT and its complications are common in patients with histologically advanced PBC. Given the adverse outcome seen with PHT in this disease screening is warranted.

PROGNOSTIC ACCURACY OF APACHE III SCORING SYSTEM IS GREATER THAN THAT OF THE CONVENTIONAL CHILD-PUGH'S SCORE IN PREDICTING SHORT-TERM HOSPITAL MORTALITY OF NON INTESTIVE CARE UNIT PATIENTS WITH LIVER CIRRHOSIS

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Objective: The aim of this study was to assess the prognostic accuracy of Child-Pugh’s score (CPS) and Acute Physiology, Age and Chronic Health Evaluation (APACHE) II and III scoring systems in predicting short-term, in-hospital mortality of patients with liver cirrhosis admitted to a gastroenterological medical ward.

Methods: 200 consecutive admissions of 147 cirrhotic patients (44% viral-associated liver cirrhosis, 33% alcoholic, 18.5% cryptogenic, 4.5% both viral and alcoholic) were studied prospectively. Clinical and laboratory data conforming to the Child-Pugh, APACHE II and APACHE III scores were recorded on day one for all patients. Statistical analysis for the prognostic variables was performed by using Hest, receiver operating characteristic (ROC) curves and area under a ROC curve (AUC), non-parametric Wilcoxon test and discriminant analysis.
Results: The in-hospital mortality was 11.5%. The mean CPS, APACHE II and III scores for survivors were found to be significantly lower than those of nonsurvivors. When ROC curves were plotted, no significant differences between Child-Pugh’s (AUC, 0.85), APACHE II (AUC, 0.75), and APACHE III (AUC, 0.81) overall performances were noticed, however the overall correctness of prediction of APACHE III was modestly better than that of the CPS (Wilcoxon test: z = 2.846, p = 0.004) and 11% greater than that of the APACHE II, namely, 87%, 78% and 76% respectively (cutoff values, 62, 10 and 15 respectively).

Conclusions: All three scores were proven to be of value in risk stratifying patients with liver cirrhosis. Although the overall performance of APACHE III system as assessed by ROC curve analysis is no superior than that of the conventional Child-Pugh’s score in predicting short term outcome of hospitalized patients with liver cirrhosis, APACHE III correctly stratifies a significantly greater number of patients.

417 HYPERURICAEMIA, GOUT AND CARDIOVASCULAR RISK AFTER LIVER TRANSPLANTATION

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Background: Hyperuricaemia and gout are recognised complications of renal and cardiac transplantation. In contrast the development of hyperuricaemia following liver transplantation has received less attention. Elevated serum uric acid has been cited as an independent risk factor of cardiovascular disease in the general population. To evaluate the prevalence of hyperuricaemia and its association with cardiovascular risk factors we reviewed the case records of 134 consecutive liver transplant recipients with a mean follow up of 52 months (range 6 – 92 months).

Results: 47% had hyperuricaemia after liver transplant. Peak uric acid correlated significantly with corresponding serum creatinine (r = 0.694). 6% of patients developed an acute episode of gout. Hypertension, hypercholesterolaemia and a body mass index > 25 kg/m² were present in 53, 46 and 48% of hyperuricaemic patients respectively and in 47, 54 and 52% of patients with normal serum urate. None of these differences were significant. Cardiovascular events comprised 1 myocardial infarct and 1 incident angina, each patient having hyperuricaemia, and 2 strokes, one of which had hyperuricaemia.

Conclusions: There is an important association between liver transplantation and hyperuricaemia. Gout is a significant cause of morbidity but occurs less frequently than after renal or cardiac transplants. There was no association between hyperuricaemia and other cardiovascular risk factors. Too few cardiac events occurred to draw any conclusions about an association with uric acid.

419 OBSTETRIC CHOLESTASIS IN SOUTH WALES

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1Department of Gastroenterology and 2Obstetrics, Singleton Hospital, Swansea, Wales, UK

Aims: A prospective study of the incidence, clinical and biochemical features, management and outcome of obstetric cholestasis (OC) in a defined population in South Wales, UK.

Methods: All pregnancies in an obstetric unit serving 270,000 were screened for OC between March 1999 and June 2001. Diagnosis of OC was based on pruritus, abnormal liver tests and exclusion of other hepatobiliary diseases.

Results: 45 OC patients were identified among 8142 pregnancies – incidence 0.5%. Age ranged from 16 - 40 years (Median 30). There were seven twin and one triplet pregnancies. Sixteen were primiparous while 29 had had 1 to 6 previous pregnancies, ten of which were complicated by OC with two associated stillbirths. Three had family history of OC. All were symptomatic: pruritus in 45, vomiting in four, diarrhoea in four and severe malaise in two. Two patients suffered hypervirfication earlier in pregnancy, two pre-eclampsia and one HELLP syndrome. Symptoms started between 8 and 39 weeks gestation (median 34). Eighteen had proven urinary tract infection either just before or after diagnosis of OC. 43 had elevated AST (31–519; median 141 U/l); Serum bile acids raised in 38 of 41 tested (15–179; median 34 µmol/l); yGT was modestly elevated (42–292; median 71 U/l) in only 14 patients while bilirubin was raised in 17 (16–34; median 20 µmol/l). Leucocytosis was seen in 28 patients.

421 SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA IN CIRRHOSIS: A NATIONAL AUDIT OF THE PRACTICE IN THE UK

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Background: Hepatocellular carcinoma (HCC) is a significant cause of mortality in cirrhotic patients. Its detection at an early stage increases the chance of curative therapy. Clear evidence of survival benefit with surveillance is limited. However, anecdotally, many clinicians undertake some form of surveillance program.

Aim: To evaluate the current practice of HCC surveillance in cirrhosis in the UK.

Methods: 1080 postal questionnaires were sent to the members of the British Society of Gastroenterologists (BSG), excluding radiologists, pathologists and paediatricians.

Results: 525 replied (49%), of these, 120 did not look after adult cirrhotics and were excluded from analysis. Of the 405 remaining respondents, 296 (73%) surveyed for HCC, 123/296 had protocols. Hepatologists and those with a large cirrhotic practice were more likely to survey. 96/296 quoted on age limit (median 70) for surveillance. 107/296 (36%) surveyed all cirrhosis regardless of their suitability for curative therapy; in contrast, 127/296 surveyed only those suitable for liver transplantation or partial hepatectomy. 166/296 (56%) chose to survey all causes of cirrhosis, whereas a smaller group (83/296, 28%) were more selective and surveyed those with Hepatitis B, C, haemochromatosis and alcoholic liver disease. The commonest mode of surveillance was a combination of abdominal ultrasound and alpha fetoprotein, with a wide range of test intervals (3 to 24 months). In those choosing to survey, 130/296 believed it increased survival, while 95/296 felt that non-surveillance might leave them legally liable. 109/405 did not survey, 58 of who quoted the lack of evidence for survival benefit, and 46 the lack of guidelines, as the reasons for their practice.

Conclusions: Despite the lack of guidelines or clear evidence for benefit, a majority of clinicians who responded performed some form of surveillance. Practice was variable with a significant number being unsuitable in the types of patients to survey. This has obvious resource implications. Guidelines are needed to rationalise and clarify practice.

422 HYDROXYCHLOROQUINE REDUCES LIVER RELATED MORTALITY IN HEPATITIS C ASSOCIATED (HCV) COMPENSATED CIRRHOSIS

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Hydroxychloroquine, a lysosomotropic and macrophage modulating agent has been reported to improve liver biochemistry in chronic viral hepatitis.

Aim: To investigate the effect of hydroxychloroquine on survival of HCV active cirrhotic patients

Methods: 162 patients (31% male, 69% female) with compensated HCV cirrhosis were prospectively evaluated. All were Child-Pugh A or B at entry into the study. 52 with active cirrhosis (increased aminotransferases) were treated with hydroxychloroquine 200 mg tid for 6 months. A 3 month treatment was reinstituted if during follow up, aminotransferases were again high. 110 patients with inactive cirrhosis were the non treated controls. Time to decompen- sation and death were recorded. Patients were followed up between 3 and 136 months.

Results: Median time to decompensation was 81 months (95% CI, 45–117 months) and was not different between the two groups...
**423 MEASUREMENT OF AFP IN PATIENTS WITH HEPATITIS C CIRRHOSIS DURING HEPATOMA SURVEILLANCE**

T. Woodall, S. Sen, A.E. Gimson, G.J.M. Alexander, D.J. Lomas, S. Vowler. Department of Medicine, University of Cambridge, Hills Road, Cambridge CB2 2QQ, UK

**Background:** Patients with chronic hepatitis C virus (HCV) infection and cirrhosis have an increased risk of hepatocellular carcinoma (HCC). Surveillance to identify early tumours based on a periodic estimation of serum alpha-fetoprotein (AFP) is unproven.

**Methods:** Surveillance was undertaken in 100 consecutive patients with chronic hepatitis C and cirrhosis, based on a minimum of 6 monthly serum AFP and ultrasound (US), for a median of 2 years (range 0.5-6). 186 US and 662 AFP measurements were undertaken. 11 patients were lost to follow up, 40 (45%) had an elevated AFP and 18 had a suspicious US. 11 patients [12%] developed HCC during surveillance.

**Results:** Of 40 with an elevated AFP, 10 (25%) also had a suspicious US and HCC was identified in 7 of those [17.5%]. The level of AFP however, was non-discriminatory. 30 of 40 (75%) had an elevated AFP with a clear US and HCC was identified in 1. The level of AFP was again non-discriminatory. Of 49 with a normal AFP, 8 [16%] had a suspicious US and HCC was identified in 3 [6%]. 22 CT Scans, 7 MR scans and 11 Angiograms were undertaken in patients who did not have HCC. As a predictive test for HCC, elevated AFP in isolation had a positive predictive value (PPV) of only 0.18, a sensitivity of 0.7 and a specificity of 0.58. In comparison, US had a PPV of 0.8, sensitivity of 0.91 and specificity of 0.89.

**Conclusion:** The incidence of HCC in this group of Hepatitis C cirrhotic patients is high. Surveillance is a considerable burden but the combination of serum AFP and US has traditionally been used for the detection of HCC. However, an elevated AFP in isolation was common, had a poor predictivity for the detection of HCC and led to numerous (expensive) investigations. Restriction surveillance to US alone would be as effective.

**424 COMBINATION PROPHYLAXIS WITH LAMIVUDINE (LAM) AND HEPATITIS B IMMUNOGLOBULIN (HBIG) PREVENTS GRAFT RE-INFECTION BY HEPATITIS B (HBV)**

V. Lai, E. Elias, K. O’Donnell, D. Mutimer. Liver Unit, Queen Elizabeth Hospital, Birmingham, Edgbaston B15 2TH, UK

Prevention of graft re-infection remains the most important issue in transplantation of HBV infected patients. Re-infection by HBV is almost inevitable if no prophylaxis is given. The course of recurrent infection is aggressive causing sub-acute liver failure or rapid progression to cirrhosis. In the early 90’s, prophylaxis comprised of regular and repeated administration of HBIG. Studies of LAM prophylaxis in this setting began in 1994. Both LAM and HBIG proved ineffective for patients with high serum HBV DNA titre.

Subsequently the combination of LAM and HBIG has been used and preliminary reports suggest the combination is effective and safe. The aim of this study is to review the QEH liver unit’s experience with combination LAM/HBIG for prevention of HBV re-infection.

This is a retrospective review of the clinical and virological outcome of these patients. Since introduction of LAM/HBIG prophylaxis in 1997, 16 HBV patients have undergone liver transplantation (15 male, median age 51). Pretreatment serum HBV DNA titres ranged from <400 copies/ml to >4 x 10^5. 3 patients died (12 days, 6 weeks and 8 month post transplant). Median follow up of survivors is 2 years (6 months - 4 years). All survivors are serum HBsAg and HBV DNA (Roche PCR-based assay) negative.

**Conclusion:** LAM/HBIG prevents HBV re-infection even in high-risk patients.

**425 DISTRIBUTION OF IL-6 IN LIVER CIRRHOSIS**

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Interleukin-6 (IL-6) has been proposed as one of the main inflammatory mediators. It is a major mediator of the acute phase response in infectious diseases and inflammatory processes inducing fever, leukocytosis, and increase in the hepatic synthesis of acute phase proteins. In this study, sera and liver biopsies from fifteen patients with clinically and pathologically diagnosed liver cirrhosis were taken. In addition sera from 7 and liver biopsies from 3 healthy controls were used. Serum levels of IL-6 were measured using ELISA kits and the cellular distribution was investigated using immunohistochemistry. We have shown that the serum IL-6 levels in cirrhotic patients [25.46 ± 11.6 pg/ml] were significantly [P <0.05] increased by comparison with the control group [12.14 ± 6.6 pg/ml]. Immunohistochemically, in the control group, IL-6 was seen only in occasional sinusoidal cells. However it was widely distributed in the cirrhotic liver. In the latter, it was mostly seen in the inflammatory cells infiltrating the liver but also expressed in the sinusoidal cells, Kupffer cells, vascular endothelial lining cells and hepatocytes. Uprolilation of IL-6 in cirrhotic patients could be due to active synthesis or defective clearance by non-functioning hepatocytes. However our findings suggest that both mechanisms are operating since we have shown high expression in inflammatory cells which could be due to oversynthesis and high expression in hepatocytes which could be due to accumulation in non-functioning cells. It is therefore clear that IL-6 showed systemic and local augmentation in cirrhotic patients and is mainly produced by inflammatory cells. Taken together these findings suggest that IL-6 production in liver cirrhosis is dependent on the inflammatory stage and the local production of IL-6 could contribute to the inflammation, fibrosis and immunological responses in the cirrhotic liver. Moreover the characteristic distribution of IL-6 in cirrhotic lobules could implicate it in the patients with liver cirrhosis. In the near future, the appropriate manipulation of IL-6 may provide a novel strategy for the treatment of patients with liver cirrhosis or at least improve the fate of cirrhosis.

**426 QUANTITATIVE STUDIES OF LIVER ATROPHY FOLLOWING PORTACAVAL SHUNT IN RATS**

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**Background:** The aim of this study was to evaluate the morphological changes in the liver that occur in portal-systemic encephalopathy after portacaval shunting (PCS).

**Materials and Methods:** Male rats underwent either PCS (n=35) or control sham operations (n=31). Blood samples were taken prior to sacrifice (weeks 5-7) for measurement of hormone concentrations. Morphological assessments were carried out on 5μm thick haematoxylin and eosin stained sections and digital electron micrographs using the Prodig 5.2 image analysis system.

**Results:** There was a significant reduction in the liver mass of PCS rats (4.98±13.65g). Testosterone was significantly reduced (2.49±10.1ng/ml; p=0.002) and oestrogen significantly increased (77.9±51.6ng/ml; p=0.0004). Morphometric analysis showed significant reductions in the average distance between peri and postsinusoidal vessels (298±499μm) in PCS rats while in zone 3 the mean area of cytoplasm was also reduced [74.3±112.9μm]. Within the PCS group there was a significant reduction in the mean area of hepatocyte nuclei from 55.5±2μm to 42.0±2μm (p<0.05). Electron microscopy revealed that further contribution to liver atrophy in this animal model.
Role of Technical Variables in Early Shunt Insufficiency Following TIPSS for the Treatment of Portal Hypertension

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Summary: Transjugular intrahepatic portosystemic stent shunt (TIPSS) has increasingly been used for the treatment of complications of portal hypertension. This study evaluated the technical predictors of early shunt insufficiency after TIPSS placement in patients with advanced liver disease.

A retrospective analysis of 399 patients undergoing TIPSS over a period of 9 years between July 1999 and July 2000 was carried out. The independent variables included technical and clinical variables in both patients and TIPSS, gastric varices in 52, refractory ascites in 42, portal hypertensive gastropathy in 8 and ectopic varices in 9 patients. TIPSS placement was successful in 383 (96.0%) patients, and failed in 16 (4.0%). The shunt remained patent without assistance in 40 (10.0%) (primary patency) and 44 (11.0%) patients developed early shunt insufficiency within 30 days from TIPSS insertion. The univariate association of 21 prognostic clinical and technical variables between patients with early shunt insufficiency and primary patency was tested by the Chi-squared or Wilcoxon rank-sum tests. Multiple logistic regression analysis was utilized to determine the relationship of multiple technical and clinical variables in predicting early shunt outcome.

The two groups were comparable and representative of the whole TIPSS cohort patients. Of the 21 technical and clinical variables, stent diameter, distance of shunt from IVC, duration of the procedure, and portal pressure gradients post TIPSS were independent predictors of early shunt insufficiency.

Based on our analysis, four technical variables at index TIPSS can reliably predict early shunt insufficiency. Total protection from early complications of TIPSS requires awareness of the risk factors and a low threshold maintained for early shunt revision.

Characterisation of Liver Infiltrating T-Cell Antigen Specificity in a Mouse Model of Primary Biliary Cirrhosis (PBC)


PBC is characterised histologically by damage to the intra-hepatic bile ducts accompanied by a T-cell rich portal tract mononuclear cell (MNC) infiltrate. PBC is characterised immunologically by autoreactive T-cell responses to the self-antigen pyruvate dehydrogenase complex (PDC). Human studies suggest that portal tract T-cells seen in PBC liver are specific for PDC, implicating autoreactive T-cell responses directed at this antigen in disease pathogenesis. We have recently demonstrated that IL-10 mice can be inoculated to break down TIPSS and splenic T-cell tolerance to self-PDC, and that this tolerance breakdown is associated with the development of portal tract inflammation and bile duct damage. In this study we set out to characterise the antigen specificity of the infiltrating portal tract T-cells in this model.

Female SJL/J mice of 10–12 weeks were sensitised (n=7) with a mixture of murine (b) and bovine (p) PDCs (study group). Control mice (n=4) received only the bovine PDC only. Mice were sacrificed at 8 weeks post-sensitisation. The spleen was removed and splenic T-cell responses were characterised by FACS and primary proliferation. Livers were perfused in situ with collagenase via the portal vein prior to removal. The liver infiltrating mononuclear cell population was isolated by further collagenase digestion and density centrifugation. T-cell responses were characterised for splenic T-cells.

Female SJL/J mice of 10–12 weeks were sensitised (n=7) with a mixture of murine (b) and bovine (p) PDCs (study group). Control mice (n=4) received only the bovine PDC only. Mice were sacrificed at 8 weeks post-sensitisation. The spleen was removed and splenic T-cell responses were characterised by FACS and primary proliferation. Livers were perfused in situ with collagenase via the portal vein prior to removal. The liver infiltrating mononuclear cell population was isolated by further collagenase digestion and density centrifugation. T-cell responses were characterised for splenic T-cells.

MR-Guided Laser Thermal Ablation of Primary and Secondary Liver Tumours


Purpose: To test the hypothesis that MR guided hepatic tumour ablation is (i) safe & feasible and (ii) improves patient survival and (iii) decreases viable tumour voulume.

Methods and Materials: 125 MR guided Laser Thermal Ablations (LTA) have been performed on 40 patients (9 females, 31 males, average age 59.1 years) between 1997 and 2001. The liver tumours include Hepatocellular Carcinoma (HCC, n=19), metastases (n=11, mainly colorectal), carcinoid (n=5) and two benign liver tumours. 3 patients were excluded from follow-up.

Results: Mean survival for all patients was 15.2 months, with an adjusted mean survival of 16 months for HCCs and 15.2 months for metastases. There were three major and five minor post-procedural complications but no deaths. An average of 57% of tumour was ablated as assessed by per-procedural thermal mapping, with an average of 49.4% of tumour ablated assessed by pre and post ablation gadolinium-enhanced MRIs. Average tumour size was unchanged after ablation. In patients with multiple liver tumours ablated tumours grew significantly less than untreated tumours over the same time period (108% compared to 196% growth over an average follow up period of 5.8 months).

Conclusions: MR guided laser thermal ablation of primary and secondary liver tumours is safe and feasible and produces a better survival in patients with HCC than would be expected in untreated patients, as well as a mean survival in patients with metastases at least equal to the longest median survival in untreated patients. Percentage of viable tumour was decreased by a mean of 49.4% per LTA session.
431 INTRAHEPATIC CHOLESTASIS OF PREGNANCY: PATTERN OF PRESENTATION AND RESPONSE TO URSEDOXYCHOLIC ACID

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Intrahepatic cholestasis of pregnancy (IHCP) can adversely affect maternal well-being and foetal outcomes. Early identification, monitoring and prompt delivery is ideal. We report our experience of IHCP with respect to presentation, pattern of LFT abnormalities, maternal and foetal outcomes and the effect of treatment with ursodeoxycholic acid (UDCA).

Results: Over a period of 18 months 29 cases of IHCP were identified, complete data was available from 18 patients. All cases presented with pruritis and were found to have abnormal LFTs. Other causes of liver disease were excluded. Symptoms started at a mean of 33.5 weeks (range 26–38). Serum bile acids were clearly elevated in 14 (mean 62 µmol/L, normal <14) and borderline in the other 4 (mean 12µmol/L). Only one patient became jaundiced (bilirubin 64 µmol/L). At presentation serum alkaline phosphatase ranged from 15 (mean 51 IU/L, normal <25) to 428 IU/L (mean 140). Of note in 10 patients the ALT was particularly high at over 100, mean 220 IU/L (range 121–468). 14 patients were treated with UDCA with a subsequent marked improvement in LFTs, bile acids and symptoms. In 10 patients the pregnancy was actively managed with induction at 38 weeks, 6 underwent a spontaneous labour (33–39 weeks) and two had caesarean sections for obstetric reasons. 2 babies were jaundiced at delivery and one went to SCBU. Both made a full recovery. There was no maternal morbidity.

Conclusions: IHCP presents with pruritis and abnormal LFTs. It is readily recognisable and responds well to UDCA with good maternal and foetal outcomes. Of particular note, the ALT is often markedly elevated, a feature that is not widely recognised and which may represent a potential source for diagnostic confusion.
of remission was evident. Presently, one patient underwent liver transplantation, one was removed from the transplant list due to marked improvement in clinical condition, one patient died after 6 weeks from variceal haemorrhage and two patients remain completely asymptomatic and are no longer being considered for transplantation.

Conclusion: Albumin dialysis (MARS) is a novel therapeutic tool which offers safe and effective, but non sustained, relief of pruritus in patients with intrahepatic cholestasis resistant to conventional therapy. The place of this technique in the long-term management of pruritus needs to be further defined.

ABNORMAL VASCULAR FUNCTION IN HEREDITARY HAEMOCHROMATOSIS: INVESTIGATING THE “IRON HYPOTHESIS”

I.S. Cadden, B.M. Mullan, M.E. Callender, D.R. McCance, I.S. Young. Royal Victoria Hospital, Belfast, Northern Ireland

Background: Iron excess has been linked with development of coronary artery disease. Haemochromatosis is a common inherited disorder of iron overload. Studies have shown carriage of the mutation for haemochromatosis is linked to cardiovascular risk. We used the non-invasive technique of Pulse Wave Analysis (PWA) to study the arterial stiffness in patients with haemochromatosis. Using application tonometry, the radial artery pressure waveform is recorded. Transfer functions are then applied producing the central aortic pressure waveform and the central aortic augmentation pressure. Reduction of PEG-IFN and RIBA. Mean pre-treatment / 3 month values for haemoglobin and neutrophils were 14.8 / 12.1 g/dl and 3.7 / 1.9 x 10^9/l.

Conclusions: These results suggest, using a non-invasive, in vivo technique that there is abnormal vascular stiffness in haemochromatosis. The tendency to excess iron stores may increase oxidative burden on the vascular endothelium causing injury. The resultant endothelial dysfunction may cause the increased cardiovascular risk which studies have suggested is associated with this condition.

THE IMPACT OF PORTAL HYPERTENSION IN PRIMARY BILIARY CIRRHOSIS (PBC)

D.E.J. Jones, R. Walter, M.I. Prince, M. Hudson. Centre for Liver Research, University of Newcastle, UK

Inter-patient variability in the rate of progression of the chronic liver disease PBC hampers the identification of high risk individuals suitable for invasive therapies such as liver transplantation. In this retrospective study we examined the role played by portal hypertension (PHT) and the presence of oesophageal varices (OV) in disease outcome in a cohort of 438 PBC patients followed up from diagnosis in a single centre. Median follow-up was 72 months with 262 subjects (60%) still alive at the study point. Survival from diagnosis of disease to death or liver transplantation was significantly worse in patients developing PHT (Kaplan Meier analysis (KMA) p<0.001; 5 year survival 56.6% v 54.6% (p=0.62). The AIx was significantly higher in the haemochromatosis group compared to controls (mean=30.1%, range=24%-38%; mean=20.5%, range=11%-31%; p=0.001).

Conclusions: These results suggest that patients with haemochromatosis was recorded as a measure of the arterial stiffness following a 10hr fast. Age- and sex-matched healthy individuals served as controls.

Results: 10 subjects were recruited to each group (7M:3F). There was no significant difference between the ages of the haemochromatosis and control subjects, 56.6yr V 54.6yr (p=0.62). The AIx was significantly higher in the haemochromatosis group compared to controls (mean=30.1%, range=24%-38%; mean=20.5%, range=11%-31%; p=0.001).

Conclusions: These results suggest, using a non-invasive, in vivo technique that there is abnormal vascular stiffness in haemochromatosis. The tendency to excess iron stores may increase oxidative burden on the vascular endothelium causing injury. The resultant endothelial dysfunction may cause the increased cardiovascular risk which studies have suggested is associated with this condition.
In the 159 patients developing OV (93 of whom bled), the one year transplant free survival following OV diagnosis was 63%. Excluding the 34 patients undergoing transplantation (leaving death as the study end-point) 1ys was 68%. In the 67 patients developing OV below the age of 65 who did not undergo transplantation 1ys was 71%.

**Conclusion:** The development of portal hypertension is associated with death or adverse outcome in PBC. The risk map to patients developing varices regardless of bleeding. The one year survival following development of varices is less than that currently being reported for transplanted PBC.

**NO ASSOCIATION BETWEEN NOD2 POLYMORPHISMS AND SUSCEPTIBILITY TO, OR PROGRESSION OF, PRIMARY SCLEROSING CHOLANGITIS**

S.N. Cullen, T. Ahmad, R.W. Chapman, D.P. Jewell. Gastroenterology Unit, University of Oxford, UK

**Background:** Nod2 is a member of a protein family which regulates apoptosis and NF-κB activation. Nod2 polymorphisms have recently been found to confer susceptibility to Crohn’s disease (CD) either by altering the recognition of components of microbial pathogens and/or via the activation of NF-κB. NF-κB plays a crucial role in the activation of the hepatic stellate cell which is the first step in the development of liver damage and fibrosis. Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease closely associated with inflammatory bowel disease (IBD), and is characterised by concentric obliterator fibrosis and bile duct strictures. This study examined the effects of 6 Nod2 polymorphisms on susceptibility to, and progression of PSC.

**Methods:** DNA was extracted from 83 patients with well-documented PSC and 349 control patients. 65 of the PSC patients had ulcerative colitis (UC), 6 had CD, and 12 had no associated IBD. Primers were designed to examine 6 polymorphisms in the NOD2 gene using an SSF-PCR method. PSC and control patients were compared using 2x2 contingency tables and a χ² test with Yates correction.

**Results:** None of the polymorphisms in the NOD2 gene was significantly associated with susceptibility to PSC. Further analyses to determine whether NOD2 polymorphisms might contribute to the development of cirrhosis or need for transplantation, were also negative. See table.

**Conclusions:** Polymorphisms in the Nod2 gene are not significant factors in determining the susceptibility of individuals to developing primary sclerosing cholangitis. In addition, despite the role of the Nod2 gene in NF-κB activation, these polymorphisms do not determine the rate of progression or outcome of the disease.

**ABNORMAL LIVER FUNCTION TESTS FOLLOWING BONE MARROW TRANSPLANTATION: WHAT IS THE AETIOLOGY AND THE ROLE OF LIVER BIOPSY?**

G.T. Ho, A. Parker1, J.F. MacKenzie, A.J. Morris, A.J. Stanley. Dept of Gastroenterology, Glasgow Royal Infirmary; 1Bone Marrow Transplant Unit, Glasgow Royal Infirmary, UK

**Introduction:** Liver dysfunction is common in bone marrow transplant (BMT) recipients. Causes are drugs, graft versus host disease (GVHD), infection and iron overload. We studied the prevalence of liver abnormalities, the causes and the use of liver biopsy to aid clinical management in these patients.

**Methods:** All the autologous and autologous BMTs undertaken in our institution between Jan 1997 and December 1998 were studied. Subsequent liver function tests, the use and indication of liver biopsy and the final cause of liver dysfunction were determined in each case.

**Results:** 121 patients (63 autologous) with BMT were studied. Abnormal LFTs were found in 71% allogeneic and 33% autologous BMTs. Final diagnoses were made without resorting to liver biopsy and these are shown in the table. Liver biopsy was required in 18 allogeneic and only 1 autologous BMT. 63% biopsies were undertaken greater than 100 days post BMT for persistently abnormal LFTs to assess possible GVHD. 16 out of 18 biopsies revealed significant iron overload with only one confirming GVHD. No fibrosis/cirrhosis was found on biopsy. No adverse effects occurred as a result of liver biopsy. In the patients with histological evidence of iron overload, the serum ferritin was also persistently elevated.

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**Abstract 441 Table showing cause of deranged LFTs**

<table>
<thead>
<tr>
<th></th>
<th>Drugs</th>
<th>Iron XS</th>
<th>GVHD</th>
<th>Sepsis</th>
<th>VOD</th>
<th>Others</th>
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<tr>
<td><strong>Autologous</strong></td>
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<td>Allogeneic</td>
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<td>10</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>4</td>
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<td></td>
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<td>3</td>
<td>5</td>
<td>0</td>
<td>3</td>
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</tbody>
</table>

| Iron XS – iron overload; VOD – veno-occlusive disease |

**Conclusion:** Liver biopsy was required in a minority of patients with abnormal LFTs post BMT, with most causes of liver dysfunction diagnosed clinically. Liver biopsy was most commonly undertaken late post BMT in the group with persistently abnormal LFTs in which chronic GVHD was suspected. However, iron overload was the commonest finding in this subgroup; and serum markers of iron excess could determine this.
Oesophagus posters 442–464

442 POSTER WITHDRAWN.

443 OESOPHAGEAL CANCER MANAGEMENT: GOOD ENOUGH GUIDELINES?
Department of Surgery, Guy’s & St Thomas’ Hospital, London, UK

Background: The incidence of oesophageal cancer is increasing yet survival is poor and perioperative mortality remains high. Recent guidelines for referral and management issued by the department of health aim at earlier detection and improved effective appropriate management-but are they helpful?

Aims and Methods: A 2-year retrospective audit of oesophageal cancer referrals April 1999 to May 2001 in a district general hospital of catchment population ~250,000. Comparison with guidelines for urgent referral (April 2000) and management (March 2001) of upper GI cancers. Patients identified with oesophageal cancer from FAS system and endoscopy database, and notes reviewed using proforma.

Results: 44 patients with oesophageal cancer identified. Mean annual incidence of 8.8/100,000/year. Median age 75 years. Histology found 57% adenocarcinoma, 23% squamous, 20% other type. Symptom analysis showed 70% presented with dysphagia, but significantly fewer with heartburn (20%) or reflux (9%) than referral guidelines. Some 37/44 (84%) fulfilled the symptom guidelines for urgent referral. Those who did not fulfill criteria presented with anemia, GI bleeding and epigastric pain, without other alarm symptoms. Endoscopy was used in diagnosis in 43/44 patients. CT scanning was used for staging in 35/44 (79%), the remainder were deemed too frail for investigation. 2 patients had preoperative PET scans. EUS is unavailable. Surgical opinion was sought in 20/44 (45%) of which 9 (20%) had resections at a tertiary centre. 2 received neo-adjuvant chemotherapy. 1 patient was found to have inoperable disease at laparotomy. Some 20/44 (45%) were referred for oncological opinion. 3 (7%) received palliative chemotherapy and 8 (18%) radiotherapy at a designated centre. Endoscopic treatment was required in 26/44 (60%), 8 (18%) having metal stents. Outcome 6 months after study period found only 10/44 (22%) alive, the median survival was 4 months from referral to death.

Conclusions: Symptom guidelines used alone would have missed 16% cancers. Management guidelines suggest a specialist team to identify those liable to benefit from treatment, but the overall outcome is likely to remain poor as comorbidity prevented treatment in many patients.

444 DEPRIVATION CATEGORY AND GASTRO-OESOPHAGEAL REFUX (GORD)
Department of Digestive Diseases and Clinical Nutrition, Ninewells Hospital, Dundee DD1 9SY, UK

Introduction: GORD and Barrett’s oesophagus have thought to be associated with greater deprivation, although recent data suggest that this may be changing. We aimed to examine the association between deprivation, GORD and it’s complications.

Methods: A cohort of patients with GORD and Newly diagnosed Barrett’s oesophagus were constructed from a database of patients with reflux symptoms. Deprivation index was obtained by utilising the post code area and sector to calculate the Carstairs Deprivation score (1 least deprived, 6 most deprived). Incidences and putative risk factors were examined.

Results: 658 patients were recruited with symptomatic GORD; when stratified for Carstairs Deprivation Category. In deprivation Category 1 (least deprived) 20% [14] had Barrett’s oesophagus and 79% [27] had GORD, in deprivation category 6 (most deprived) 10% [22] had Barrett’s oesophagus and 90% had GORD (Chi Squared for trend P<0.01). Symptom score, Acid suppression therapy exposure, Body Mass Index (BMI), Smoking (pack years), and Alcohol consumption (units/week) were further stratified for diagnosis and deprivation category. There was no difference in symptom score according to deprivation category or diagnosis (P>0.05). BMI, Smoking or Alcohol Consumption was equal for diagnosis and deprivation category. There was no difference in symptom score according to deprivation category or diagnosis (P>0.05). BMI, Smoking or Alcohol Consumption was equal for diagnosis and deprivation category. Patients with Barrett’s oesophagus but not GORD in deprivation category one had a greater exposure and duration of therapy to proton pump inhibitors (PPI) compared with deprivation category 6 (Chi Squared for trend P=0.011) There was no difference in for Histamine 2 Receptor antagonists (H2RA).

Conclusions: Barrett’s oesophagus seems to be associated with less deprivation and more proton pump inhibition, compared with GORD which is associated with more deprivation and less acid suppression therapy. This unusual finding may represent differing aetiologies for GORD and Barrett’s oesophagus.

445 AMBULATORY INTRALUMINAL ELECTRICAL IMPEDANCE: A RELIABLE METHOD IN THE INVESTIGATION AND DETECTION OF GASTRO-OESOPHAGEAL REFUX
Department of Surgery, Guy’s & St Thomas’ Hospital, London, UK

Introduction: Intraluminal Electrical Impedance (IEI) is a measure of resistance to current flow between two electrodes. The presence of a bolus in the oesophagus can be monitored with IEI. This preliminary study looks at ambulatory IEI (out-patient basis) in the investigation of reflux episodes (RE), comparing this to pH monitoring and manometry.

Patients and Methods: A preliminary sample of 10 patients with symptoms of gastro-oesophageal reflux disease prospectively underwent manometry. This was prior to an ambulatory study (for up to 24-hours). The combined catheter consisted of 4 pressure transducers placed at 0, 5, 10 and 23 cm with 2 impedance electrode pairs at 0 and 5 cm proximal to the pH sensor. The pH sensor was sited 5 cm proximal to the lower oesophageal sphincter. A pH-RE occurred where the distal oesophageal pH was less than 4, (>2 secs). A manometric RE (Man-RE) occurred where there was a distinct simultaneous increase in intra-oesophageal pressure (>10 mmHg) in 2/3 distal pressure sensors, with no evidence of peristalsis or upper oesophageal sphincter activity. An IE-RE occurred where IEI values dropped by 50% from the baseline (>2 secs).

Results: Overall pH-RE had an associated IE-RE on 310/538 (57.6%) occasions. IE-RE were definitively acid (associated pH-RE) in 310/505 (61%) and non-acid in 105/505 (21%). Gas RE were detectable using IEI. See table.

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Total Monitored Reflux Episodes (RE)</th>
<th>pH-RE</th>
<th>IEI-RE</th>
<th>Man-RE</th>
<th>Gas RE</th>
<th>Non-acid RE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>310</td>
<td>505</td>
<td>140</td>
<td>130</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>538</td>
<td>310</td>
<td>52</td>
<td>43</td>
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</table>

Conclusions: Ambulant IEI has a good correlation with pH-monitored reflux events. IEI is a useful adjunct to pH monitoring in studying reflux, particularly in detecting gas and non-acid reflux events. Manometry is insensitive in detecting pH-RE, but provides information regarding gas, reflux and swallow events. This preliminary study highlights both the potential and the need for further validation and modification of IEI technique as an ambulatory technique.

446 SELF EXPANDING METAL STENTS: AN AUDIT OF 100 CONSECUTIVE CASES
B. Smith, J. Bagshaw, S.A. Riley. Department of Gastroenterology, Northern General Hospital, Sheffield, UK

Background: Many patients with oesophageal carcinoma present with advanced disease and relief of dysphagia is often the principal goal of therapy. SEMS have become a popular method of palliation but some have expressed concern that quality of life may be less good following SEMS insertion than following ablative methods of palliation. We have therefore undertaken a retrospective audit to identify factors that might predict a less favourable outcome.

Methods: Hospital records were reviewed in 100 consecutive patients in whom an oesophageal SEMS had been placed from June 1998 onwards. Pre-placement clinical characteristics were reviewed in relation to postplacement symptoms and survival.
BARRETT'S OESOPHAGUS ON THE INTERNET: A MISINFORMATION HIGHWAY?
S.J. Dwyerhouse, A.D. Hollowood, C.P. Armstrong. Department of Surgery, Frenchay Hospital, Bristol, UK

Introduction: Barrett's oesophagus can be a difficult subject to understand even for those with a special interest in it. For a newly diagnosed patient, getting to grips with the causes, risks and management of Barrett's oesophagus can be daunting. It is, therefore, important that patients have access to all the relevant information they need to help them understand the implications of their condition.

Aims: The aim of this study was to assess the adequacy of information on the controversies surrounding Barrett's oesophagus available on the internet.

Methods: Using the search term “Barrett’s oesophagus”, an internet search was carried out using 3 commonly used search engines (HotBot, Yahoo and AltaVista). The top 50 sites identified by each search were assessed for their relevance to patients and their discussion of cancer risk, surveillance and treatment.

Results: Only 98 of the 150 sites visited related specifically to Barrett’s oesophagus and of those designed for patients, 60% were professionally produced, 30% were from organisations and 10% were from charities. The rest were from commercial interests. 33% (33/98) of sites mentioned surveillance of Barrett’s and 38% (37/98) discussed treatment options for Barrett’s oesophagus.

Conclusions: The information about Barrett’s oesophagus on the internet provides an inaccurate perspective on the controversies related to this condition. In particular, the information is potentially misleading with regard to cancer risk, value of surveillance and treatment. We should take a lead in ensuring accurate, balanced information is available to our patients from all sources including the internet.

BARRETT'S OESOPHAGUS AND ASSOCIATED ADENOCARCINOMA: SIX YEAR EXPERIENCE AND AUDIT OF A SURVEILLANCE PROGRAMME
D. Durai, E.D. Srivastava, M.C. Allison. Royal Gwent Hospital, Newport, Wales, UK

Background: Forthcoming BSG guidelines favour endoscopic surveillance of Barrett’s oesophagus, which could lead to a major and increasing hospital workload and prove inconvenient for patients.

Aims: (i) to examine numbers of new patients entering our surveillance programme each year; (ii) to find how many Barrett’s patients should and should not have entered the surveillance programme; and (iii) to review all Barrett’s associated high-grade dysplasia and adenocarcinoma seen during 1995–2000 and examine the impact of surveillance.

Criteria for surveillance: Patients with Barrett’s segment of 5cm or more, aged up to 70 years and without major co-morbidities, who could potentially withstand surgery, are offered annual endoscopic surveillance.

Results: There were 374 patients with endoscopic diagnosis of Barrett’s oesophagus aged between 27 and 97 years. At January 1995 there were only 7 patients under surveillance. Between 1995 and 2000 99 further patients entered the programme. During the 6 years 24 Barrett’s associated adenocarcinomas were diagnosed, of which 22 were symptomatic and found on index endoscopy and 3 had been detected in the surveillance group (one of which was an interval cancer). One 47-year-old man had potentially curative surgery of an asymptomatic surveillance cancer in 1999 and is well, but the other two were unfit for surgery. One 78-year-old woman with high-grade dysplasia was referred for photodynamic therapy. During the six years 29 other patients were lost to the surveillance programme because they had died or were discharged due to age/comorbidity or lost to follow-up. This still left 74 patients under surveillance, but as a result of this audit 21 further patients could be rejected from the programme: 19 had Barrett’s <5cm and 2 were aged over 70 years.

Conclusions: Endoscopic surveillance presents an increasing burden year by year as asymptomatic cases are diagnosed. The yield of surveillance in relation to our commonly diagnosed Barrett’s associated cancers is disappointing. Regular audits of this kind are needed to ensure that surveillance is targeted towards those patients most likely to benefit.

EXPRESSON OF CARBONIC ANHYDRASE ISO-ENZYMES IN GASTRO-OESOPHAGEAL AND LARYNGOPHARYNGEAL REFLUX DISEASES
N. Johnston1, P.E. Rossi1, P.W. Delttmar2, M. Panettë1, J.A. Kaufman1.

Background: Gastro-oesophageal reflux disease (GORD) is a common condition that has been extensively studied. It is now recognised that patients with laryngeal disease and voice disorders may also suffer from reflux of gastric contents into the upper aero-digestive tract (laryngopharyngeal reflux - LPR). Cellular defence mechanisms are important in protecting the mucosa from the damaging effects of gastric refluxate. It has been suggested that carbonic anhydrase (CA) enzymes may be important in this regard, generating HCO3 ions. This study aimed to investigate any change in expression of CA I in the presence of LPR.

Aims: To investigate the pattern of expression of CA iso-enzymes in oesophageal and laryngeal mucosal biopsy specimens from patients with reflux disease.

Methods: The localisation and expression of CA iso-enzymes were determined in oesophageal and laryngeal mucosal biopsy specimens using standard immunofluorescent (IF) staining techniques combined with Western blot analysis.

Results: Oesophageal samples taken from patients with GORD demonstrate an increased expression of CA I & III in inflamed squamous epithelium, together with evidence that the enzymes were more widely expressed throughout the epithelium. Further increases in the level of expression of both CA iso-enzymes were detected in Barrett’s mucosa and adenocarcinoma although in Barrett’s mucosa IF studies revealed that the distribution of the immunoreactive enzyme was patchy. In contrast, laryngeal squamous epithelium did not demonstrate any change in expression of CA I in the presence of LPR but there was a notable increase in CA III immunoreactivity. The yield of surveillance in relation to our commonly diagnosed Barrett’s associated cancers is disappointing. Regular audits of this kind are needed to ensure that surveillance is targeted towards those patients most likely to benefit.

ESOMEPROZOLE 20 MG COMPARED WITH Lansoprazole 15 MG FOR MAINTENANCE THERAPY IN PATIENTS WITH HEALED REFUX OESOPHAGITIS
K. Lauritzen1, on behalf of the Metropole Study Group, O. Junghard 2, S. Eklund3 (introduced by P. Richardson). 1Odense Hospital, Odense, Denmark; 2AstraZeneca R&D Mölndal, Mölndal, Sweden

Aim: This study was conducted to compare the standard maintenance dose of esomeprazole 20mg daily (od) with the maintenance dose of lansoprazole 1.5mg od for the prevention of recurrence of reflux oesophagitis (RO).

Methods: 1391 patients with endoscopically verified RO (LA classification) were enrolled in this randomised, double-blind, parallel-group, 14 country multi-centre trial. During the initial, healing phase of the study, all patients received 4–8 weeks op open treatment with esomeprazole 40mg. 1236 healed identified by endoscopy at 4
and 8 weeks) and symptom-free (i.e. no heartburn or acid regurgitation during the last 7 days of treatment, investigator assessment) patients were randomised to 6 months maintenance treatment with esomeprazole 20 mg od or lansoprazole 15 mg od. Time to relapse (relapse of RO and/or discontinuation due to symptom recurrence) was analysed using a log-rank test.

Results: Esomeprazole maintained a significantly higher proportion of patients in remission than lansoprazole over the 6-month course of treatment (p<0.0001, ITT analysis-log rank test). After 6 months' treatment, 83% of esomeprazole recipients were in remission compared with 74% of lansoprazole recipients (Life Table estimates). Higher remission rates were consistently achieved with esomeprazole irrespective of baseline LA grade assessed at the beginning of the healing phase. Significantly more patients were free from heartburn in the esomeprazole group compared to the lansoprazole group at 1, 3 and 6 months (p=0.035, Chi-square test). Significant differences at 6 months between esomeprazole 20 mg od and lansoprazole 15 mg od were also observed for control of epigastric pain and acid regurgitation (p<0.05 and p<0.001, respectively, Chi-square test).

Conclusion: Esomeprazole 20 mg od is more effective than lansoprazole 15 mg od for maintaining healed RO and controlling accompanying GORD symptoms.

### Abstract 452

**Tooth wear (mean [sd]) and regurgitation**

<table>
<thead>
<tr>
<th>Tooth wear</th>
<th>Regurgitation</th>
<th>No regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.52% (5.9%)</td>
<td>0.65% (1.63%)</td>
<td>P=0.048</td>
</tr>
<tr>
<td>Salivary flow rate [median (range)] and hoarseness</td>
<td>Hoarseness</td>
<td>No hoarseness</td>
</tr>
<tr>
<td>0.66 ml/min (0.4–1.1)</td>
<td>1.6 ml/min (11–2.6)</td>
<td>P=0.011</td>
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</table>

### Abstract 451

**PSYCHOLOGICAL FACTORS MUST BE CONSIDERED IN THE EVALUATION OF SYMPTOMS OF BENIGN OESOPHAGEAL DISEASE**

S.E. Jackson, J. Weinman, A. Chandra, A. Anggiansah, W.J. Owen. Department of Surgery, Guy’s & St Thomas’ Hospital, London, UK

Introduction: In a number of patients with symptoms of gastro-oesophageal reflux disease (GORD), investigations find no organic cause and the literature suggests that psychological factors may play a role. The aim of the study was to prospectively evaluate psychological profiles of symptomatic patients attending for investigation.

Patients and Methods: Of the 79 patients approached, 71 agreed to complete the questionnaire. This contained scales such as the revised Illness Perception Questionnaire (IPQ), which included a measure of perceived illness coherence, and the Positive and Negative Affect Schedule (PANAS). All patients underwent manometry and 24-hour ambulatory pH monitoring. GORD was defined where total percentage reflux time was greater than 5.78% (reflux occurred where the distal oesophageal pH was less than four). Analysis was performed on the questionnaires results, diagnosis after investigation, manometry and pH result. Spearman’s rank correlation was used to examine correlations in the whole sample. The Mann-Whitney test for non-parametric non-independent data was used to examine differences between groups.

Results: Illness coherence as measured by the IPQ was inversely correlated with total percentage reflux time (R= -0.33, p=0.007). There was a significant difference (p=0.008) in the illness coherence mean score between GORD (n=37, mean=8.26) and non-GORD (n=34, mean=10.23) groups. Mean values of positive affect as measured by the PANAS differed significantly (p=0.044) between subjects defined manometrically as having abnormal motility (n=46, mean=36.9) and those with normal motility (n=20, mean=33.5).

Conclusions: Patients who have a low positive affect tend to have normal motility when studied with manometry. A greater score of illness coherence implies a reduced understanding of and mystification by the illness. Those who had a greater illness coherence score did not have GORD. The presence of psychological factors as determined by this study seems to distinguish a subset of patients with no organic disease.

### Abstract 452

**TOOTH WEAR, SALIVA AND SYMPTOMS OF GORD: IS THERE A RELATIONSHIP?**

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Introduction: Dental erosion and gastro-oesophageal reflux disease (GORD) are reported to be associated. However, the role of saliva in both conditions is unclear. This study aimed to investigate the relationship between saliva, dental erosion and reflux symptoms.

Patients and Methods: 104 patients attending the oesophageal laboratory complaining of symptoms of GORD were assessed at 0 A detailed history was obtained regarding the patients’ diet, their oesophageal (heartburn, regurgitation, dysphagia and retrosternal pain) and extra-oesophageal (hoarseness, globus and chronic cough) symptoms. Tooth wear was assessed by grading each tooth surface using 4 pathological scores 2–5 with increasing severity. Score 2 represents dentine exposure whilst scores 4 and 5 represent severe wear either involving the pulp or needing treatment. Stimulated salivary flow rate and buffering capacity of these patients were assessed using a standard protocol. The patients subsequently had standard manometry and 24-hour pH tests.

Results: See table. The severity of tooth wear varied between patients. The mean (sd) tooth wear score of 3 for all sites was 4.3% (13.4%) and for scores 4 and 5 grouped together was 2.5% (12.5%). There were no associations between other symptoms of reflux or presence of GORD to tooth wear and no relationship between salivary parameters and tooth wear.

Conclusions: Regurgitation was associated with increased tooth wear. Hoarseness was associated with decreased salivary flow rate. In this group of patients saliva was not associated with tooth wear or GORD.

### Abstract 453

**DOES COOLING SENGSTAKEN-BLAKEMORE TUBES AID INSERTION?**

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Introduction: Balloon tamponade using Sengstaken-Blakemore (SB) tubes for oesophageal varices has been in use for almost 50 years. Despite the development of endoscopic techniques, SB tubes still have an important role in the management of variceal bleeding. Standard teaching recommends the use of a cooled SB tube that increases tube stiffness and aids insertion. We surveyed current clinical practice of SB tube use in our region and also assessed whether cooling SB tubes alters the stiffness of the tubes.

Methods: A telephone questionnaire was conducted of gastroenterology registrars and ITU departments in the North Thames region. The current clinical practice and the basis for this practice were determined in each case. The stiffness of SB tubes was measured at 0°C and 23°C by calculating the slope of the plot of load (kg) vs. strain (tube stretch/initial tube length). The time for tube warming from 0°C to 23°C when in stationary air and when in contact with skin was also measured.

Results: Fifty registrars were contacted and twenty ITU departments were surveyed. All ITU departments involved the gastroenterologists in the management of acute variceal bleeds. Eight registrars had never placed an SB tube. The majority of the remainder (93%) used a cooled SB tube. All of the registrars based this practice upon their clinical teaching, and 75% of these registrars thought cooling aided the insertion of the tube. There was no difference in the stiffness of the tubes at 0°C and 23°C. The time for SB tube warming from 0°C to 23°C was 120 seconds in stationary air, and 20 seconds when in contact with skin.
Conclusion: The current clinical practice of trainees for SB tube insertion is to cool the tubes in the belief that this ‘standard’ practice aids tube insertion. We found no change in SB tube stiffness even after cooling to temperatures that would not be achieved during routine insertion. Furthermore, the rapid rise in tube temperature means that tubes approach room temperature by the time they reach the bedside. In the present era of evidence-based medicine the current dogma that SB tubes should be cooled must be discarded.

**454 PHOTODYNAMIC THERAPY (PDT) FOR BARRETTL’S OESOPHAGUS: ESTABLISHING THE OPTIMUM DOSE OF 5-AMINOLAEVULINIC ACID (ALA)**

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**Introduction:** Adenocarcinoma of the oesophagus is increasing in incidence more rapidly than any other cancer in the Western World. The major risk factor is Barrett’s oesophagus (BO), an acquired condition where the normal squamous lining is replaced by columnar epithelium showing intestinal metaplasia. This metaplastic change confers a lifetime risk for developing adenocarcinoma of 10–15%. ALA-PDT is effective in the treatment of BO, but an optimal dosage regimen has yet to be established. Therefore the aim of this study is to determine the optimum dose and timing of ALA administration in PDT for BO.

**Materials and Methods:** Twenty-five patients with biopsy proven BO (median length 4cm, range 2–15cm) were randomised into 5 groups (n=5) and received: 30 or 60mg/kg ALA at 6 hours, 30 or 60mg/kg ALA at 6 hours, 30mg/kg at 6 hours and 4 hours before light activation. All patients underwent laser endoscopy under sedation using a balloon applicator and 635nm light at 68mW/cm². Light activation was repeated 4 weeks later.

**Results:** All patients showed a macroscopic reduction in the length of BO, with biopsy proven squamous re-epithelialisation. This was greatest in the fractionated and 30mg/kg groups (median 60%, range 25–100%). There was no significant difference between groups (median 60%, range 20–100% across all groups). Side effects were minimal.

**Conclusions:** Low dose ALA-induced PDT with red light appears to be an effective protocol for safe and effective ablation of BO. It seems appropriate to use a lower dose to reduce cost, improve safety and minimise potential side effects.

**455 THE PREVALENCE OF BARRETTL’S OESOPHAGUS (BO) IN A U.K. CENTRE OVER 15 YEARS**

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**Background:** In the absence of population studies there are no reliable data on the prevalence of BO in the general population. However, the prevalence of BO found in a large endoscoped population should provide information on the pattern of distribution by age and sex.

**Objective:** To establish the prevalence of BO by age and sex over a 15 year period in a district general hospital.

**Methods:** Prevalence was calculated from all histologically proven cases of BO between the ages of 20–89, identified between 1982–96 and the number of first endoscopies, all stratified by age and sex.

**Results:** 491 cases of BO (316 in males, 175 in females) were identified in 21,899 endoscopies (10,939 in males, 10,960 in females). Prevalence rose incrementally from age 20–29, from 0.16% in males and 0% in females to a maximum at age 70–79 of 4.89% in males and 3.75% in females, prevalence declined in both sexes at age 80–89 to 3.21% and 2.44% respectively (see table). Binary logistic regression shows that the prevalence of BO in men was double that of females, OR 2.01, [95% CI 1.67–2.43]. Fitted curves showed a ten year shift in prevalence between males and females.

**Discussion:** This study shows that the prevalence of BO rose steeply with age in both sexes. However, in females this rise was far slower between the ages of 20–59 than in males, reflected in a 10 year delay in the onset of BO in females. This delay probably accounted for the 2:1 male:female ratio in the prevalence of BO. These results suggest that pre-menopausal females are to some degree protected against the development of BO.

**Conclusion:** The prevalence of BO in a population is strongly influenced by its age and sex composition.

**456 BARRETTL’S OESOPHAGUS, AN INCREASING HAZARD? THE VIEW FROM A UK DISTRICT GENERAL HOSPITAL (DGH)**

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**Introduction and Aim:** We present our 20 year experience of Barrett’s oesophagus identified from the open access endoscopy programme 1977–1996 and followed up in our DGH until 31.12.00. Patients (pts), methods Barrett’s was diagnosed by histology or visually if ≤3cm length. Pts were treated with H2RA or PPI and followed by endoscopy and biopsy or by clinical means alone (including telephone survey) if elderly or unwell.

**Results:** see table. 1. Incidence 4.3% of reflux pts have Barrett’s and the prevalence of both is rising. 2. Demography Barrett’s pts are a decade older than reflux pts (mean age at diagnosis 62y vs 52y) and both have a slight male preponderance (58%, 55%). 3. Complications Presentation with haemorrhage and/or anaemia is more common in Barrett’s (20% vs 5%) and oesophageal stricture is seen more often this group (11% vs 2%). 4. Mortality During a mean follow-up of 7.5 years (range 0–21y) 123/368 (33%) died, mean age 78y, 24 from oesophageal adenocarcinoma (OAC), 18 from other tumours and the remainder mainly from cardio-respiratory causes. 5. Risk of malignancy 5 presented with, and 5 developed OAC within a year (and are excluded as incident cancers). 20 of the remaining 358 (5.6%) developed OAC, mean follow-up 6.7y, range 1.1–14y i.e. 1 tumour per 136 patient years, at a mean age of 72y. 12 occurred during endoscopic follow-up (4 were cured after resection of whom 1 died 8 years later of an unrelated cause) and the other 8 were patients whose general condition precluded serial endoscopy.

**Discussion and Conclusion:** 1. Barrett’s affects an older reflux population and is associated with more complications. 2. One in twenty develop an OAC, generally lethal, but five more die from other causes. 3. As the prevalence of Barrett’s continues to rise, the population risk of OAC is likely to increase.

**457 TRANSFECTION INTO AND EXPRESSION OF P53 IN THE HUMAN OESOPHAGUS: AN EX VIVO STUDY**

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**Background:** Oesophageal cancers have a poor prognosis; treatment of these cancers by chemotherapy, radiotherapy and surgery improves this in only a small minority. Mutations in the p53 gene are common in oesophageal cancer and is a poor prognostic indicator. The introduction of a wild type copy of p53 may, therefore, provide a novel treatment for oesophageal cancers. In this study we aim to determine the feasibility of introduction of wild type p53 into human oesophageal tissue.
Methods: Human normal oesophageal pinch biopsies, obtained at endoscopy were transfected with a human wild type p53 using liposomes as a vector; control biopsies were transfected with a control plasmid lacking the p53 gene. After transfection the biopsies were set up in short term organ culture. Samples were subsequently analyzed by semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and/or Western blotting to assess the expression of p53 and also its downstream transcriptional target p21\(^{\text{waf1}}\).

Results: RT-PCR demonstrated that 11.1% of biopsies showed an accumulation of p53 mRNA following transfection with the p53 gene but not with the control construct. In other biopsies (44.4%), p53 transcripts were detected both in the control and in the p53-transfected samples. However, by comparison to the level of expression of β-actin, used as an internal standard, p53 expression levels were elevated in these latter samples. Similarly, an elevation in the levels of p21\(^{\text{waf1}}\) mRNA was shown to occur in biopsies that had been transfected with the p53 gene as compared to the control. An increase in p53 expression was not detected by Western blotting, although p21\(^{\text{waf1}}\) protein was readily detectable in biopsies transfected with the p53 gene, at levels significantly higher than those seen in the control samples.

Conclusions: We have demonstrated that it is possible to introduce wild type p53 into human oesophageal tissue at sufficient dose so that this gene is expressed and its product causes activation of p21\(^{\text{waf1}}\), a gene downstream in the pathway to cell cycle arrest. This has therapeutic potential.

**459 INVESTIGATION OF BILE ACID COMPOSITION IN GASTRIC JUICE SAMPLES FROM PATIENTS WITH GORD**
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Pre-malignant Barrett’s oesophagus and reflux oesophagitis are associated with the reflux of stomach contents into the lower oesophagus. Although the role of acid and pepsin as damaging agents within this refluxate has been well established, attention is now becoming focused on the potential effect of bile acids. This study aims to determine the bile acid composition of refluxate in patients with GORD, so that an in vitro model can be set up to determine the effect bile acids may have, in inducing cellular injury to oesophageal epithelium.

Methods: Gastric juice samples were obtained from 170 patients with gastro-oesophageal reflux disease (112 with oesophagitis and 58 Barrett’s oesophagus). The bile acid composition was determined by gas chromatographic analysis.

Results: Conjugated bile acids were detected in 95% of samples with concentrations ranging from 1.2 µmol/l to 6.4 mmol/l, however only 11 samples contained concentrations exceeding 1 mmol/l. Mean concentrations of the primary bile acids, cholate and chenodeoxycholate were calculated to be 119 mmol/l and 112.1 mmol/l respectively. However, the mean concentration of the secondary bile acid deoxycholic acid was 63.2 mmol/l. In comparison the much lower mean concentration of lithocholic acid, a particularly toxic bile acid, was found (mean concentration = 17 mmol/l). Sixty four percent of patients had unconjugated bile acids present in their gastric juice with only 18 patients having concentrations in excess of 20 mmol/l.

Conclusions: Bile acids are normally present in the gastric juice of patients with both Barrett’s oesophagus and oesophagitis. For both groups conjugated bile acids are the predominant species, with primary bile acids being in excess of secondary. The presence of toxic bile acids within gastric juice suggests that they may have a role in the pathogenesis of GORD. Furthermore the present data have indicated appropriate concentrations of individual bile acids for investigating the effect of bile acids on apoptotic and stress responses in established oesophageal cells lines. This research was funded in part by Reckitt Benckiser Healthcare (UK) Ltd, Hull, UK.

**460 OESOPHAGEAL ACID EXPOSURE AND PROTON PUMP INHIBITOR REQUIREMENTS IN SCLERODERMA**
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Gastro-oesophageal reflux disease (GORD) is a cause of significant morbidity in scleroderma (SSc). Proton pump inhibitors (PPI) are frequently used yet information is limited regarding their effect on oesophageal acid exposure in SSc.

The aim of this study was to examine the nature of pathological oesophageal acid exposure in SSc and, in addition, to evaluate PPI requirements.

SSc patients with reflux symptoms and who fulfilled ACR diagnostic criteria were recruited. Subjects underwent 24-hour ambulatory oesophageal pH monitoring. The following pH parameters were recorded: percentage of study time at pH<4 for the total, erect and supine periods, the number of long reflux events (>5 minutes) and the duration of the longest reflux event. Those subjects with exposure times above previously determined normal values were commenced on PPI therapy. Treatment was sequentially increased, with repeat pH monitoring after each increment, until a treatment endpoint of normalisation of acid exposure was reached.

Twenty-two subjects were recruited. Fourteen (64%) had an abnormal oesophageal pH profile. The median % of the total study time at pH<4 was 11.3% (normal <4.9%), for the erect period 11.9% (normal <6.2) and for the supine period 4.1% (normal <1.2). The median

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**Abstract 456**

<table>
<thead>
<tr>
<th>Year</th>
<th>Reflux</th>
<th>Barrett’s</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>1977-81</td>
<td>714</td>
<td>43(6%)</td>
<td>757</td>
</tr>
<tr>
<td>1982-86</td>
<td>1587</td>
<td>53(3.3%)</td>
<td>1640</td>
</tr>
<tr>
<td>1987-91</td>
<td>2381</td>
<td>121(5.1%)</td>
<td>2502</td>
</tr>
<tr>
<td>1992-96</td>
<td>3812</td>
<td>151(4%)</td>
<td>4163</td>
</tr>
<tr>
<td>Total</td>
<td>8494</td>
<td>368(4.3%)</td>
<td>8862</td>
</tr>
</tbody>
</table>

\(^1\) Newly developed GORD; \(^2\) Barrett’s at presentation or at follow-up
number of long reflux events was 7 with a median longest event of 23 minutes. The longest reflux event occurred in the erect period in 6 (43%) and in the supine period in 8. Seven subjects (50%) had acid exposure normalised after 1 dose-study sequence on once daily PPI therapy. Six (43%) required 2 dose-study sequences and normalised on twice daily PPI therapy. One patient required 3 dose-study sequences and normalised on three times daily therapy.

The majority of SSC patients with reflux symptoms have pathological acid exposure. Abnormal exposure is common in both the erect and supine positions. Modest PPI doses were required in most patients to normalise acid exposure. Refractory acid reflux was not seen.

### Aims:
To develop a database for patients with Barrett's Oesophagus, which would aid clinical follow up, monitoring of disease progression and facilitate research studies.

### Methods:
We have developed a Barrett’s Oesophagus Database for Sheffield patients (BODS). This has been produced in Microsoft Access® and employs a drop down menu system to facilitate data entry and allows for the recording of patient demographics, relevant drug and past medical history, endoscopy summaries, 24 hour pH and manometry studies, histology, treatment, and follow up.

### Results:
Over 300 patients have been entered into BODS, we have found it to be user friendly and versatile e.g., the operator can choose an endoscopic surveillance interval for each individual patient, complete reports of a patients record with endoscopic findings and histology results can be easily produced. The query tool will automatically calculate future endoscopy intervals and dates thereby reducing clerical errors.

### Conclusions:
BODS is proving to be an effective tool in both the clinical and research settings and a rival to other systems such as Endoscribe™. In the future, it could be used in other hospitals and modifications could allow flexibility to include other conditions. A multimedia presentation will demonstrate data entry, analysis, and report production.

### BODS ENTRY AND REPORTS

#### 461 INSERTING EXPANDABLE METAL OESOPHAGEAL STENTS WITHOUT X-RAY

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Expanding metal oesophageal stents are widely used for palliation of oesophageal cancer. These stents are designed to be inserted by endoscopy with fluoroscopic guidance. This need for X-ray can be limiting for endoscopists in centres with limited or no fluoroscopic services. Even with fluoroscopy, external marking of the position of the tumour can be inaccurate and internal marking of the tumour can be time consuming.

We have used a modified deployment technique, guided by direct endoscopic visualization without the need for Fluoroscopy. Microvasive (Boston Scientific) stents were used. The proximal location of the stent is marked with a white proprietary marker paint (Tippex). A guide wire is inserted through the endoscope which is then removed. The stent is inserted over the wire, the endoscope is re-inserted and the stent is then deployed by direct visualization of the proximal end of the stent and the proximal end of the stent.

We inserted 47 stents in 43 patients with obstructive malignant oesophageal strictures; 27 male, mean age 79 years (range 44–97). Histologically there were 22 adenocarcinomas, 7 squamous carcinomas, 7 undifferentiated cancers and 1 severe dysplasia. Covered and uncovered stents of 10, 15 and 17cm were used.

In 4 patients with almost complete stenosis, the stenosis was first dilated but the stents were inserted by the method described above. There were no cases of malposition and there were no immediate complications of stent insertion.

In our experience, stent insertion by direct endoscopic visualization was technically simple and successful. We found it simpler and more accurate than techniques that involve internal or external marking of the tumour followed by fluoroscopy. This technique is of particular use in centres with limited or no fluoroscopic services.